LECTURE 7

An important aspect of the modeling process consists in identifying the most appropriate variables and knowledge to be used, i.e., we must ask:
- what do we model?
- what do we know that can help writing equations?

If the focus is on processes occurring within a cell (e.g., biochemical reactions) or across the cell membrane (e.g., transport or action potentials), we saw that the modeling machinery includes:

VARIABLES:	KNOWLEDGE:
• concentration of substrates or ions	• Law of Mass Action • Fick's Law
• gating variables	• Nernst's Equilibrium
• electric potentials	• Ohm's Law
• flux density	

We move now the focus onto aggregates of countless cells that absolve together one or more complex function ⇒ We need to define new variables and to identify a different set of laws and knowledge

We will consider here the case of the CIRCULATORY SYSTEM, which is the organ system that permits blood to circulate through the body and to transport substances (e.g., nutrients, O_2, hormones, etc.) to and from the cells

In particular, we will focus on a few aspects of the circulation of the blood. A model for these aspects can help explain physiological conditions:

* Flow of the blood in the vessels

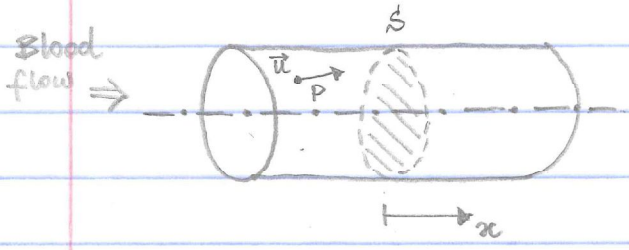
Blood pressure: it is the force per unit area exerted by the blood on the walls of the blood vessels

- It varies in time and space (i.e., the farther from the heart the lower)
- It ranges between:
  - $p_{min} \triangleq$ diastolic pressure (the lowest value during ventricular relaxation)
  - $p_{max} \triangleq$ systolic pressure (the highest value during ventricular contraction)

$p_{min} \cong 80$ mm Hg

$p_{max} \cong 120$ mm Hg

Let us consider a generic vessel as in figure:



We would like to determine the quantity of blood Q that flows through the cross-section S per unit time (i.e., flux through S)

Assumptions:

- We neglect the effects of gravity (i.e., we assume that gravity has the same effect everywhere along the circulatory system)

- The radius of the vessel and the shape of the vessel are fixed (i.e., the walls of the vessel are rigid)

- The blood is a viscous, incompressible fluid that flows slowly and steadily

Under these assumptions, the velocity of the blood in any point of the vessel can be defined by a vector $\vec{u}$, i.e., we can define a vector field $\vec{u}(P)$

The motion of a viscous, incompressible fluid through a rigid vessel is described by the Navier-Stokes equations, i.e., at any point P in the vessel we have:

$$\rho\left(\frac{\partial \vec{u}}{\partial t} + (\vec{u}\cdot\nabla)\vec{u}\right) = -\nabla p + \mu \nabla^2 \vec{u} \qquad (**)$$

$\rho \triangleq$ density of the blood $\qquad \vec{u} \triangleq u_x \hat{i} + u_y \hat{j} + u_z \hat{k}$

$\mu \triangleq$ viscosity of the blood

$$(\vec{u}\cdot\nabla)\vec{u} \triangleq \left(u_x \frac{\partial u_x}{\partial x}, u_y \frac{\partial u_y}{\partial y}, u_z \frac{\partial u_z}{\partial z}\right)^T \text{ - It's a } 3\times 1 \text{ vector}$$

$$\nabla^2 \vec{u} \triangleq \left(\frac{\partial^2 u_x}{\partial x^2}, \frac{\partial^2 u_y}{\partial y^2}, \frac{\partial^2 u_z}{\partial z^2}\right)^T \text{ - It's a } 3\times 1 \text{ vector}$$

$$\nabla p \triangleq \left(\frac{\partial p}{\partial x}, \frac{\partial p}{\partial y}, \frac{\partial p}{\partial z}\right)^T \text{ - Gradient of the blood pressure } p \text{ at position } P$$

Conceptually, this set of equations work as the reaction-diffusion equations do for the passive transport of molecules across the cell membrane, i.e., it provides a point-wise, instantaneous relationship between the blood pressure gradient and the velocity of the blood

A solution can be determined at steady-state:

$$SS \Rightarrow \frac{\partial \vec{u}}{\partial t} = 0 \Rightarrow \rho(\vec{u}\cdot\nabla)\vec{u} + \nabla p = \mu \nabla^2 \vec{u}$$

Moreover, in case of blood flowing steadily, we have: $(\vec{u}\cdot\nabla)\vec{u} \cong 0$

Hence, equations (**) can be simplified as:

$$\nabla p = \mu \nabla^2 \vec{u}$$

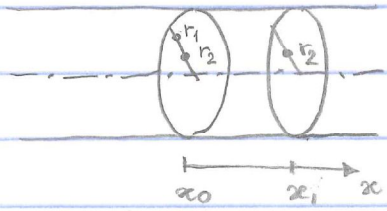
To solve this equation, let us make some considerations:

- We are interested in a solution $\vec{u}$ that explains how blood flows through the vessel slowly and steadily $\Rightarrow$ We look for a solution that has only an axial component, i.e., $\vec{u} = u_x \hat{i}$

- The fluid is incompressible $\Rightarrow \frac{\partial u_x}{\partial x} = 0$ (***)

Note that (***) does not mean that $u_x = \text{const}$ within the vessel. It simply states that two points on the same longitudinal axis have the same velocity (i.e., it is a laminar flow)

Moreover note this:



Two points, with radial distance r_1 and r_2 from the axis but same absoissa x_0, may have different velocities, while two points with abscissa x_0 and x_1 but similar radial distance have the same velocity

It is appropriate to express u_x in cylindrical coordinate (r, ϑ, x)

where: $r \triangleq$ coordinate in radial direction

$\vartheta \triangleq$ angular coordinate (it is always zero here)

$x \triangleq$ coordinate in longitudinal direction

In cylindrical coordinates:

$$\nabla \beta = \mu \nabla^2 \vec{u} \iff \frac{d\beta}{dx} = \mu \frac{1}{r} \frac{d}{dr}\left(r \frac{du_x}{dr}\right)$$

For sake of simplicity, let us write: $u \triangleq u_x$ - velocity in the x-direction.

Also, because the flow is laminar and slow, it is reasonable to expect that β is independent of r and varies linearly with the longitudinal distance

$\Rightarrow$ It must be: $\frac{d\beta}{dx} = \text{const}$

Hence, we can write:

$$\mu \frac{1}{r} \frac{d}{dr}\left(r \frac{du}{dr}\right) = \frac{1}{2r} \frac{d}{dr}\left(\frac{d\beta}{dx} r^2\right) \iff r \frac{du}{dr} = \frac{r^2}{2\mu} \frac{d\beta}{dx}$$

↑ under the derivative operator

Integrating by parts from the walls of the vessel (radius: r_0) to the generic position P (radius: $r < r_0$) and noticing that $u(r_0) = 0$ (i.e., the walls are rigid) we have:

$$u(r) = \frac{1}{4\mu} \frac{d\beta}{dx}\left(r^2 - r_0^2\right)$$

Hence, the flux through the section S will be:

$$Q = \int_0^{r_0} 2\pi r\, u(r)\, dr =$$

$$= \frac{\pi}{2\mu} \frac{d\beta}{dx}\left[\int_0^{r_0} r^3\, dr - \int_0^{r_0} r_0^2\, r\, dr\right] =$$

$$= \frac{\pi}{2\mu} \frac{d\beta}{dx}\left[\frac{1}{4} r_0^4 - r_0^2 \cdot \frac{1}{2} r_0^2\right] = \underbrace{-\frac{\pi}{8} \frac{r_0^4}{\mu} \frac{d\beta}{dx}}_{(*)}$$

Formula (*) indicates that the radius of the vessel is very important to determine the blood flow. Also, from (*) we can determine:

Average blood velocity over the cross-section S:

$$v \triangleq \frac{Q}{A_0} = -\frac{dP}{dx}\frac{r_0^2}{8\mu} = -\frac{dP}{dx}\frac{A_0}{8\pi\mu}$$

A_0: area of S. It is $A_0 = \pi r_0^2$

Note that if P decreases with x (i.e., $\frac{dP}{dx} < 0$) then $v > 0$, i.e., the blood flows opposite to the direction of the pressure gradient ($\Rightarrow$ that's why the blood can leave the heart and flow to the periphery)

Also, if – for sake of simplicity – the circulatory system is made of N vessels, each with cross-section area $A_0 = \pi r_0^2$, then the total flux through the system is:

$$Q_{tot} = N \cdot \left(-\frac{\pi}{8}\frac{r_0^4}{\mu}\frac{dP}{dx}\right) = N \cdot \left(-\frac{A_0^2}{8\pi\mu}\frac{dP}{dx}\right) = -\frac{dP}{dx}\frac{1}{8\pi\mu}A_0\underbrace{(NA_0)}_{\text{total cross-section area for the system}}$$

$$v = \frac{Q_{tot}}{A_{tot}} = \frac{Q_{tot}}{NA_0} = -\frac{dP}{dx}\frac{A_0}{8\mu\pi}$$ – It remains the same!

In a more realistic scenario, we do not have N identical vessels. Nonetheless, the flux Q_{tot} must be constant everywhere (otherwise, there would be stagnation)

$\Rightarrow \frac{dP}{dx} A_0 A_{tot} = \text{const} \Rightarrow \frac{dP}{dx}$ and $A_0 A_{tot}$ have opposite dynamics

Also, in the circulatory system, a decrease in vessel diameter is associated to an increase in total cross-section area (i.e., increase in the number N of vessels) $\Rightarrow$ In this way, the velocity v can be kept small even in the capillaries

* A more refined model of the vessels

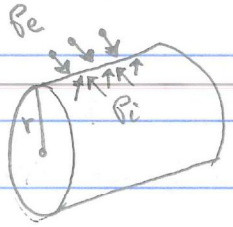
We determined the blood flow in a vessel by solving the equation:

$$\frac{du}{dr} = \frac{dp}{dx}\,\frac{r}{2\mu}$$

with boundary condition: $u(r_0) = 0$

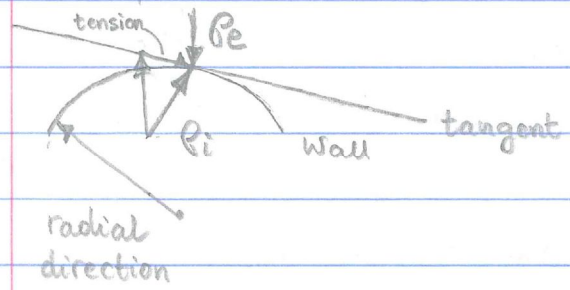
There is a number of reasons why this model is a coarse approximation of the reality. One of these is the assumption that the vessel is rigid

The walls of a vessel are elastic ⇒ Volume of the vessel and blood pressure are related. Suppose that the pressure outside the vessel is uniform and fixed (p_e):

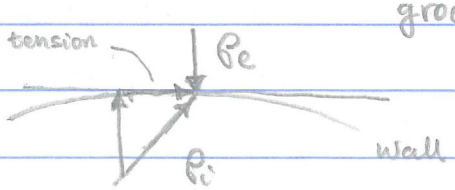


- If p_i (pressure inside the vessel) grows ⇒ V (volume) grows
- If r (radius) grows ⇒ V (volume) grows
- If H (wall tickness) grows ⇒ V (volume) decreases

This depends on the tension in the wall:



If r grows, then the tangent rotates, then a larger p_i is needed to balance p_e ⇒ tension grows



This relationship is captured by the Laplace's Law:

$$T = \frac{\Delta P \, r}{M}$$

$T \triangleq$ tension in the wall

$\Delta P \triangleq$ transmural pressure (i.e., $\Delta P = |P_e - P_i|$)

Note: the Laplace's Law provides a qualitative explanation of the effects of dilated cardiomyopathy:

The heart becomes greatly distended $\Rightarrow$ r increases greatly $\Rightarrow$ T increases greatly $\Rightarrow$ P_i must increase in order to balance T and P_e

$\Rightarrow$ A dilated heart needs more energy than a normal one to pump the same amount of blood

A general assumption is that, under uniform P_i and P_e, and constaut P_e, volume V of the vessel and blood pressure P_i are related through a linear relationship:

$$V = \tilde{V}_0 + C \cdot P_i \qquad (1)$$

$\tilde{V}_0 \triangleq$ volume for $P_i = 0$ (it is $\tilde{V}_0 > 0$ because the blood cells have a volume)

$C \triangleq \frac{V - \tilde{V}_0}{P_i}$ - COMPLIANCE OF THE VESSEL

Sometimes, by assuming that the vessel is a cylinder of volume $V = A \cdot L$, (cross-section area, length) we can write:

$$A = \tilde{A}_0 + c P_i \qquad (2)$$

$c \triangleq \frac{C}{L}$ - COMPLIANCE PER UNIT OF LENGTH

Note that the compliance C is a parameter that varies with vessel ⇒ It captures the differences between arteries and veins and between different portions of the circulatory system (e.g., lungs versus periphery)

Furthermore, (1) needs that P_i is uniform while (2) may be satisfied in cases when P_i is not uniform (i.e., it holds for each cross-sectional area A over which the blood pressure is P_i)

For sake of simplicity, let us write $P \triangleq P_i$. Also, let us recall the formula we defined earlier to calculate the flux:

$$Q = -\frac{A_0^2}{8\pi\mu}\frac{dP}{dx}$$

By replacing A_0 with $A = \tilde{A}_0 + cP$, we have:

$$Q = -\frac{(\tilde{A}_0 + cP)^2}{8\pi\mu}\cdot\frac{dP}{dx}$$

At steady-state $Q = const$ (i.e., the flux must be the same everywhere) and we can write:

$$x = -\frac{1}{8\pi\mu Q}\int_{P(0)}^{P(x)} (\tilde{A}_0 + cP)^2 dP$$

$$= -\frac{1}{8\pi\mu Q}\cdot\frac{1}{3c}(\tilde{A}_0 + cP)^3\Big|_{P(0)}^{P(x)}$$

$$\Rightarrow x = -\frac{1}{8\pi\mu}\cdot\frac{1}{3cQ}\left[(\tilde{A}_0 + cP(x))^3 - (\tilde{A}_0 + cP(0))^3\right]$$

If we choose: $x = L$ (length of the vessel) and we call: $P_0 \triangleq P(0)$; $P_1 \triangleq P(L)$, then we have:

$$Q = \frac{1}{8\pi\mu L} \cdot \frac{1}{3} \frac{\tilde{A}_o^3}{c} \left[-\left(1 + \frac{c}{\tilde{A}_o} P_1\right)^3 + \left(1 + \frac{c}{\tilde{A}_o} P_o\right)^3 \right]$$

Let us call: $R \triangleq \frac{8\pi\mu L}{\tilde{A}_o^2}$; $\gamma \triangleq \frac{c}{\tilde{A}_o}$ - Then, we can write:

$$Q = \frac{1}{R} \cdot \frac{1}{3\gamma} \left[-3\gamma P_1 - 3\gamma^2 P_1^2 - \gamma^3 P_1^3 + 3\gamma P_o + 3\gamma^2 P_o^2 + P_o^3 \gamma^3 \right]$$

$$Q = \frac{1}{R} (P_o - P_1) \left[1 + \gamma \frac{(P_o^2 - P_1^2)}{(P_o - P_1)} + \frac{\gamma^2}{3} \frac{(P_o^3 - P_1^3)}{(P_o - P_1)} \right]$$

$$\uparrow \qquad\qquad \uparrow$$

$$(P_o + P_1) \qquad (P_o^2 + P_o P_1 + P_1^2)$$

$$Q = \frac{1}{R} (P_o - P_1) \left[1 + \gamma (P_o + P_1) + \frac{\gamma^2}{3} (P_o^2 + P_o P_1 + P_1^2) \right]$$

When $\gamma \to 0 \Rightarrow Q \to \frac{1}{R} (P_o - P_1)$ (Ohmic relationship)

When $\gamma >> 0 \Rightarrow$ Q is an increasing function of γ $\Rightarrow$ A compliant vessel can carry a given flux Q by using a smaller pressure drop $\Delta P = P_o - P_1$

In fact, by approximating $-\frac{dP}{dx} \cong \frac{\Delta P}{L}$, we have:

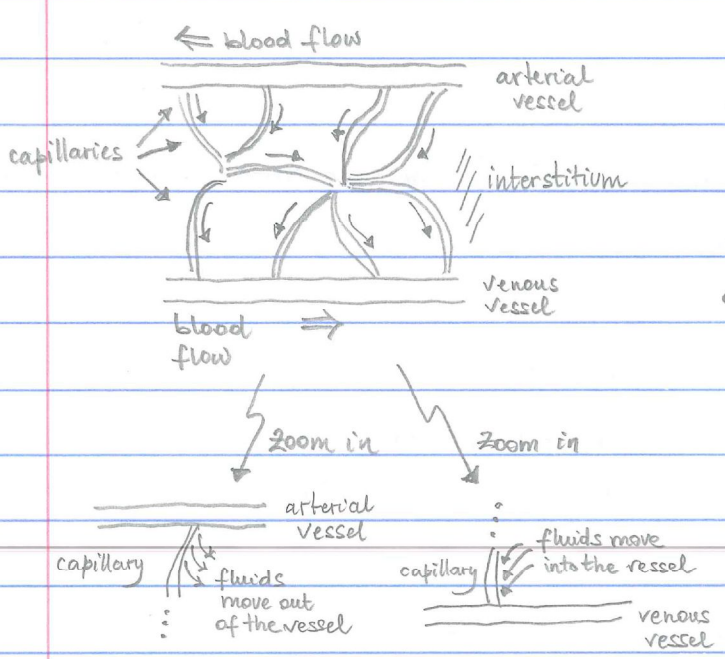
- NON-COMPLIANT VESSEL: $Q = \frac{\tilde{A}_o^2}{8\pi\mu L} \Delta P = \frac{1}{R} \Delta P$

- COMPLIANT VESSEL: $Q = \frac{1}{R} \Delta P \left[1 + \underbrace{\gamma (P_o + P_1) + \frac{\gamma^2}{3} (P_o^2 + P_o P_1 + P_1^2)}_{>0} \right]$

Note: $C \uparrow \Rightarrow \gamma \uparrow \Rightarrow \Delta P \downarrow$ (for a given flux Q) $\Rightarrow$ This explains why the pressure drops much less in veins than arteries

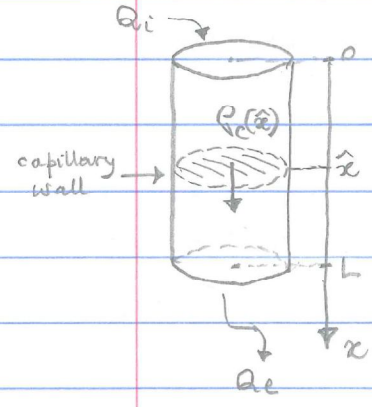
* Microcirculation in the capillaries

The blood that ultimately arrives into the smallest vessels (i.e., the capillaries) has to (1) release nutrients and O_2, (2) remove cellular waste, and (3) transition into the venous system in a continuous way. This is accomplished via the processes of microcirculation and filtration



- The blood is forced to move through the capillary system until it reaches the veins (MICROCIRCULATION)
- As the blood flows into the capillaries, the exchange of nutrients, O_2, and waste products with the interstitium occurs through the capillary walls (FILTRATION)

In order to model the flow of blood in the capillaries, let us consider the following case:



$Q_i \triangleq$ influx of blood from arterial vessels

$Q_e \triangleq$ efflux of blood into the venous vessels

} It must be: $Q_i = Q_e$

Fluids can leave and re-enter the capillary at every position x, provided that the net values Q_i and Q_e are preserved. Let us define:

$q(x) \triangleq$ blood flow at point x along the capillary

$P_c \triangleq$ hydrostatic pressure at point x

We have: $\frac{dP_c}{dx} = \rho\, q(x)$ where $\rho \triangleq$ coefficient of capillary resistance

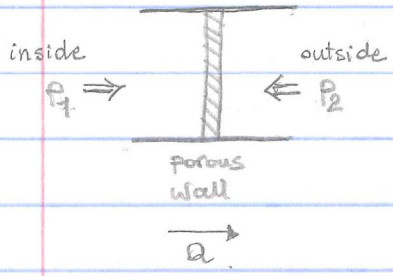
The influx or efflux of fluids at point x determines a variation in $q(x)$ and it is ultimately due to the gradient of pressure:

$$\frac{dq}{dx} = k_f \left(P_{tot}^{ext} - P_{tot}^{int} \right)$$

$P_{tot}^{j} \triangleq$ total pressure inside the capillary (j = "int") or in the interstitium (j = "ext")

$k_f \triangleq$ capillary filtration rate

In order to determine P_{tot}^{int} and P_{tot}^{ext}, we need to introduce the concept of "osmosis" for physiological systems:



$P_{1,2} \triangleq$ pressures

$Q \triangleq$ flux of water through the wall

$r \triangleq$ resistance to the flow of water

$r \cdot Q = P_1 - P_2$

If a solute is added to water with different concentration inside and outside the cell, and if the solute cannot pass through the porous wall, then the concentration of water inside (S_1) and outside (S_2) is different $\Rightarrow$ There will be a flow due to concentration gradient. In particular, let us consider the case:

- $P_1 > P_2 \Rightarrow Q > 0$, i.e., water is forced to leave the cell (or the system)
- $S_1 < S_2 \Rightarrow$ There is a flux $Q_1 < 0$ toward the cell (or the system)

As a result, if the concentrations S_1 and S_2 are given, we can vary the pressure difference $P_1 - P_2$ such that: $Q + Q_1 = 0$. The value $P_1 - P_2 = \pi_S$ such that $Q(\pi_S) + Q_1 = 0$ is called "OSMOTIC PRESSURE".

As a result, in order to have a net flow of water leaving the cell (or the system) we must have:

$$rQ = P_1 - \pi_S - P_2$$

π_S is the minimum pressure difference that prevents water from going into the system. The flux of water inside the system due to the osmotic pressure π_S is called "OSMOSIS"

Note that an effect of osmosis is the growth of the volume of the cell (or the system) $\Rightarrow$ It can be potentially dangerous and requires regulatory mechanisms.

Let us go back to the original problem (i.e., capillary filtration). We have:

- Plasma (inside the capillary) has osmotic pressure π_c ($\cong 28$ mmHg)
- Interstitial fluid has osmotic pressure π_i ($\cong 8$ mm Hg)
- The pressure inside the capillary is $P_c(x)$
- The pressure P_i in the interstitium is typically uniform and constant ($P_i \cong -3$ mmHg)

$$\Downarrow$$

$$\frac{dq}{dx} = k_f \left(P_i - \pi_i - P_c(x) + \pi_c \right) \qquad \text{STARLING EQUATION}$$

By applying the derivative to both sides and recalling the formula for $\frac{dP_c}{dx}$:

$$\frac{d^2q}{dx^2} = -k_f \rho \, q(x) \qquad \text{with: } q(0) = q(L) = Q_i$$

A possible solution to this ODE is symmetric about $x = L/2$ and is given by:

$$q(x) = B \cosh\left(\beta \left(x - L/2 \right) \right)$$

where: $\beta \triangleq \sqrt{k_f \rho}$

From the boundary conditions:

$$q(L) = Q_i \Rightarrow B = \frac{Q_i}{\cosh(\beta L/2)}$$

From the solution $q(x)$, one can determine a formula for $P_c(x)$:

$$\frac{dq}{dx} = k_f\left(P_i - \pi_i + \pi_c - P_c\right) \Rightarrow P_c(x) = (P_i - \pi_i + \pi_c) - \frac{1}{k_f}\frac{dq}{dx}$$

$$\Rightarrow P_c(x) = (P_i - \pi_i + \pi_c) - \frac{Q_i \beta}{\cosh(\beta L/2)\, k_f} \sinh\left(\beta\left(x - L/2\right)\right)$$

Hence, the total drop in pressure from $x=0$ to $x=L$ that is necessary to perform filtration is:

$$\Delta P_c = P(0) - P(L) = 2\frac{Q_i \beta}{k_f \cosh(\beta L/2)} \sinh\left(\frac{\beta L}{2}\right) =$$

$$= 2\frac{Q_i \beta}{k_f} \operatorname{tgh}\left(\frac{\beta L}{2}\right)$$

From this formula, we can also derives a comparison to the previous models of blood flow. In fact, we have:

$$Q_i = \frac{\Delta P_c}{\operatorname{tgh}\left(\frac{\beta L}{2}\right)} \cdot \frac{k_f}{2\beta} = \frac{\Delta P_c}{\operatorname{tgh}\left(\beta L/2\right)} \cdot \frac{k_f \cdot \beta L}{2\beta^2 L} = \frac{\Delta P_c}{R} \cdot \frac{\beta L/2}{\operatorname{tgh}\left(\beta L/2\right)}$$

$\beta^2 = \rho k_f$, $R \triangleq \rho L$

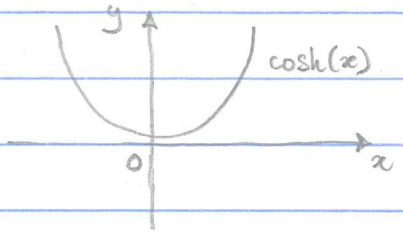
For $\beta \neq 0$, $\frac{\beta L}{2} > \operatorname{tgh}\left(\beta L/2\right) \Rightarrow$ The equivalent resistance of the leaky capillary is lower than the resistance of the nonleaky vessels considered before

Finally, note this:

$q(x)$ - minimal at $x = L/2$

$\Downarrow$

The flow from the capillary to the interstitium is maximal at $x = L/2$



The quantity $Q_f \triangleq Q_i - q(L/2)$ is called "FILTRATION RATE"

It follows: $Q_f = Q_i - \frac{Q_i}{\cosh(\beta L/2)} \cosh(0) \Rightarrow Q_f$ depends on the parameter

$\beta L = \sqrt{\rho k_f} L \Rightarrow$ If $k_f \uparrow$ (i.e., the vessel is leaky) and $\rho \uparrow$ (which happens when the radius of the vessel is small), then filtration is enhanced (i.e., $Q_f \uparrow$)

* Cardiac Output

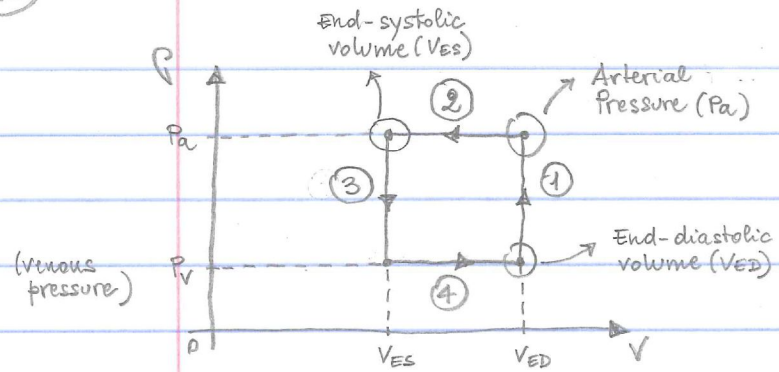
All the models we have considered in this lecture ultimately have two pieces of information that are given: (1) the amount of blood flowing into the circulatory system; (2) the blood pressure as the blood leaves the heart.

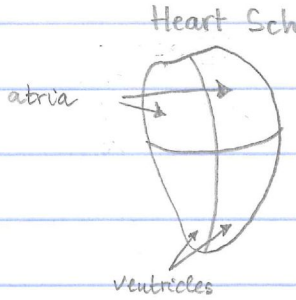
We develop a model for (1):

CARDIAC OUTPUT $\triangleq$ total amount of blood pumped by the ventricles $\Rightarrow$ It is a function of the volume of the ventricle (V) and the pressure exerted in the ventricle (P) due to tissue contraction

Consider the $P-V$ diagram over consecutive heartbeats:

(16)



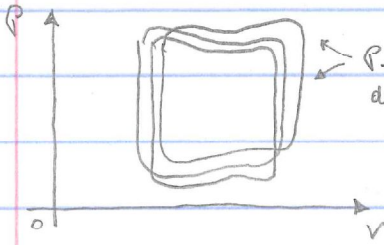


Phase ①: The valve is closed while the ventricle contracts ⇒ V - constant
P - increases

Phase ②: When P reaches a critical value, the valve opens ⇒ V - decreases
P - roughly const.

Phase ③: At the end of contraction, the valve closes ⇒ V - constant
P - decreases

Phase ④: When P reaches a critical value, the valve between atrium and ventricle opens and blood flows in again ⇒ V - increases
P - constant



P-V loops for different heartbeats ⇒ We model this by envisioning the heart as a single compliant vessel, where the compliance C and the volume at rest V_0 are time-varying:

$$V(t) = V_0(t) + C(t)P(t)$$

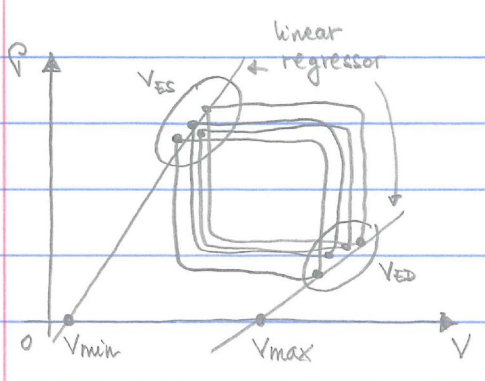
$V_0(t)$: It is due to beat-to-beat variability

$C(t)P(t)$: It accounts for phase ① - ④

In phase ④: V_0 and C increase over time (max compliance)

In phase ②: V_0 and C decrease over time (min compliance)

In phase ① and ③: $C(t) \cong 0$



One approximation is:

$$V_{ED} = V_{max} + C_d P_v$$

(P_v: venous pressure)

$$V_{ES} = V_{min} + C_s P_a$$

(P_a: arterial pressure)

$C_d, C_s \triangleq$ intercepts of the linear regressors (they have the dimensions of compliance)

Hence, for each loop, the max variation in volume (which corresponds to the volume of blood pumped during the stroke) is:

$$V_{stroke} = V_{ED} - V_{ES} = V_{max} - V_{min} + C_d P_v - C_s P_a$$

$$\Downarrow$$

Cardiac Output: $CO = \sum_{\#\,beats} V_{stroke} \cong F \tilde{V}_{stroke}$

where: $F \triangleq$ heart rate (beats/unit of time)

$\tilde{V}_{stroke} \triangleq$ average V_{stroke} across the beats, i.e.:

$$\tilde{V}_{stroke} = V_{max} - V_{min} + C_d \tilde{P}_v - C_s \tilde{P}_a$$

($\tilde{P}_v$, $\tilde{P}_a$: average pressures)

REFERENCE:

Textbook (volume 1): chapter 2, sec. 2.7

(volume 2): chapter 11, sec. 11.1; 11.2; 11.3; 11.4