Ear canal and cerumen production

CHOOSE-FOCUS-ANALYZE (CFA) EXERCISE

BY

RAVI BADWE

BT04B026

“Anatomy teacher asked a question to the student

Teacher- What is the main function of ear wax?

Student- Someone's brain must have fallen out. That's ear wax's main function, to stop that happening.”

Table of contents:

1. Introduction

2. Question

Modeling

- ⇨ Glucose utilization
- ⇨ Cholesterol production

Use of the models to predicts the values

3.1 Model for the glucose (considered as the only substrate) utilization by the cartilaginous portion of the human ear canal.

3.2 Model for squalene, lanosterol, and cholesterol production.

*3.3 Time required filling the half the volume of the cartilaginous portion of the auditory canal (the wax producing region) by **Cerumen** (i.e. 20% to 40% hearing loss).*

4. Results and discussion.

5. Limitations of the analysis.

6. Conclusion

7. Future work

8. Acknowledgement

9. References

1. Introduction:

The **ear** is the sense organ that detects sound. The vertebrate ear shows a common biology from fish to humans, with variations in structure according to order and species. It not only acts as a receiver for sound, but plays a major role in the sense of balance and body position.

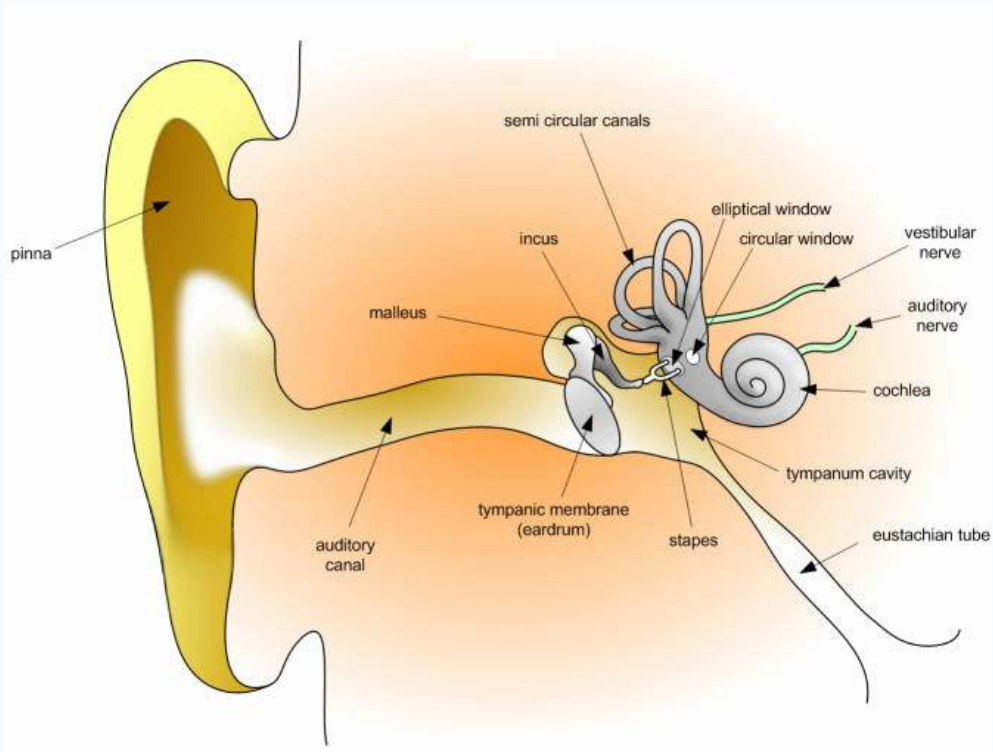


Fig. 1 above figure shows anatomy of the ear

Outer most part of the ear is known as outer ear consist of Pinna, Ear Canal, Surface of Ear Drum. Each has specific functions. For example Ear Canal is involved in production of ear wax which in turn keeps the ear free of dead cells and dust. The ear canal is shaped somewhat like an hourglass-narrowing part way down. The skin of the outer part of the canal has special glands that produce earwax. This wax is supposed to trap dust and dirt particles to keep them from reaching the eardrum. Usually the wax

accumulates a bit, dries out and then comes tumbling out of the ear, carrying dirt and dust with it. Or it may slowly migrate to the outside where it can be wiped off. The ear canal may be blocked by wax when attempts to clean the ear push wax deeper into the ear canal and cause a blockage. Wax blockage is one of the most common causes of some hearing loss.

Earwax, also known by the medical term **cerumen**, is a yellowish, waxy substance secreted in the ear canal of humans and many other mammals. Earwax [1] is composed of more than 40 different substances including not only wax and oil but also dead skin cells. In fact, the primary component of earwax is keratin, an extremely fibrous protein substance found in the outermost layer of the skin. Cerumen is produced in the outer third of the cartilaginous portion of the human ear canal. It also consists of mixture of viscous secretions from sebaceous glands and less-viscous ones from modified ceruminous glands. The main components of earwax are the final products in the HMG-CoA reductase pathway, namely, squalene, lanosterol, and cholesterol. The percentage of these compounds varies within a short range and hence our analysis will be based on these compounds.

2. In our analysis we will try to model the following:

2.1 Glucose utilization by the glands in the auditory canal of the human ear.
2.2 The concentration of squalene, lanosterol, and cholesterol as the function of time.

Also we answer the following question:
Suppose the person has cleaned his ear just now. Since the ear wax production is a continuous and has almost constant rate (given the other factors are constant) his Cerumen production will again start. We will try to help that person by telling him that when he needs to again clean his ear. (Assumption- the person is very lazy and will clean only when his hear will be affected by about 20-40% i.e. 50% of the cartilage portion is filled with cerumen.)

3.1 Model for the glucose (considered as the only substrate) utilization by the cartilaginous portion of the human ear canal:

Outer part of the auditory canal is made of the tissue involved in ear wax production. Cerumen is produced in the outer third of the cartilaginous portion of the human ear canal. Wax produced only in this portion and not in the bony region of the canal. **Cartilage** is a type of dense connective tissue. ***It is composed of cells called chondrocytes which are dispersed in a firm gel in the form of glands-like ground substance, called the matrix. Cartilage is avascular (contains no blood vessels) and nutrients (like glucose) are diffused through the matrix.***

3.1.1 In ear the Cartilaginous portion [2]

1. Makes up the outer 1/3rd of the canal
2. Is supported by elastic cartilage (immobilized glands)

3.1.2 It consists of:

1. Hair follicles - to protect from foreign bodies
2. Large sebaceous glands (make sebum- an oily material to keep hair and skin soft and waterproof)
3. Ceruminous glands- produce ear wax (cerumen)

In this part of analysis ceruminous glands as well as sebaceous glands have been included because ear wax is composed of secretions of both the glands.

*Since the glands are present in the **matrix** so the model which we will follow is gel entrapped immobilized cells.*

3.2.1 Assumptions:

1.3.1 All the cells present in the matrix are equivalent and one gland is considered as the one unit. (Since there are only glands present and no free cells). Also they are uniformly arranged in the matrix.

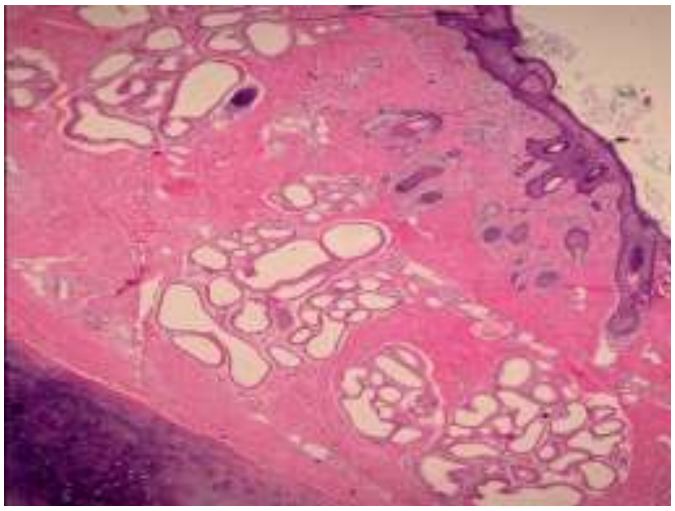


Fig2.

1.3.2 The Cartilaginous portion (1/3) of the auditory canal is a perfect hollow cylinder.

1.3.3 The number of the glands are constant.

1.3.4 Rate limiting step in the glucose utilization by the cells is the transport through the cell membrane. Glucose uptake follows “monod kinetics”.

$$u = u_m \left(\frac{S}{K_S + S} \right)$$

The transfer of glucose happens by diffusion in the matrix and its value is in the order of the 10^{-6} cm^2 s^{-1} [3]. When the concentration of glucose become low the, it’s uptake kinetics become first order. Therefore Monod equation becomes

$U_s = (U_{max} / K_s)$ G=KG..... [1]
Where K is specific rate constant and G is the concentration of the glucose.

1.3.5 Every gland is considered as single units and all the glands are equivalent.

3.2.2 Let us take an elemental cylinder at distance r from the axis of cylinder of thickness dr.

According to fick’s law

$$j = - \mathrm{D} \cdot \nabla \cdot c$$

Where D is diffusion constant which depends on the temperature and $\nabla \cdot c$ is the concentration gradient.

Applying mass balances across this elemental cylinder on glucose (cylindrical coordinates) (substrate (G)).

. . . .

I-O+G-C= dS/dt

- ⇨ Diffusive flux at (r+δr)-Diffusive flux at r –Amount reacted in volume 2πrLδr=Accumulation of the glucose

Accumulation of the glucose is equal to zero because there can not be the accumulation of glucose in between the cells i.e. in tissues and muscles.

- ⇨ $\{-2\pi D_{eff} l\ (rdG/dt)_{r+\delta r}\} - \{-2\pi D_{eff} l\ (rdG/dt)_r\} = 2\pi Lr\delta r\ KG$

Where D_{eff} is the effective diffusion coefficient because the cells are present in glands (lumps). Since the body temperature is constant and hence D_e is also constant.

- ⇨ $-2\pi\ D_e\ L\{(rdG/dt)_{r+\delta r} - (rdG/dt)_r\} = 2\pi Lr\delta r\ KG$ (L is the length of the wax producing Cartilaginous portion)

- ⇨ $-D_e\ \{(rdG/dt)_{r+\delta r} - (rdG/dt)_r\}/\delta r = rK$

Taking the limit $\delta r \rightarrow 0$ we will get

- ⇨ $-D_e\ d[rdG/dt]/dr = rK$

- ⇨ $-D_e\ [dG/dr + rd^2G/dr^2] = rK$

- ⇨ $d^2G/dr^2 + (dG/dr)/r + KG/D_e = 0$

let $(K/D_e)^{.5} = \lambda$

- ⇨ $d^2G/dr^2 + (dG/dr)/r + \lambda^2 G = 0$

This is a zero order Bessel's equation whose solutions is given by

⇨ $G=AJ_0(\lambda r) + BY_0(\lambda r)$

$J_0(\lambda r)$ and $Y_0(\lambda r)$ are the solution of first and second kind of Bessel's equation respectively.

$$J_o(x) = 1 - \frac{(x/2)^2}{(1!)^2} + \frac{(x/2)^4}{(2!)^2} - \frac{(x/2)^6}{(3!)^2} + \cdots$$

$$Y_o(x) = \frac{2}{\pi}\left[\left(\ln\frac{x}{2} + C\right)J_o(x) + \frac{2}{1}J_2(x) - \frac{2}{2}J_4(x) + \frac{2}{3}J_6(x) - \cdots\right]$$

Where $x= \lambda r$

We have boundary condition

1. At $r=r_b$ concentration of glucose is G_b (concentration of glucose in blood).

2. At $r=r_a$ concentration of glucose is zero (inside the ear auditory canal).

Putting the boundary conditions in the above equation the parameters A and B are found to be

$$B = G_b J_0(\lambda r_a) / \{J_0(\lambda r_a) Y_0(\lambda r_b) - J_0(\lambda r_b) Y_0(\lambda r_a)\}$$
$$A = - G_b K_0(\lambda r_b) / \{J_0(\lambda r_a) Y_0(\lambda r_b) - J_0(\lambda r_b) Y_0(\lambda r_a)\}$$

3.3.1. The value of the [5,3]
r_a =7mm, thickness of matrix=1215 microns (r_b=7.1215 mm)

V_{max} = 0.56–4.0x10^{-13} mol $cell^{-1}$ h^{-1} for chondrocytes,

K_m = .35mM, D_{eff}= 9.2x10^{-6} cm^2 s^{-1}, G_b =110mg/dl (average)

Since $\lambda = (K/ D_e)^{.5}$

- ⇨ λ= .01402 m^{-1}

3.3. 2. It has been know that [4]
If x<<<<1 then

- ⇨ $J_0(x) \simeq 1- x^2/2$
- ⇨ $Y_0(x) \simeq \ln(x) J_0(x) + x^2/4$

And on the basis of above data it can be easily proved that λr is in order of 10^{-5}.
Therefore

- ⇨ $J_0(\lambda r_a) = 1$
- ⇨ $J_0(\lambda r_b) = 1$
- ⇨ $Y_0(\lambda r_a) = -9.23$
- ⇨ $Y_0(\lambda r_b) = -9.07$

We know all the constants of the model (G_b = 1.1 kg/m^3)
Therefore

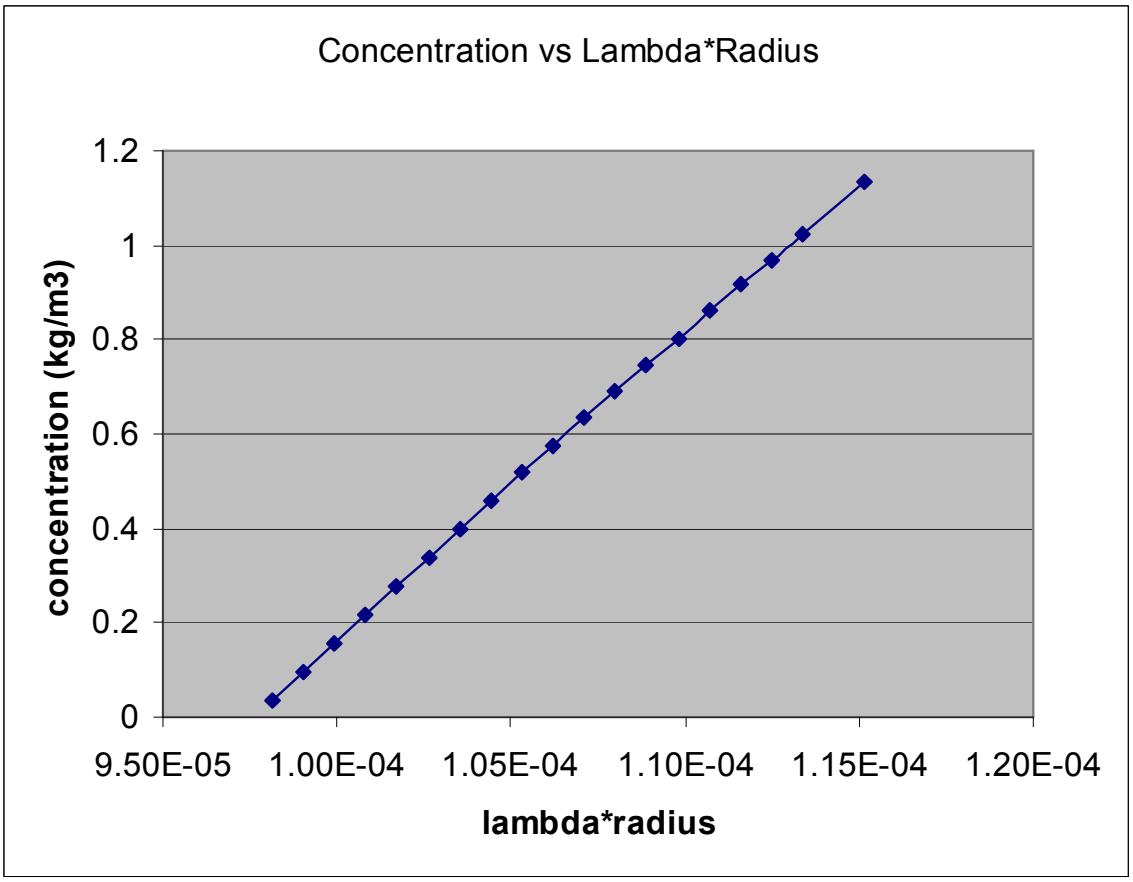
- ⇨ A= 63.437 kg/m^3
- ⇨ B= 6.875 kg/m^3

Therefore

⇨ $G=63.437J_0(\lambda r) + 6.875Y_0(\lambda r)$

Putting the values of $J_0(\lambda r)$ and $Y_0(\lambda r)$ in terms of λr (assuming that its values remain same in the same order)

⇨ $G = 63.437 + 6.875\ln(\lambda r) - 29.997(\lambda r)^2 - 6.875(\lambda r)^2\ln(\lambda r)$



Graph 1

(Radius is increasing in the outward radial direction i.e. toward the blood capilaries)

3.2. Model for squalene, lanosterol, and cholesterol production:

Cerumen is produced in the *outer third* of the cartilaginous portion of the human ear canal. It is a mixture of viscous secretions from sebaceous glands and less-viscous ones from modified apocrine sweat glands. The components of earwax are the final products in the HMG-CoA reductase pathway, namely, squalene, lanosterol, and cholesterol (1).

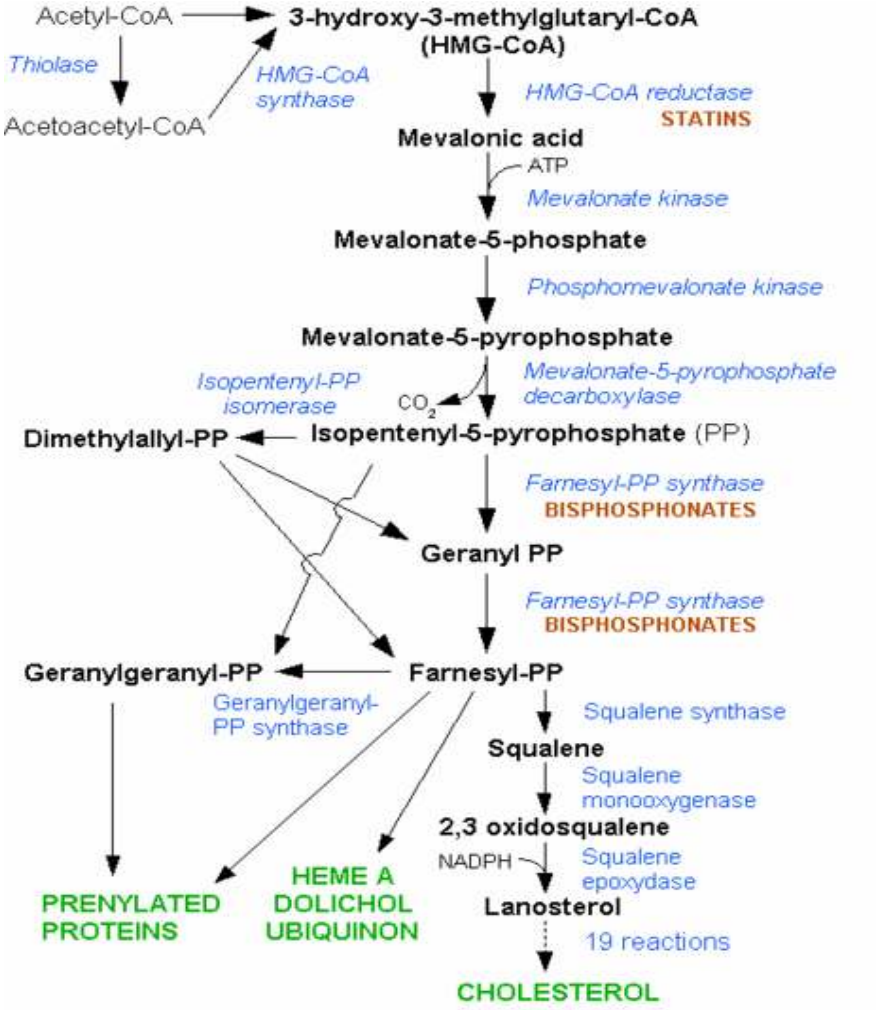


Fig.5 HMG-CoA reductase pathway

The HMG-CoA reductase pathway is a complex pathway complex. More over the intermediates of this pathway are involved in production of other compounds also. We will concentrate on three compounds: Squalene, lanosterol, and

cholesterol (which make part of ear wax) because they are only involved in cholesterol production. In Eukaryotes, the initial steps of cholesterol biosynthesis probably occur mainly in the cytosol, and the later steps in the ER [6, 8] i.e. the production of Squalene, lanosterol, and cholesterol takes place in the ER (conversion of lanosterol to cholesterol also occur in Peroxisomes but we will not consider that reaction). Also it has been found that these enzymes are present in the membrane of the ER. *So our system will be ER including the membrane*.

3.2.1 In order to come out with a model we need to take certain assumption:

3.2.1.1. The enzymes follow the simple Michael mentis equation

$$V=V_{max}S \exp(-k_d t) /(S+k_s)$$

Where
k_d= specific rate of deactivation of the enzyme.
k_s= Michael mentis constant.
S= Substrate concentration.
V_{max}=Maximum rate of substrate utilization.
V= Rate of substrate utilization.

3.2.1.2. In the cell there is very low rate of degradation of enzymes and also there is continuous replacement of enzymes so we can safely assume that k_d =0.

3.2.1.3. The concentration of the intermediates is in order of micrograms/liters and value of k_s varies are from .1 to 2 grams/liters.
Therefore k_s>>S. Therefore our equation becomes

$$\Rightarrow V=V_{max}S/ k_s =KS \ldots\ldots\ldots\ldots\ldots\ldots [2]$$

3.2.1.4. The process is in between fed batch and continuous. But mathematical evaluation of time dependent parameters of the fed batch is very difficult. So we will consider it as a continuous process.

3.2.1.5. As such there are various steps involved in the conversion of Squalene to cholesterol (via lanosterol) but we will consider only two steps because the intermediates are not involved in any other pathways and also they took place in ER.

Squalene $\longrightarrow$ lanosterol $\longrightarrow$ cholesterol

Reactions in the cell are usually non steady state processes. So we can calculate accurately by introducing an accumulation term which will take care of all. The enzymes involved in these reactions are found to be in the membrane of the ER but we can not consider them as the immobilized enzymes because they can move along the membrane. So we will go for the model in which each enzyme is restricted in certain region and in that region the enzymes can move freely.

Fig. 6 shows the schematic diagram for the cholesterol production. D (dilution factor) in this case can be defined as the average time required for the enzyme to convert one molecule of substrate into the products. In *other words as soon as the reaction takes place the reactants and the products are move out given system.* In cell there is continuous removal of products via vesicular transportation and that also at constant rate. So we can assume that *D is fairly constant.*

3.3 Applying mass balances on our systems:

3.3.1. Mass balance on A (system 1):

$\dot{I}-\dot{O}+\dot{G}-\dot{C}= dS/dt$

$F_oA_o - F_0A - V_1K_1A = V_1dA/dt \qquad (\dot{C} = V_1K_1A$ from eq.2)

Time is defined with respect to starting of the formation of B.

Dividing the equation by V_1

$D_0A_0 - D_0A - K_1A = dA/dt$

$\Rightarrow$ $dA/dt + (K_1+ D_0)A = D_0A_0$..... [2]

Above is first order linear differential equation whose solution is

$A = \exp(-(K_1+D_0)t) [\exp((K_1+D_0)t) D_0A_0/(K_1+D_0) + C_1)$

Where C_1 is the constant

At $t=0$ $A= A_0$

Therefore
$C_1= A_0 - D_0A_0/(K_1+D_0)$

$A = D_0A_0/ (K_1+D_0) + C_1\exp(-(K_1+D_0)t)$

Let us define $D_0A_0/(K_1+D_0) = C_0$

$\Rightarrow$ $A = C_0 + C_1 \exp(-(K_1+D_0) t)$

3.3.2. Applying mass balance on B (system2):

$\dot{I}-O+\dot{G}-\dot{C}= dS/dt$

$\dot{G} = \dot{O}$

$\Rightarrow \dot{O} = K_1A = K_1[C_0 + C_1\exp(-(K_1+D_0)t)]$ .....[3]

3.3.3. Applying mass balance on B (system 3)

$\dot{I}-O+\dot{G}-\dot{C}= dS/dt$

$\Rightarrow \dot{G} - \dot{C} + O = dB/dt$

$K_1[C_0 + C_1\exp(-(K_1+D_0)t)] - D_0B - K_2B = dB/dt$ [from eq. 2&3]

Time is defined with respect to starting of the formation of B

Rearranging the terms

$\Rightarrow dB/dt + (D_0 + K_2)B = K_1[C_0 + C_1\exp(-(K_1+D_0)t)]$

Above is again a linear differential equations whose solution is (only when K_1 is not equal to K_2)

$\Rightarrow B= \exp(-(D_0 + K_2)t) [K_1C_0\exp((D_0 + K_2)t)/ (D_0 + K_2) + K_1C_1\exp(-(K_1- K_2)t)/(K_1-K_2) + C_2]$

Where C_2 is the constant

At t=0 B=0

$\Rightarrow C_2 = -[K_1C_0/(D_0 + K_2) + K_1C_1/(K_1-K_2)]$

Therefore

$B= K_1C_0/(D_0 + K_2) + K_1C_1\exp(-(K_1+D_0)t)/(K_1-K_2) + C_2 \exp(-(D_0 + K_2)t)$

3.3.4. Mass balance on C (system 3):

$\dot{I}-\dot{O}+\dot{G}-\dot{C}= dS/dt$

$\Rightarrow \dot{G} - \dot{C} = dC/dt$

Again there will be the formation of linear differential equation and its solution is

$\Rightarrow C = K_2[K_1C_0/(K_1+D_0) - C_1\exp(-(K_1+D_0)t)/(K_1-K_2) - C_2\exp(-(K_2+D_0)t)/K_2 + C_3\exp(-D_0t)]$

3.4. Results:

$\Rightarrow A = C_0 + C_1 \exp(-(K_1+D_0)\ t)$

$\Rightarrow B= \exp(-(D_0 + K_2)t)\ [K_1C_0\exp((D_0 + K_2)t)/\ (D_0 + K_2) + K_1C_1\exp(-(K_1-K_2)t)/\ (K_1-K_2)\ + C_2\ ]$

$\Rightarrow C = K_2[K_1C_0/(K_1+D_0) - C_1\exp(-(K_1+D_0)t)/(K_1-K_2) - C_2\exp(-(K_2+D_0)t)/K_2 + C_3\exp(-D_0t)]$

Above are the time dependent equations depicting the concentration of squalene, lanoster and cholesterol for one cell.

*3.3 Time required filling the half the volume of the cartilaginous portion of the auditory canal (the wax producing region) by **cerumen** (i.e. 20% to 40% hearing loss):*

The result of the above analysis gives a equations for one cell. We can extend the results to the level of gland assuming that all the cells contribute same to the production of squalene, lanosterol, and cholesterol. But there are many parameters which needs to be determined before finding the time required. But the value of all the parameters are not known. Actually D_0 is the complex function of various unknown factors (determined by the cell itself) which is difficult to calculate in vitro. So we need to simplify our equations so that some parameters will be removed from the equation. *Our system will be gland and not the cell and we will focus on the concentrations of squalene*. Let us assume that all the *squalene* produce is moved out of the gland i.e. no accumulation inside the gland and everything is going to the ear wax. Also the concentration of squalene *inside or produced* by the cell is same as that in the gland. Also there is no removal of ear wax from the ear.

3.1 Mass balance on A (gland)

⇨ $DA_0 - DA - K_1A = 0$ .....[4]

Where
n is the number of cells in the gland
A_0 = total squalene produced within the cells of the gland i.e. (Lanoster + cholesterol + squalene)
A = concentration of squalene coming out of cells

D = Flow rate/ volume of gland (this D is slighty different from the D0 described in eax wax modeling in literal meaning)
K_1 = specific rate of utilization of *squalene*

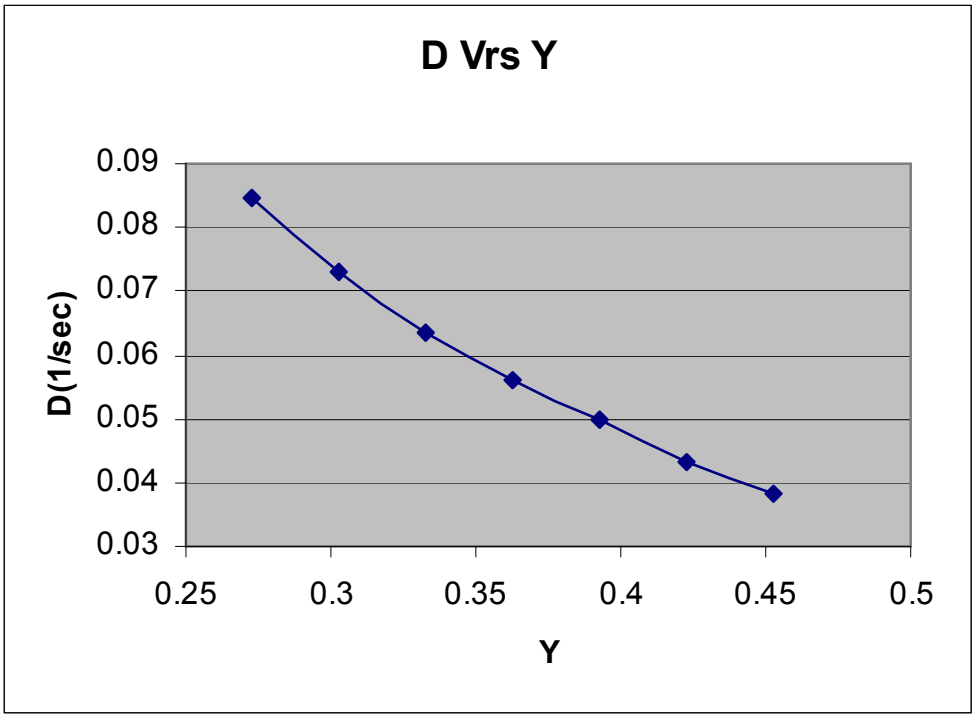
It has been know 12% -16% of the ear wax composed of *squalene* and 10% - 6% of the lanosterol and cholesterol together[7]. Let us define yield of the products (lanosterol and cholesterol) with respect to squalene

⇨ $Y_{P/A} = (A_0 - A)/A_0$..... [5]

From equation 4 and 5 we have

⇨ $D = K_1 (1- Y_{P/A})/ Y_{P/A}$

In an in vitro experiment [9] it has been found that K_1 of the enzyme that converts squalene to lanoster equals to 13.072 sec^{-1}. Since the composition of the ear wax is not constant therefore we will get the series of values of $Y_{P/A}$. Let us plot the graph of D vrs$Y_{P/A}$ (using excel 2003)



Graph 2

D_{mean} = Area under the curve/ (change in $Y_{P/A}$)

$D_{mean} = [\int [(K_1 (1- Y_{P/A})/ Y_{P/A}) dY_{P/A}]]/ [(Y_{P/A})_2 - (Y_{P/A})_1]$

$D_{mean} = K_1 [(\ln ((Y_{P/A})_2/ (Y_{P/A})_1) - ((Y_{P/A})_2 - (Y_{P/A})_1)]/ [(Y_{P/A})_2 - (Y_{P/A})_1]$

Putting the values

⇨ D_{mean} = 23.62 sec^{-1}(approx)

3.1.2 It has been known that total number of glands responsible [10] for ear wax varies from 1000-2000. So we will assume the value of 1500 for our analysis. Volume of one gland is [11] is equal to 993 X 10^{-3} um^3 (approx). Volume of the cartilaginous portion of ear canal is $\pi r^2 L$ (cylinder)

⇨ Time required = *Volume (%) / Flow rate*

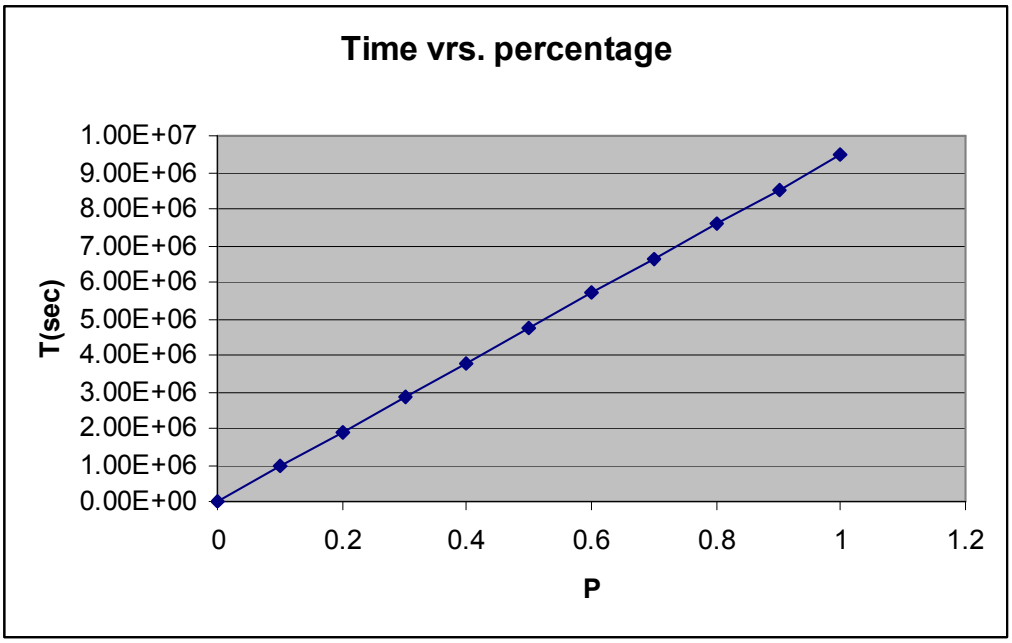
Flow rate = volume of the gland x no. of glands x D_{mean} (approx)

⇨ $t = (\pi r_a^2 L) \times (p)/(993 \times 10^{-3} um^3 \times 1500 \times D_{mean})$

Where p is the fraction of volume filled with ear wax.

⇨ $t = \pi r_a^2 L(p)/(993 \times 10^{-3} \times (10^{-9}) \times D_{mean} \times 1500)$

Since p varies from 0 to 1 [where L=26mm, r_a= 7 mm (12)] we will get a series of values of time. Let us plot a graph of t vs. p (using excel 2003)



Graph 3

t_{mean} = area under the curve/ change in p

⇨ $t_{mean} = [\int [\pi r_a^2 L\, p / (993 \times 10^{-3} \times (10^{-9}) \times 1500 \times D_{mean})]dp]]/[p_1 - p_0]$

⇨ $t_{mean} = [\pi r_a^2 L[p_1^2 - p_0^2]/ (993 \times 10^{-3} \times 1500 \times (10^{-9}) \times D_{mean})]/2/[p_1 - p_0]$

⇨ $t_{mean} = [\pi r_a^2 L/ (993 \times 10^{-3} \times (10^{-9}) \times 1500 \times D_{mean})]\ [p_1 + p_0]/2$

Putting the values of r_a, D_{mean} and L

⇨ $t_{mean} = 9.48 \times 10^6\ sec^{-1}$

⇨ t_{mean} = 109.7 ≃ 110 days

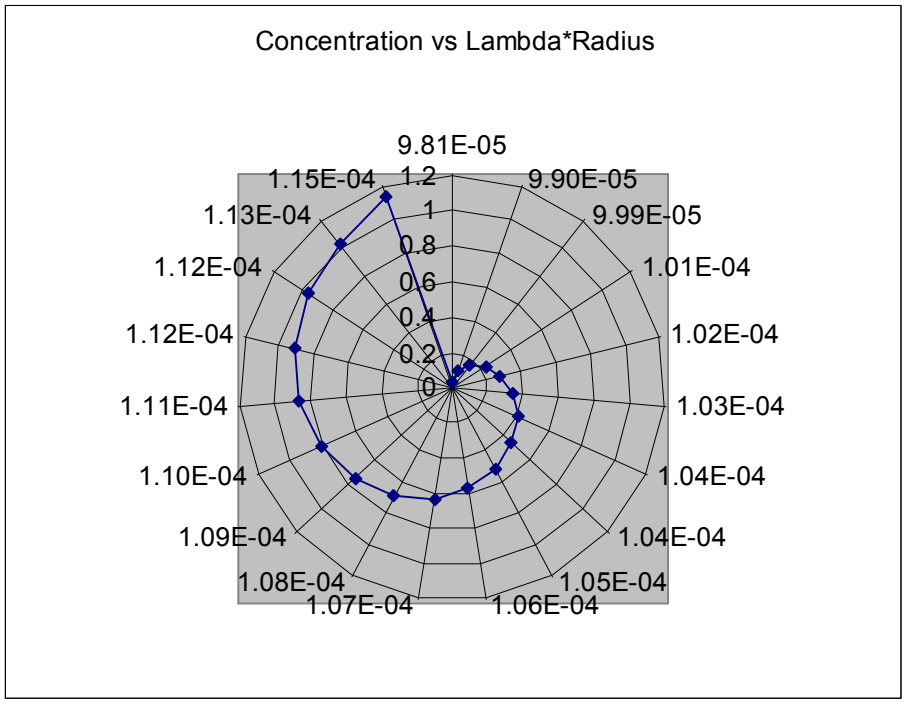
That means approximately in three months the person will lose 30% of his hearing ability *if there is no means by which ear wax can come out*.

4. Results and discussion:

1. The concentration of glucose as the function of time is given by

$$\Rightarrow \quad G = 63.437 + 6.875\ln(\lambda r) - 29.997(\lambda r)^2 - 6.875(\lambda r)^2\ln(\lambda r)$$

In the above equation value of third and fourth term are negeligible as compared to remaining terms which is also relevant by the shape of the graph 1.



Graph 4

Graph 4 predicts the concentration as the function of lambda (constant) time's radius which is giving the clear idea that there is actually the exponential fall in the concentration of glucose in the matrix which supports the above fact.

2. The results of the analysis done on the ER shows that

$$\Rightarrow \quad A = C_0 + C_1 \exp(-(K_1+D_0)\ t)$$

- ⇨ $B = \exp(-(D_0 + K_2)t)\ [K_1C_0\exp((D_0 + K_2)t)/\ (D_0 + K_2) + K_1C_1\exp(-(K_1-K_2)t)/\ (K_1-K_2)\ + C_2\ ]$

- ⇨ $C = K_2[K_1C_0/(K_1+D_0) - C_1\exp(-(K_1+D_0)t)/(K_1-K_2) - C_2\exp(-(K_2+D_0)t)/K_2 + C_3\exp(-D_0t)]$

3. Time required for auditory canal to get fill up to 50% (by volume) is three months (approx)

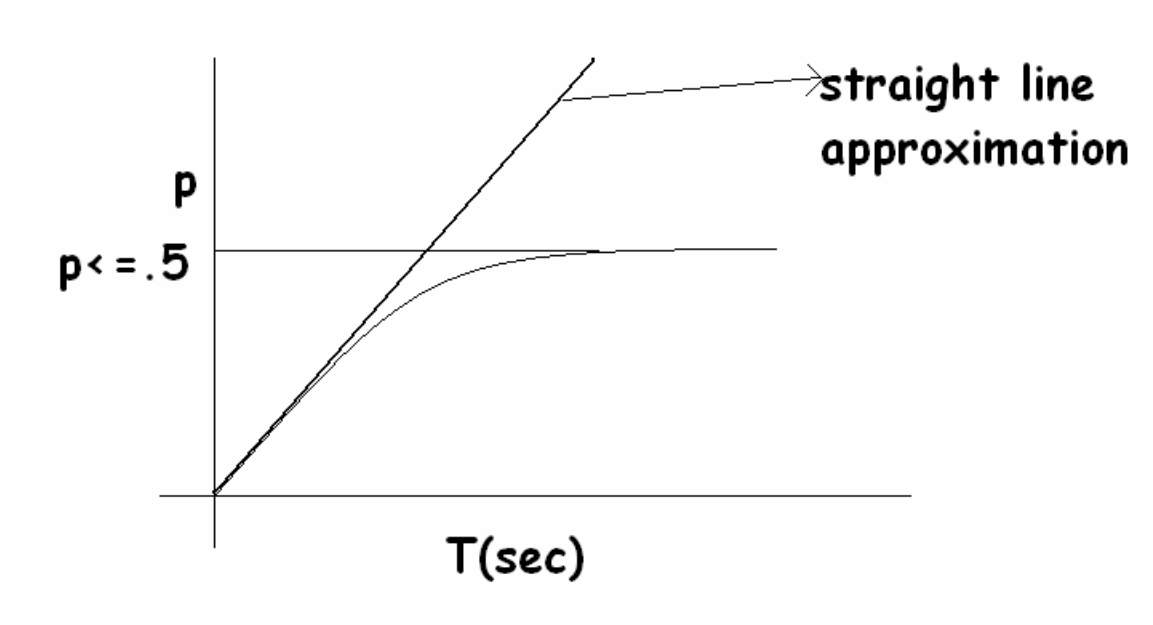
5. Limitations:

1. The model of glucose utilization does not account for the particular arrangement of the glands in the cartilage. There is arrangement of glands such that none of the cell dies due to lack of food. Also the geometry of cartilaginous portion is not perfect cylindrical. It is slightly conic and have uneven surface.

2. Model for squalene, lanosterol, and cholesterol production does not account for the feed back mechanism of the cholesterol by which the ear wax production is controlled.

3. In reality p (percentage of volume occupied) never reaches to even 50%. Before that only, wax by some process comes out of the ear (or it production is slowed down by the negative feed back of the cholesterol). So the volume of wax reaches a constant value so the equation which can approximately predict p as the function of time is $p = at/\ (b+t)$ *(it's like enzyme kinetics)*

Where *a* and *b* are constants and depend on the system in focus.



Graph 3

Graph 3 is a comparison between the approximately true model and the model with we predicted.
So our model (straight line) can predict up to 50% and not more than that because there are various processes which somehow keep the mass of ear wax inside the ear constant. So instead of 110 days it will reach that point in some more time say 3-4 months.

6. Conclusion:

Practically it has been observed that ear wax production depend on the seasons and various other external conditions also. Some interesting features have been observed regarding the ear wax production for example it has been observed that during the months July to August there is a fall in the ear wax production. Some other factors like genes, working conditions and climate also effect the wax production. Cholesterol itself blocks the HMG-CoA reductase pathway by negative feed back. Above analysis is an oversimplified model for the process to describe. Assumptions themselves are the source of limitation for the applicalibility of the model. But still it predicts some of the interesting and useful aspects. It's a step towards the better models.

7. Future work:

If we can come out with a model which can relate both the above models then it will be of great application because we will know the direct relation between the concentration of glucose and cholesterol. This is intact not very easy because there exist a complex relationship between all the intermediate and also the kind of relationship varies from system to system. Generalization of such model over the different parts body can also help in fabricating various devices which will be useful in medical application.

8. Acknowledgement:

I would like to express my gratitude to Prof. G.K. Suraishkumar for giving opportunity to work on CFA exercise.

I am thankful to my friend Vishal Surana (CH04B048) for helping me in the computational part of the CFA exercise. Also I am grateful to Mayur Vaidya (MM05B032) for his help and valuable advices.

Ravi Badwe

9. References:

1. Bortz, J.T., Wertz, P.W., Downing, D.T. (1990). "**Composition of cerumen lipids**", *J.Am.Acad.Dermatol*,23 (5): 845-849.

2. **"Anatomy and Physiology for Speech, Language, and Hearing"** by Anthony J. Seikel, Douglas W. King, David G. Drumright

3. **"Nutrient Utilization by Bovine Articular Chondrocytes: A Combined Experimental and Theoretical Approach"**, Bram G. Sengers, Journal of Biomechanical Engineering.

4. **"Advance engineering mathematics"** by Peter V.O'Neil

5. **"Skin layer thickness at the ear of the domesticated pig, with special reference to the use of the ear integument for human dermatological research"** by Meyer W and Zschemisch NH.

6. Stephen R. Cronin, Afif Khoury, Dana K. Ferry, and Randolph Y. Hampton (2000). **"Regulation of HMG-CoA Reductase Degradation Requires the P-Type ATPase Cod1p/Spf1p"**. The Journal of Cell Biology, Volume 148: 915–924.

7. **"Impacted cerumen: composition, production, epidemiology and management"** J.F. Guest, M.J. Greener, A.C. Robinson and A.F. Smith, Q J Med 2004; 97:477–488 doi:10.1093/qjmed/hch082.

8. **"Role of Peroxisomes in Isoprenoid Biosynthesis",** Nahla Aboushadi, William Harrison Engfelt, Vincent G. Paton, and Skaidrite K. Krisans, Volume 47(9): 1127–1132, 1999
The Journal of Histochemistry & Cytochemistry.

9. **"In vitro labeling of Peroxisomal cholesterol with radioactive precursor"** Eeva-Liisa Appelknist, Biosciences Report, Vol.7, no. 11, 1987.

10. *"Ear and Temporal Bone Pathology"*, Ken Berean, University of British Columbia, study material.

11. **"Development of a Nude Mouse Model to Study Human Sebaceous Gland Physiology and Pathophysiology"**, Marta J. Petersen, John J. Zone, and Gerald G. Krueger, The American Society for Clinical Investigation, Volume 74, October 1984, 1358-1365.

12. http://en.wikipedia.org/wiki/Ear_canal

Sites visited:

1. http://www.entnet.org/healthinfo/ears/earwax.cfm
2. http://www.tchain.com/otoneurology/disorders/hearing/wax2.html
3. http://www.doctorhoffman.com/wax.htm
4. http://www.pouet.net/prod.php?which=26952
5. http://uimc.discoveryhospital.com/main.php?id=2355