MAA Short Course presentation

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A one-dimensional random walk.

Starting from the origin $x = 0$, consider a random walk as follows: in each time increment Δt, a step of size Δx is taken to the left or right depending on a coin toss. If the outcome is Heads (H), with probability 1/2, then the step is to the right, if Tails (T), the step is to the left.

After n such steps, done in time $t = n(\Delta t)$, the walk will end at the point $x = m(\Delta x)$ if there have been r steps to the right and $\ell = n - r$ steps to the left with $m = r - \ell$. This happens with probability

$$p(m, n) = \binom{n}{r} \frac{1}{2^n}, \qquad m = r - \ell = 2r - n.$$

There are always two steps between each possible ending point, thus if n is even, so is m.

If we record the results of a large number of trials of this experiment, we obtain a bell shaped frequency distribution as shown in the figure.

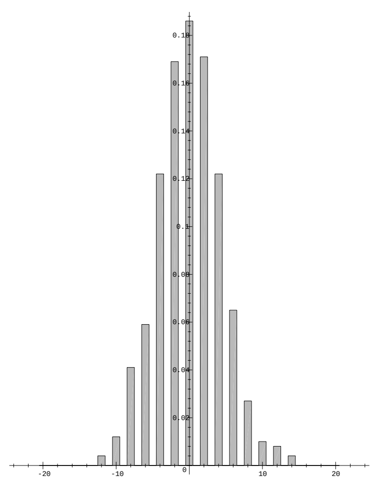

Figure 1

Such figures were known to DeMoivre around 1756, who, like others, found the combinatorial hard to calculate

$$\binom{n}{r} = \frac{n!}{r!(n-r)!}$$
$$= \frac{\sqrt{2\pi n}\, n^n e^{-n}}{\left(\sqrt{2\pi r}\, r^r e^{-r}\right)\left(\sqrt{2\pi(n-r)}(n-r)^{n-r} e^{-(n-r)}\right)};$$

the third member of this equation follows from Stirling's formula which was not available to DeMoivre of course.

Since the Stirling approximation to the combinatorial is asymptotically correct, we take the limit of the above as n and m tend to infinity (but with the ratio m^2/n fixed) and we get

$$\binom{n}{r}\frac{1}{2^n} \approx \sqrt{\frac{2}{\pi n}}e^{-m^2/2n}.$$

That this approximation is quite good can be seen in the next figure which compares the two for $n = 20$, $-20 \le m \le 20$.

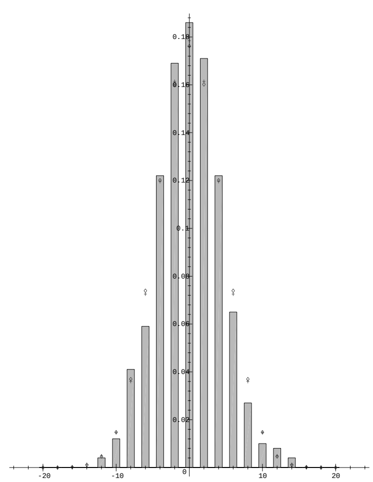

Figure 2

Instead of deriving this approximation via Stirling's formula, we will proceed more like DeMoivre did. We will use the Central Limit Theorem and approximate the bell shaped curve by the normal density function.

The number of steps to the right, r, is a binomial random variable with mean

$$\bar{r} = n\frac{1}{2}$$

since 1/2 is the probability of a step to the right. The variance of r is

$$\text{var}(r) = E(r - \bar{r})^2 = n\frac{1}{2}\frac{1}{2} = \frac{n}{4}.$$

Therefore the mean and variance of m, the end point of the walk, are

$$\bar{m} = \overline{2r - n} = 2\frac{n}{2} - n = 0$$

as expected, and

$$\begin{aligned}\text{var}(m) &= E(m^2) - \bar{m}^2 = E\left((2r - n)^2\right) - 0 \\ &= 4E\left((r - \frac{n}{2})^2\right) = 4\text{var}(r) = n.\end{aligned}$$

This result contains the very important piece of information that the root mean square (RMS) dispersion of "walkers" is proportional to the square root of the time of the walk,

$$\text{stddev(m)} = \sqrt{\text{var}(m)} = \sqrt{n}.$$

Now the density function of a normal random variable with mean 0 and variance n is

$$\text{Pr(walk ends in interval of width } dm \text{ at } m) = \frac{1}{\sqrt{2\pi n}} e^{-\frac{m^2}{2n}} dm,$$

and noting that $dm = 2$, we get the approximation above.

Our last refinement is to let Δx and Δt tend to 0 and thereby obtain the distribution for a continuous walk. Thus

$$u(x,t) = \lim_{\substack{\Delta x \to 0 \\ \Delta t \to 0}} \frac{p(\frac{x}{\Delta x}, \frac{t}{\Delta t})}{dm} = \frac{e^{-x^2/4Dt}}{\sqrt{4\pi Dt}}$$

in which we have taken $dm = 2(\Delta x)$ as noted above and kept the ratio

$$D = \frac{\Delta x^2}{\Delta t}$$

fixed as Δx and Δt tend to 0. This is because, as we have noted, the square of dispersion is equal to time, thus the ratio D acts like "velocity;" it is called the *diffusion coefficient* or the *diffusivity*.

In the table we give some diffusivities of biological importance.

Table 1 Diffusion coefficients in solution.

molecule	solvent	T, ^{o}C	D (10^{-6} cm^2/sec)
O_2	blood	20	10.0
Acetic acid	water	25	12.9
Ethanol	water	25	12.4
Glucose	water	25	6.7
Glycine	water	25	10.5
Sucrose	water	25	5.2
Urea	water	25	13.8
Ribonuclease	water	20	1.07
Fibrinogen	water	20	2.0
Myosin	water	20	1.1

And in the figure we show $u(x,t)$ for times $t = 1$, 2, 4, and 8. This models the diffusion of a substance initially concentrated at the origin, as time increases the distribution spreads out.

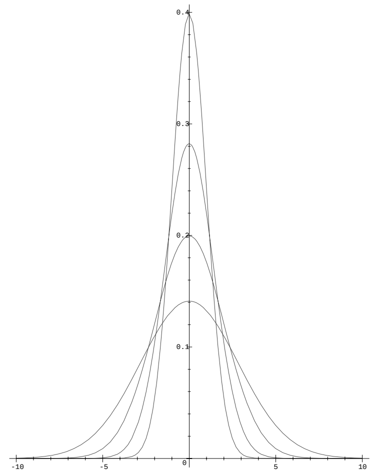

Figure 3

Page 1

Diffusion of Oxygen Across the Placenta

Our objective here is to formulate a diffusion model for the transport of oxygen from the maternal blood stream to the fetal blood stream and, if possible, decide if diffusion is a feasible mechanism. The following table gathers together some pertinent data; the source of the data are two papers by the authors Bartels, Metcalfe, and Moll who did pioneering work on this topic in the 1960's.

Table 2 Placental Oxygen and Flow Rate Data

umbilical artery	pO_2: 15 mm Hg, pH: 7.24 [BMM, 1962]
umbilical vein	pO_2: 28 mm Hg, pH: 7.32 [BMM, 1962]
umbilical flowrate	250 ml per minute [BMM, 1962]
maternal artery	pO_2: 40 mm Hg [BMM, 1962]
maternal vein	pO_2: 33 mm Hg [BMM, 1962]
maternal flowrate	400 ml per minute [BMM, 1962]
placental membrane surface	12 square meters [MBM, 1967]
placental membrane thickness	3.5×10^{-4} cm [MBM, 1967]
pO_2 diffusivity (see text)	3.08×10^{-8} cm^2/min/mm Hg [MBM: pp802]

In addition, these authors carefully measured the oxygen dissociation curve, presented in the following figure.

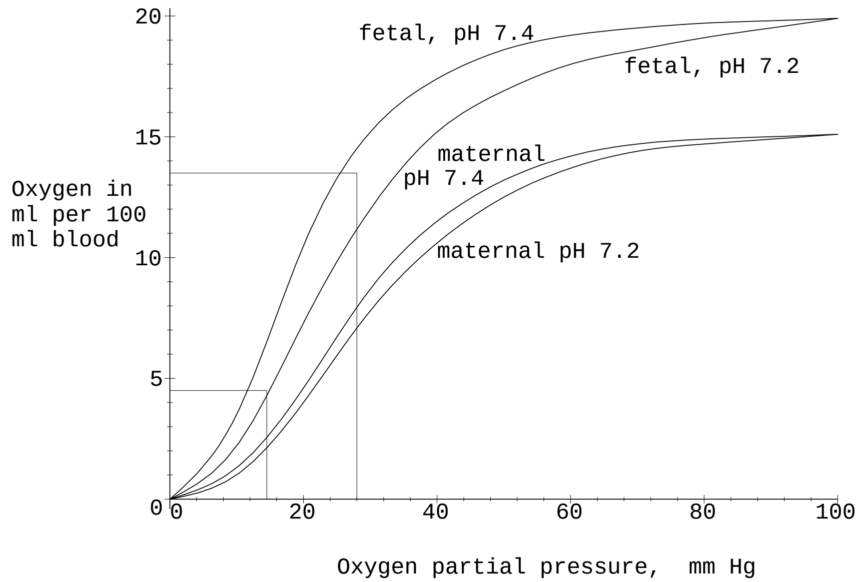

Figure 4

We begin by calculating the fetal oxygen consumption. By direct measurement, oxygen partial pressure and blood pH at the umbilical cord are as shown in Table 2.

It follows from figure 4 that each 100 ml of venous blood in the fetus contains approximately 13.5 ml O_2 while for arterial blood it is about 4.5 ml.

Evidently an O_2 balance for fetal circulation measured at the umbilical cord is given by,

$$O_2 \text{ in } - O_2 \text{ out } = O_2 \text{ consumed.}$$

For each minute this gives

$$\begin{aligned} \text{rate } O_2 \text{ consumed} &= 250 \frac{\text{ml blood}}{\text{min}} \times (13.5 - 4.5) \frac{\text{ml O}_2}{100 \text{ ml blood}} \\ &= 22.5 \text{ ml O}_2/\text{min}. \end{aligned}$$

Next we estimate the maximal oxygen diffusion rate. Fick's First Law relates the rate of movement of a substance across an interface, J, to the concentrations, c, which exist on either side of the interface; in one-dimension this is

$$J = -D \frac{\partial c}{\partial x}.$$

We approximate the concentration gradient $\partial c / \partial x$ by the ratio of finite differences $\Delta c / \Delta x$ where Δx is the thickness of the membrane separating the maternal and fetal blood streams.

For the concentration difference, we must recognize that the oxygen is a dissolved gas and its concentration is measured in terms of partial pressure. The relationship between concentration and partial pressure is one of proportionality given by Henry's Law

$$c = \delta(\text{pO}_2)$$

for some constant of proportionality δ.

Actually, Metcalfe,Bartels,Moll (1967) cite the product of δD directly from measurements on brain tissue; their value is [MBM,p802]

$$\delta D = 3.9 \times 10^{-7} \ \frac{\text{cm}^2}{\text{sec–atm}} = 3.9 \times 10^{-7} \frac{\text{atm}}{760 \text{ mm Hg}} \frac{60 \text{ sec}}{\text{min}}$$
$$= 3.08 \ \frac{\text{cm}^2}{\text{min} - \text{mm Hg}}.$$

Note that D represents the diffusivity within the placental membrane.

For the pO_2 difference, we note from the table that the fetal values range from 15 to 28 mm Hg for an average of 21.5 and the maternal values range from 33 to 40 for an average of 36.5 mm Hg.

Hence using this pO_2 difference, and the values $12\text{m}^2 = 12 \times 10^4\text{cm}^2$ for the area S of the placental membrane, and 3.5×10^{-4} cm for the average membrane thickness, we get

$$O_2 \text{ diffusion rate} = SJ = -\delta D \frac{S}{\Delta x} \Delta(pO_2)$$
$$= 3.08 \times 10^{-8} \frac{12 \times 10^4}{3.5 \times 10^{-4}} (36.5 - 21.5) = 158 \ \frac{\text{cm}^3}{\text{min}}.$$

Of course this is very crude estimate but it does give an order of magnitude analysis, as shown by animal studies (on goats for instance) and shows that diffusion is sufficient to explain the transmission of oxygen across the placenta.

Major factors to take into consideration to improve the precision of the estimate would be: the effect of differences in O_2 concentrations due to blood flow, pH effects due to the reverse diffusion of CO_2 from the fetal system to the maternal system, the changing weight of the fetus and size of the placenta.

Lab Problems (what if questions)

1. Suppose the placenta becomes injured or impaired, how much of it is necessary in order to deliver adequate amounts of oxygen?
2. From the table, maternal pO_2 falls from 40 mmHg to 33 mmHg in its course through the placenta traveling at 400 ml/min. How much O_2 was delivered? (Compare with the text calculation.) If the flow rate fell to 300 ml/min, what must be the corresponding pO_2 difference to maintain this rate?
3. For fetal blood at 28 mmHg pO_2, what is the amount of dissolved oxygen for a pH of 7.4? If the pH shifts to 7.2, what must be the pO_2 so the blood contains the same amount? Extrapolate to a pH of 7.0.
4. For maternal blood at 40 mmHg pO_2, what is the amount of dissolved oxygen for a pH of 7.4? If the pH shifts to 7.2, what must be the pO_2 so the blood contains the same amount? Extrapolate to a pH of 7.0.

5. Modify the calculation to account for the diffusion of O_2 through 1 micron of plasma before reaching the placental membrane on the maternal side and 1 micron of plasma upon leaving the placental membrane on the fetal side before entering an erythrocyte.
6. Assume carbon monoxide, CO, in the maternal blood reaches 5% (as is typical for smokers). Also assume CO binds 220 times more readily than O_2 to hemoglobin. Recalculate the diffusion under these conditions.