BME 7410 – Quantitative Methods in Biomedical Engineering
Fall 2022

Instructor: M.R. King (mike.king@vanderbilt.edu)
Office hour: Thursdays 1:00 – 2:00pm; ESB 442

Course Guide Description: The application of numerical and statistical methods to model biological systems and interpret biological data, using the MATLAB programming language.

Recommended Text: Numerical and Statistical Methods for Bioengineering: Applications in Matlab, by M.R. King and N.A. Mody, Cambridge University Press, 2011.

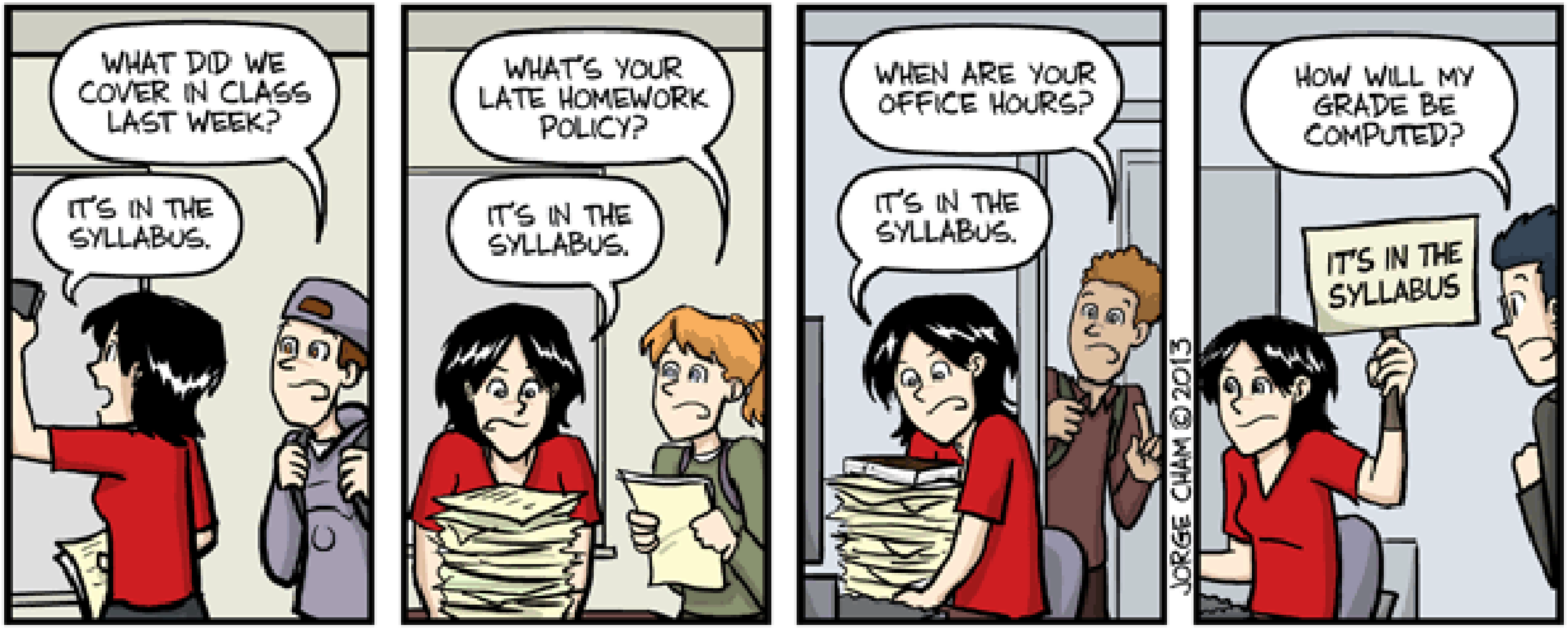
Objectives:
1. Learn the fundamentals of numerical computing and statistics in engineering.
2. Gain exposure to mathematical models and data sets from biomedical engineering.
3. Develop proficiency in writing efficient MATLAB programs.

Grading:
5% class participation (Top Hat. Join code: 629969)
30% weekly programming assignments
25% midterm hour exam (TUESDAY OCTOBER 18th, in class)
40% final exam (THURSDAY DECEMBER 15th at 9:00am)
0–4% extra credit final project on quantifying the visual inclusiveness of scientific graphs and diagrams.
No late homeworks will be accepted. No make-up exams.

COVID-19 considerations: Masks are still recommended while in our small classroom. If you are symptomatic or test positive, please quarantine away from class until you are no longer a viral spreader… your classmates or instructor will help you catch up on the class material.

Course Outline:

1. *Week 1:* Introduction to numerical computation. Examples of numerical errors. **Ch1**
2. *Weeks 2-3:* Linear model regression. `polyfit`, Normal eqns, error analysis. **Ch2/3**
3. *Guest lecture:* Finding and evaluating open data sets in the biomedical sciences. (Drs. Alex Carroll and Josh Borycz, VU Libraries)
4. *Weeks 3-4:* Statistics and probability. Gaussian dist'n. Propagation of error. **Ch3**
5. *Weeks 5-6:* Nonlinear root finding. `fzero`, Newton, secant, and bisection methods. Multidimensional root finding, Newton's method and the Jacobian. **Ch5**
6. *Weeks 6-7:* Nonlinear model regression. `fminsearch`, Newton's multivariate optimization method, SSE. **Ch8**
7. *Week 8:* Numerical quadrature. `quad`, trapezoidal, Simpson's rule, Gaussian quadrature. **Ch6**
8. *Weeks 9-10:* Integration of ODEs. `ode45`, Runga-Kutta, shooting method. **Ch7**
9. *Weeks 10-12:* Hypothesis testing and tests of significance. Confidence intervals; *P*-values; *t*-test; chi-squared for goodness-of-fit test, single factor ANOVA. **Ch4**
10. *Week 13:* Fourier Methods. Fourier approximation and interpolation, Radix-2 Fourier transforms, Mixed-radix FFT. **Ch10 (LV Fausett, Pearson Prentice Hall 2008)**
11. *Week 14*: Bioinformatics and computational biology. Introduction to web-based tools for accessing and analyzing genomic data. **Ch9**



IT'S IN THE SYLLABUS

This message brought to you by every instructor that ever lived.

WWW.PHDCOMICS.COM

"Piled Higher and Deeper" by Jorge Cham

You wanna be Top Gun? Read the book!

Examples of Roundoff Error and Overflow/Underflow

Vancouver stock exchange

- Short-lived index devised at the Vancouver stock exchange (McCullough and Vinod 1999).
- At its inception in 1982, the index was given a value of 1000.000.

- After 22 months of recomputing the index and <u>**truncating to three decimal places**</u> at each change in market value…
- the index stood at 524.881, despite the fact that its "true" value should have been 1009.811 !

Ariane Euro rocket 1996

- Ariane rocket launched on June 4, 1996 (European Space Agency 1996).
- In the 37th second of flight, the inertial reference system attempted to convert a 64-bit floating-point number to a 16-bit number…
- but instead triggered an **<u>overflow error</u>** which was interpreted by the guidance system as flight data…
- causing the rocket to veer off course and be destroyed!

Patriot missile defense system

- The Patriot missile defense system used during the Gulf War was also rendered ineffective due to roundoff error (Skeel 1992, U.S. GAO 1992). The system used an integer timing register which was incremented at intervals of 0.1 s. However, the integers were converted to decimal numbers by multiplying by the **binary** approximation of 0.1,

$$0.00011001100110011001100_2 = \frac{209\,715}{2\,097\,152}.$$

- As a result, after 100 hours (3.6×10^6 ticks), an error of

$$\left(\frac{1}{10} - \frac{209\,715}{2\,097\,152}\right)(3600 \cdot 100 \cdot 10) = \frac{5625}{16\,384} \approx 0.3433 \text{ second}$$

  had accumulated.
- This discrepancy caused the Patriot system to continuously recycle itself instead of targeting properly.
- As a result, an Iraqi Scud missile could not be targeted and was allowed to detonate on a barracks, killing 28 people.

Real world example of 1-D diffusion equation

Similar to Box 1.1 (w/o reaction)

Approximation of 1st derivative: see §1.6

Drug Permeation Through Human Skin: Theory and *in Vitro* Experimental Measurement

A. S. MICHAELS, S. K. CHANDRASEKARAN and J. E. SHAW

ALZA Corporation
950 Page Mill Road
Palo Alto, California 94304

The penetration of drugs and other micromolecules through intact human skin can be regarded as a process of dissolution and molecular diffusion through a composite, multilayer membrane, whose principal barrier to transport is localized within the stratum corneum. A mathematical model of the stratum corneum as a two-phase protein-lipid heterogeneous membrane (in which the lipid phase is continuous) correlates the permeability of the membrane to a specific penetrant with the water solubility of the penetrant and with its lipid-protein partition coefficient.

Correspondence concerning this paper should be addressed to S. K. Chandrasekaran.

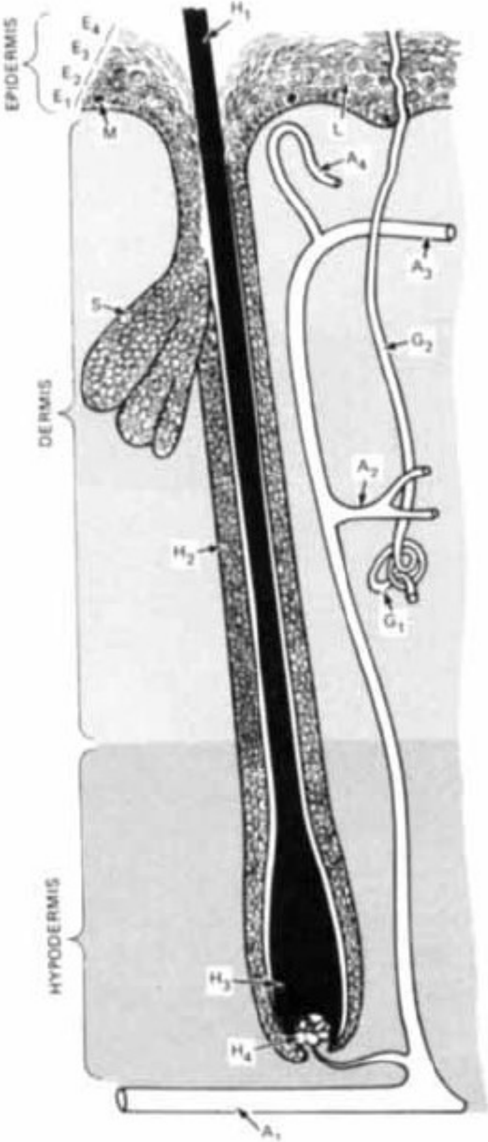


DIAGRAM OF STRUCTURE OF NORMAL SKIN

E_1, BASAL CELL LAYER
E_2, PRICKLE CELL LAYER
E_3, GRANULAR CELL LAYER
E_4, HORNY CELL LAYER
L , LANGERHANS CELL
M , MELANOCYTE
S , SEBACEOUS GLAND
H_1, HAIR SHAFT
H_2, INNER AND OUTER HAIR ROOT SHEATHS
H_3, HAIR MATRIX
H_4, DERMAL PAPILLAE
A_1, SUBCUTANEOUS VESSEL
A_2, DEEP VASCULAR PLEXUS
A_3, SUPERFICIAL VASCULAR PLEXUS
A_4, PAPILLARY CAPILLARY
G_1, ECCRINE SWEAT GLAND
G_2, ECCRINE SWEAT DUCT

Fig. 1

HAMSTER CHEEK-POUCH EPITHELIUM AFTER EXPANSION

(MACKENZIE, I.C. AND LINDER, J.E.
J. INVEST. DERMATOL. 61, 245 (1973))

Fig. 2

biguity. If the tissue layer is assumed to be homogeneous, and to permeate the penetrant by simple molecular diffusion, then the flux J can be represented by Fick's equation:

$$J = -D_M \frac{dC_M}{dx} \cong D_M \frac{\Delta C_M}{t} \tag{1}$$

where D_M is the penetrant diffusivity in the membrane, ΔC_M is the penetrant concentration decrement across the membrane, and t is the membrane thickness. In most the tissue as a trilayer laminate, each layer of which transmits penetrant by normal Fickian diffusion, with partition equilibrium of penetrant being maintained at the interlayer boundaries. Under these assumptions, the flux across the tissue is given simply by

$$\frac{Jt_0}{C} = \overline{P}_0 = \frac{t_0}{\dfrac{t_1}{P_1} + \dfrac{t_2}{P_2} + \dfrac{t_3}{P_3}} \tag{10}$$

or

$$J_{\max(0)} = \frac{1}{\dfrac{1}{J_{\max(1)}} + \dfrac{1}{J_{\max(2)}} + \dfrac{1}{J_{\max(3)}}} \tag{11}$$

IDEALIZED MODEL OF THE STRATUM CORNEUM

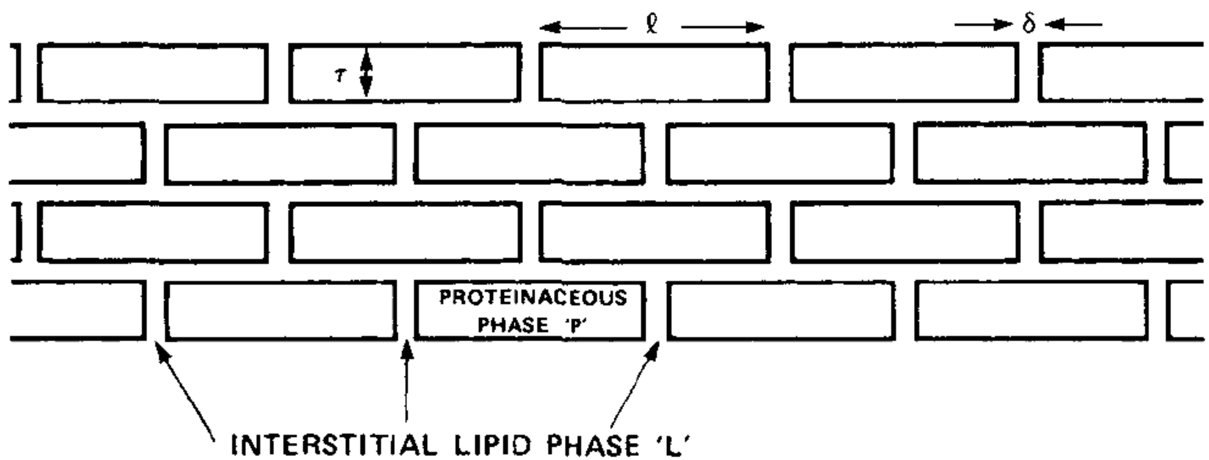


Fig. 3

Permeation Apparatus

Skin permeabilities were measured in glass premeation cells as shown in Figure 5; a piece of skin separated two aqueous solution filled compartments, one containing concentrated drug solution and the other virtually drug free solution. The stratum corneum surface of the skin was always exposed to the concentrated upstream compartment. Each compartment was about 13 ml in volume, with a port for removal of solution samples and a port for the removal of any air bubbles that may form on the skin surface; the solutions were stirred by Teflon impellers powered by 400 rev./min. synchronous motors. Sixteen cells

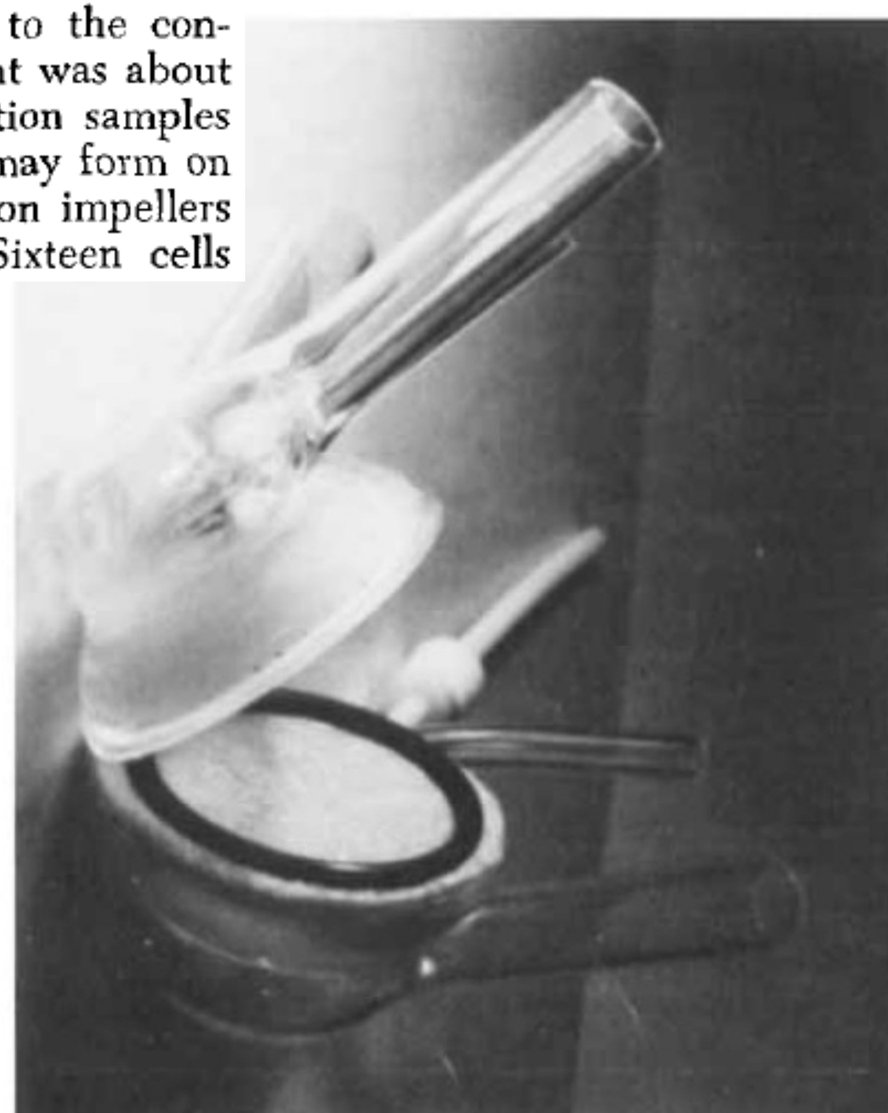


Fig. 5. Typical Permeation Cell.

Table 1. List of Drugs Studied

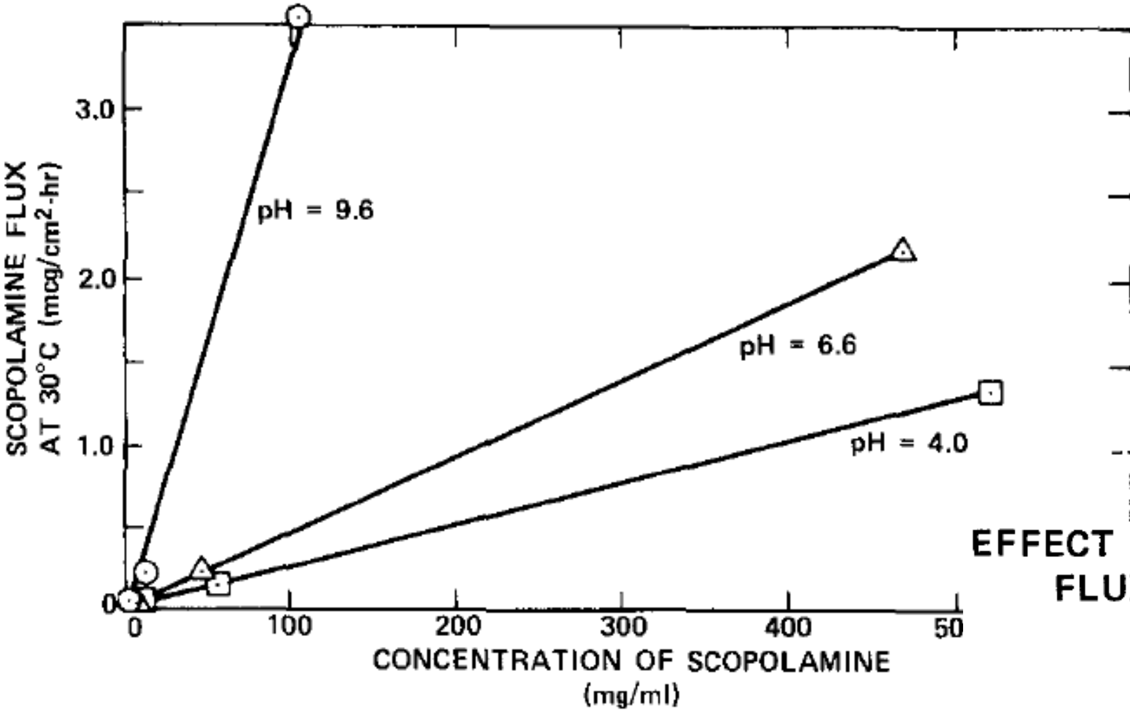
Drug	Formula	Molecular weight
Atropine	$C_{17}H_{23}NO_3$	289
Chlorpheniramine	$C_{16}H_{19}ClN_2$	275
Diethylcarbamazine	$C_{10}H_{21}N_3O$	199
Digitoxin	$C_{41}H_{64}O_{13}$	765
Ephedrine	$C_{10}H_{15}NO$	165
Estradiol	$C_{18}H_{24}O_2$	272
Fentanyl	$C_{22}H_{28}N_2O$	337
Nitroglycerin	$C_3H_5N_3O_9$	227
Ouabain	$C_{29}H_{44}O_{12}$	585
Scopolamine	$C_{17}H_{21}NO_4$	303

Table 2. Summary of Experimental Results

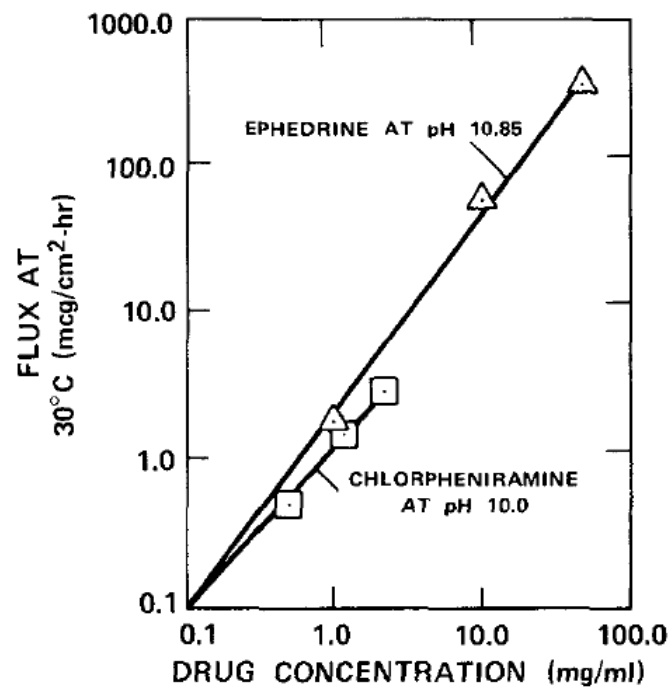
Drug	Source of radiolabel drug*	Radiolabel	Water solubility mg/ml at 30°C	Mineral oil/water partition coefficient at 30°C	pK	Solution pH	No. of skin donors	Number of permeation experiments	Range of $J_{S(max)}$ $\mu g/cm^2$ hr. at 30°C	$J_{S(max)}$ avg $\mu g/cm^2$ hr. at 30°C	$\overline{J}$ avg cm/hr. $\times 10^3$ at 30°C
Ephedrine	NEN	Carbon^{14}	50	1.0	9.65	10.8	3	8	250 to 400	300	6.0
Diethylcarbamazine			800	0.064		10.0	2	6	83 to 120	100	0.13
Nitroglycerin			1.3	10		—	2	4	10 to 25	13	11
Scopolamine	ICN	Tritium	75	0.026	7.35	9.6	5	10	2.0 to 8.0	3.8	0.05
Chloropheniramine	ICN	Tritium	1.6	0.46	9.1	10.3	4	8	2.9 to 3.9	3.5	2.2
Fentanyl	McNeill	Tritium	0.2	200		8.0	5	10	0.8 to 3.8	2.0	10
Atropine	A/S	Tritium	2.4	0.006		8.0	2	5	0.01 to 0.05	0.02	0.0086
Estradiol	NEN	Tritium	0.003	12		7.0	4	8	0.01 to 0.03	0.016	5.2
Ouabain	NEN	Tritium	10	0.00026		7.0	2	4	0.005 to 0.02	0.008	0.00078
Digitoxin	NEN	Tritium	0.01	0.014		7.0	1	2	0.00012 to 0.00014	0.00013	0.013

* A/S = Amersham/Searle; NEN = New England Nuclear Corporation; ICN = International Chemical & Nuclear Corp.

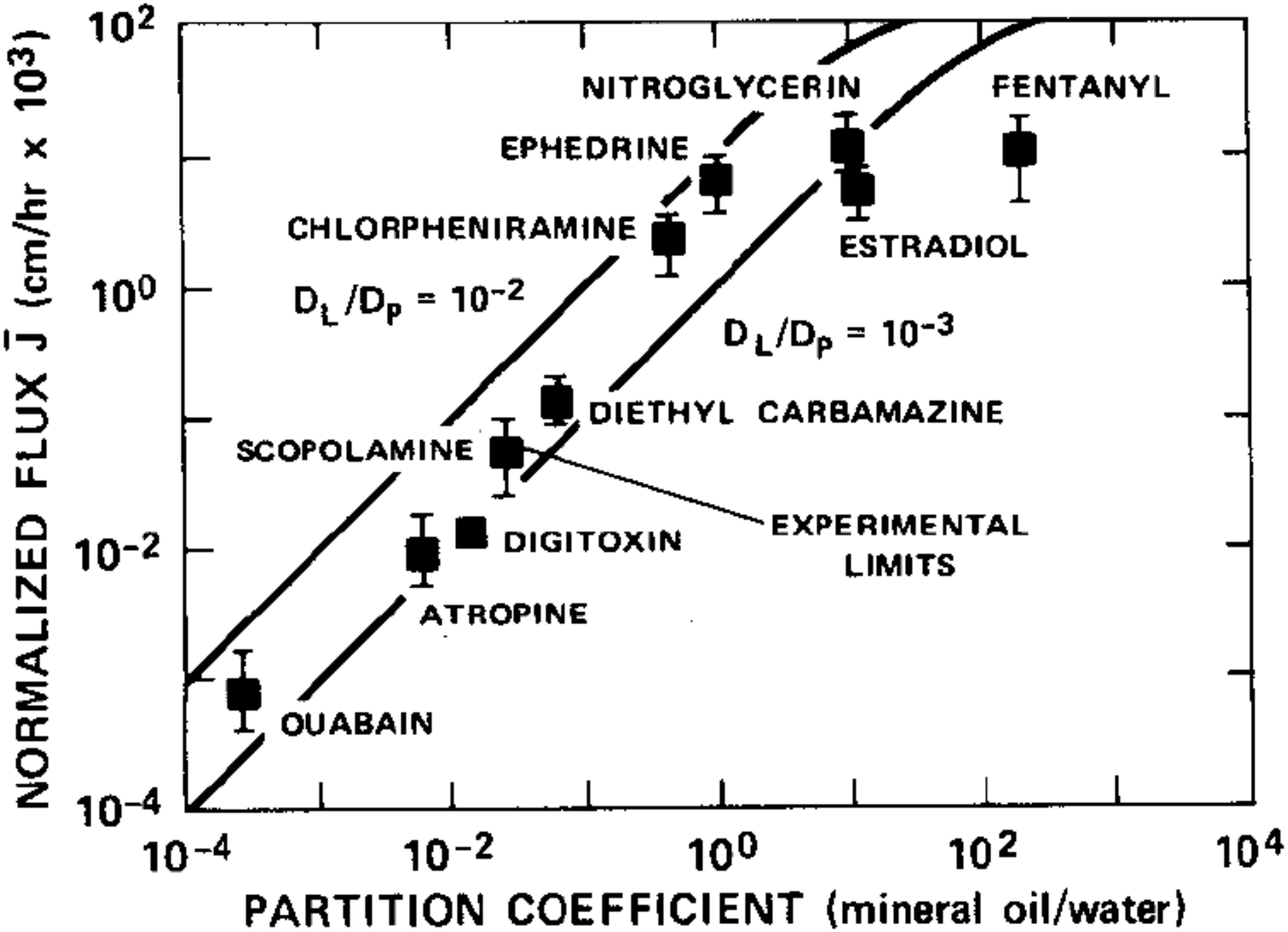
EFFECT OF CONCENTRATION AND pH ON SCOPOLAMINE FLUX THROUGH HUMAN SKIN



EFFECT OF CONCENTRATION ON TRANSDERMAL FLUX THROUGH HUMAN SKIN IN VITRO



VARIATION OF NORMALIZED TRANSDERMAL FLUX WITH PARTITION COEFFICIENT



When are numerical methods needed?

- Nonlinear problems for which analytic solutions may not exist
- Functions involving several variables for which analytic solutions are difficult
- Functions involving large quantities of data, such as curve fitting and regression
- Control where you need fast quantitative solutions (e.g., pacemaker, automated infusion pump)
- Even when analytic solution is available, to interpret results through graphical presentation and quantitative values

- Therefore, numerical techniques are invaluable in engineering!

- Numerical methods can be implemented using <u>algorithms</u> and computer programs.

How do computers represent numbers?

- Computers store numbers in a finite amount of memory. In single precision this means that you only get a finite number of significant digits.
- Single precision corresponds to 32 binary digits.
- If an integer, can represent all integers from

$$-2^{31} < N < 2^{31} - 1$$

where one bit is used to determine sign

- $2^{31} = 2{,}147{,}483{,}648$ which isn't very big.

How do computers represent numbers?

- To store larger numbers or fractions, use scientific notation.
- Typically 24 bits for mantissa, 8 bits for exponent (inc. sign)
- Thus, largest number is

$$1.11111\ldots \times 2^{+127} \sim 10^{38}$$

(in base 2)

How do computers represent numbers?

- Any number larger or smaller than this yields <u>overflow</u> or <u>underflow</u>.
- The 24 bit mantissa yields ~7 significant digits in decimal form ($2^{23} = 8.4 \times 10^6$)

- What is the result of a finite number of digits?

  → <u>round-off error</u>

How do computers represent numbers?

- Nobody (usually) cares about the 8^{th} significant digit since the error is much smaller than the measurement error in physical quantities…
- …e.g., about 13 feet in distance from Earth to the moon…
- But small round-off error can lead to O(1) errors in results of calculations due to different algorithms!

Example: Suppose we want to calculate $f(x) = e^{-x}$

- We can use the Taylor series approximation:

$$f(x) = f(x_0) + f'(x_0)(x - x_0) + \frac{f''(x_0)(x - x_0)^2}{2!} + \cdots + \frac{f^n(x_0)(x - x_0)^n}{n!} + \cdots, \tag{1.11}$$

We will use this expansion over and over throughout the course!

- For $f(x) = e^{-x}$ we get:

$$e^{-x} = 1 - x + \frac{x^2}{2!} - \frac{x^3}{3!} + \frac{x^4}{4!} - \frac{x^5}{5!} + \cdots .$$

Expanded about $x_0 = 0$

Example: Suppose we want to calculate $f(x) = e^{-x}$

- What is the error?
- Suppose each term in the series has a little error of ε~10^{-8} x (magnitude of term) due to rounding of the last significant figure.
- The summed error is thus:

$$\text{error} = \epsilon \cdot 1 + \epsilon \cdot x + \epsilon \cdot \frac{x^2}{2!} + \epsilon \cdot \frac{x^3}{3!} + \epsilon \cdot \frac{x^4}{4!} + \epsilon \cdot \frac{x^5}{5!} + \cdots = \epsilon \cdot e^x.$$

use + sign because errors add together!

- The error in using this algorithm is thus:

$$e^{-x} = e^{-x} \pm \epsilon \cdot e^x = e^{-x}\left(1 \pm \epsilon \cdot e^{2x}\right).$$

Example: Suppose we want to calculate $f(x) = e^{-x}$

$$e^{-x} = e^{-x} \pm \epsilon \cdot e^{x} = e^{-x}\left(1 \pm \epsilon \cdot e^{2x}\right).$$

- If x=1, error is small, but if x=9, then error is O(1)!
- Note that the expansion was exact and converges (eventually) for all x, but due to round off errors, we get a large error for e^{-9} or smaller!
- Do not design algorithms so that in a series you subtract large numbers to get small ones, as this leads to round-off errors.

Example: Suppose we want to calculate $f(x) = e^{-x}$

- So how do we get e^{-x}? Easy!

$$e^{-x} = \frac{1}{e^x} = \frac{1}{1 + \frac{x}{1!} + \frac{x^2}{2!} + \frac{x^3}{3!} + \cdots}.$$

- The error is always $O(\varepsilon)$ for $x>0$

  (you can use the same analysis to convince yourself of this)

Another example: Finite differences

- Suppose we want

$$f'(x_0) \cong \frac{f(x_0 + h) - f(x_0)}{h},$$

- What is the error of this forward difference approximation as a function of h?
- The error comes from algorithm error (due to h being non-zero) and round-off error.
- First we examine the algorithm error… using the Taylor series.

Another example: Finite differences

$$f(x) = f(x_0) + f'(x_0)(x - x_0) + \frac{f''(x_0)(x - x_0)^2}{2!} + \cdots + \frac{f^n(x_0)(x - x_0)^n}{n!} + \cdots, \tag{1.11}$$

Rearranging...

$$f'(x_0) = \frac{f(x_0 + h) - f(x_0)}{h} - \frac{f''(x_0)h}{2!} - \frac{f'''(x_0)h^2}{3!} + \cdots$$

- Or, truncating

$$f'(x_0) = \frac{f(x_0 + h) - f(x_0)}{h} - \frac{f''(\xi)h}{2!}, \qquad \xi \in [x_0, x_0 + h]$$

- The last part is the algorithm error and is proportional to h.
- What about the numerical error?

Another example: Finite differences

- There is round-off error in both $f(x_0+h)$ and $f(x_0)$.
- Thus we expect: round error ~ $2\varepsilon f(x_0)/h$

  which scales as 1/h !

Thus, error will be a minimum for some intermediate h.