

Ten Equations that Changed Biology: Mathematics in Problem-Solving Biology Curricula

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Abstract: Mathematics has played exceptionally important roles throughout the history of biology. Too frequently, these roles have been unappreciated in biology curricula because textbook authors assume that biology students have an inadequate mathematical preparation. This practice: (1) deskills many biology students, (2) is inconsistent with our requirements, (3) misrepresents contemporary biological research, and, hence, (4) underprepares students to read many articles or to contribute to many areas of biology. However, the recent calculus reform movement has empowered thousands of American undergraduate biologists to become proficient in the use of mathematical software packages that could be used to investigate the behavior of many famous mathematical models in biology. But where can they look? There are numerous recent texts in mathematical biology, research journals, web sites, and some advanced biological texts which are replete with numerous models. However, there is a need to identify a succinct list of achievements that represent the power of mathematics in biology. Hence, ten equations and a brief description of their historical importance are presented here in order to draw students' and faculty's attention to a variety of mathematical models that have been intrinsic to many of the significant discoveries in biology in the twentieth century.

Key words: mathematical biology, history of biology, models, equations, evolution, population genetics, medical imaging, phylogenetic trees, genetic maps, allometry, biodiversity, island biogeography, enzyme kinetics, genetic codes, neuron, membrane potential, logistic, predator-prey, mutation, fluctuation test, tests of teleology

Why is mathematics required for biology majors if they never use it throughout their education in biology? How can we generate a problem-solving based curriculum reform in biology if we, professors of biology, do not introduce appropriate mathematical tools which could help them solve problems? Does the beauty, power, historical importance, and utility of mathematics in biological research belong in undergraduate biological curricula? Is this just special pleading from a mathematical biologist in the ever ending struggles for space in undergraduate curricula? I hope not because I sincerely believe that mathematics plays five distinct and important roles in undergraduate biological education: (1) for conceptual understanding and historical appreciation, (2) through simulation and modelling, (3) for visual aesthetics and graphical representation, (4) as intrinsically embedded in tools of analysis, measurement, and data collection, and (5) within the everyday practices and equipment in the laboratory and field. I have briefly elaborated each of these five in a description of the 1997 BioQUEST Curriculum Consortium workshop entitled: "BIOLOGICAL AFTERMATH: What can we learn from contemporary mathematics reform?" (Jungck, 1997). Herein I instantiate the conceptual and historical importance of mathematics in biology by privileging ten equations (Figure 1) that warrant these claims.

I assert that we can help students deal more effectively with the massive explosion in technical information

and with personal/social issues of empowerment by: (1) privileging curricular reform via problem-solving, collaborative learning, critically reflexive, and less-is-more approaches, (2) sharing elegant, robust, scalable, highly visual, and transferable mathematical approaches, (3) employing models that work in several different areas in biology to reduce the ever increasing size of introductory textbooks, and (4) better preparing students to be more responsible researchers and citizens.

Gross (1994) summarized Ellison's¹ survey of the mathematics requirements of many biology departments across the nation:

Given the need for quantitative training, what do current curricula require of students? First, quantitative training is typically isolated in mathematics or statistics courses that are weakly, if at all, coupled to the life science courses in the curriculum. ... on average ... such students are required to take slightly less than two semesters of quantitative courses, with approximately 79% of programs requiring some calculus, 16% requiring some statistics, and 13% requiring some computer science. Fully 10% of the programs either had no requirement for quantitative courses or required only high-school-level quantitative skills.

¹anonymous ftp to mhc.mtholyoke.edu in file/pub/ecology/ecomath.csv

Figure 1. Ten Equations That Changed Biology.

These equations were selected upon the basis of wide-spread recognition of the value of the models as indicated by their: (1) being cited in common undergraduate biology textbooks, (2) being the subject of biographies of the names associated with these equations, (3) appearance in historical monographs on biology, and/or (4) receipt of public awards such as Nobel prizes and British Knighthood.

Fisher's "Fundamental Theorem of Natural Selection"

$$\partial_{NS} M_t / \partial t = W_t \text{ where } M = \partial_{NS} M_t + \partial_{EC} M_t$$

"The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time."

Cormack Computer Assisted Tomography

$$g(r, \theta) = \sum_{n=-\infty}^{+\infty} g_s(r) i n^\theta$$

where

$$g_n(r) = \frac{1}{2\pi} \int_0^{2\pi} g(r, \theta) C^{-in^\theta} d\theta$$

Genetic Mapping (The Haldane Function)

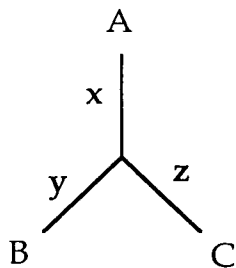
$$C_{AB} = \frac{1}{2} (1 - e^{-2x_{AB}})$$

C_{AB} = recombination fraction between loci A and B
 x_{AB} = map distance between loci A and B

Fitch-Margoliash Little Maximum Parsimony Algorithm for Phylogenetic Tree Construction

	A	B	C
A	∅	d_{AB}	d_{AC}
B		∅	d_{BC}
C			∅

Distance matrix



$$x = (d_{AB} + d_{AC} - d_{BC}) / 2$$

$$y = (d_{AB} - d_{AC} + d_{BC}) / 2$$

$$z = (-d_{AB} + d_{AC} + d_{BC}) / 2$$

Tree topology and branch lengths

Lotka-Volterra Interspecific Competition Logistic Equations

$$\frac{dN_1}{dt} = r_1 N_1 \left(\frac{K_1 - N_1 - \alpha N_2}{K_1} \right)$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(\frac{K_2 - N_2 - \beta N_1}{K_2} \right)$$

N_i = population size of species i
 T = time
 r_i - instantaneous or intrinsic rate of increase
 K_i = carrying capacity

Hodgkin-Huxley (Goldman) Equations for Neural Axon Membrane Potential

$$\frac{dv}{dt} = \frac{-1}{c} [g_{Na}(V)(V - V_{Na}) + g_K(V)(V - V_K) + g_L(V - V_L)]$$

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

where $g_{Na} = \bar{g}_{Na} m^3 h$ and

Micaelis - Menten Equation for Enzyme Kinetics:

$$V = \frac{V_{max} [S]}{k_m + [S]}$$

Allometry: E.g., MacArthur-Wilson Theory of Island Biogeography Species-Area Law

$$S = CA^z$$

Hypothesis Testing: Luria-Delbrück Fluctuation Test for Mutations in Viruses

$$p(\text{proportion of zero class}) = e^{-\mu n}$$

μ = mutation rate
 n = population size

Crick - Griffith - Orgel Comma-free Coding Theory for the Adaptor Hypothesis of Genetic Coding

$$W_k(n) \leq \frac{1}{k} \sum_{d/k} \mu(d) n^{k/d}$$

$W_k(n)$ = number of comma-free code k -letter words with alphabet n
 $\mu(d)$ = Möbius function
 summation is extended over all divisors d of k

Based on a systematic personal examination of introductory biology textbooks designed for majors, Blystone (personal communication) argues that equations have been replaced by pictures in texts over the past fifty years. Even though Blystone specializes in biological visualization, and, hence, deeply loves good illustrations. Thus, Blystone and Cooper (1996) are currently developing tools for students in biology and statistics to mutually inform one another's investigations of biological images. He wants students to move beyond simply acquiring pictures. This exclusion of equations in textbooks has three unfortunate consequences; namely, a lack of respect for, consistency with, and empowerment of students.

RESPECT: First, this exclusion connotes an explicit lack of respect for the intellect and talents of our students. Our students are dealing with the mathematics in their calculus courses as well as in other frequently required courses such as physics. Many students have already illustrated success in high school and college mathematics courses. Almost all biology students come with a variety of computational skills and heuristics for reasoning quantitatively. In a democratic society, can we afford such a deep lack of respect?

CONSISTENCY: Second, this condescension leads to deskilling behavior. Instead of building upon the foundation of mathematical thinking developed in other courses, the students learn that professors have not taken their own requirements seriously because these professors are not regularly building upon this foundation and that they can get by even if they let their mathematical skills atrophy. Is this not inconsistent, as well hypocritical?

EMPOWERMENT: Third, this hidden curriculum plays into the hands of the "star" system or produces a tracking component that has differential career consequences because as Gross (1994) has reported: the more mathematics background that a biologist has, the better that she or he does economically, on average. A lack of mathematical background deprives students the opportunity to read a rich primary literature without skipping over the mathematics contained therein. One of the most regular comments that I hear from alumnae in graduate school programs in biology is that they end up having to learn a large amount of mathematics in order to be able to comprehend many of the papers that they are assigned to read and discuss. Go to your library and open a variety of biological journals; the diversity and richness of mathematics therein may surprise you. Why shouldn't this literature be accessible to far more of our students?

² (<http://www.math.duke.edu/faculty/moore/pcalc.html>)

³ (<http://alan.sewanee.edu:8080/sc/links.html> (provides 18 links on this project))

⁴ (<http://www-cm.math.uiuc.edu/>)

What should we do to begin a transformation? Gross (1996) has explicitly addressed this issue:

"Lessons from the Above

It is unrealistic to expect many math faculty to have any strong desire to really learn significant applications of math that students will readily connect to their other course work, though there is a core group who might do this.

So what do we do to enhance quantitative understanding across disciplines? Below is what I say to life science faculty: Who can foster change in the quantitative skill of life science students?

Only you, the biologists can do this!

Two routes:

1. Convince the math faculty that they're letting you down
2. Teach the courses yourself

Note: Math faculty will not take you seriously unless you show them how the quantitative topics you insist that they cover will be used in your own courses!

This means biology courses must become less of a "litany of conclusions," and more an exploration of how and why natural systems came to be as they are.

Unfortunately, this battle must be fought over and over at each institution."

This is a real call to action! I am eager to explore ways in which we biologists can collaborate with our collegial mathematicians in developing the mathematical background of our biology students. We have three particular opportunities at this juncture to undertake a significant reform for greater inclusion of mathematics in biology education.

First, we truly can do "biological aftermath" in terms of curricular reform. The recent successes in mathematical education reform; e.g., Project CALC², the Harvard calculus reform³, and Calculus & Mathematica⁴, despite some retrograde recalcitrance (Wilson, 1997), have transformed the mathematical education of many of our students already and is having an impact on more and more institutions at an increasing rate. We should build on these successes. Jim

Cornette at Iowa State University and Fred Adler at the University of Utah both have calculus texts forthcoming that explicitly deal with many biological applications.

Second, several mathematicians and biologists are already collaborating in ventures that we can use as models. For example, as already mentioned, Bob Blystone and Rick Cooper are teaching coordinated sections of statistics and biology and are developing materials for use in both; Sandy Lazarowitz and Jerry Uhl⁵ have developed a course entitled BioCalc at the University of Illinois - Champaign-Urbana wherein they have almost completely done away with lectures and have a series of *Mathematica*TM notebooks with biologically informed calculus education projects; Lou Gross' group⁶ at the University of Tennessee - Knoxville has collected an enormous set of world wide web resources for a quantitatively based biology curriculum; and many mathematical biologists such as Leah Edelstein-Keshet (1988) at the University of British Columbia and John Tyson at Virginia Tech are able to teach courses by themselves that equally treat both biology and mathematics in depth.

Third, the BioQUEST Curriculum Consortium has evaluated, field tested, and distributed (Jungck *et al.*, 1996) over fifty simulations, tools, and texts, many of which enhance a mathematically informed biological problem solving curriculum.

Hence, my main point here is to embrace the efforts of my colleagues by sharing a perspective from my personal vantage as a historian of biology, an evolutionary biologist, and an educator. Based on thirtyfive years of discussion, I believe that many biologists deeply believe that mathematics is irrelevant to biological research. While I was allowed to minor in mathematics as an undergraduate, I was actively discouraged from taking mathematics and computer science courses as a graduate student, both at the masters and doctoral levels at two different institutions. In pre-tenure years, my research was not viewed as serious by some senior colleagues at three different institutions if I did not maintain a wet lab. Students at five institutions have frequently challenged me as to why they had the peculiar misfortune to have mathematically informed courses in evolution, genetics, developmental biology, biochemistry, cellular and molecular biophysics, and population biology. Often faculty or student friends would say: "Well, yes, mathematics is important in X or Y, but, of course, it doesn't apply to my field Z." On the other hand, each per-

sonal negotiation has catalytically provided an opportunity to seek out examples that they would enjoy, would run counter to their assertions, or as a challenge to develop computer simulations to illustrate the beauty or power of mathematically informed biological perspectives. It is from this personal history that I share some examples which have served me well in such challenging situations.

The most recent motivation for this exercise is twofold. First, in 1995 at the International Society for the History, Philosophy, and Social Studies of Biology meeting at the University of Leuven in Belgium, Evelyn Fox Keller challenged me to come up with examples where informed mathematical thinking was critical to historically important biological research programs. I was deeply bothered because, distinct from the above group of challengers, Professor Keller is a distinguished mathematical biologist (Keller and Segel, 1970; 1971) as well as a major cultural historian and feminist critic of biology. Second, while pondering my discouragement, I began looking at some popular expositions of contemporary and historically important aspects of mathematics on my bookshelves and noted the conspicuous absence of biology. While I could cite exceptions of course, none of them take the point of view of mathematical biologists that biology has contributed much to mathematics as presented by Simon Levin⁷.

Later that year, Michael Guillen (1995), ABC TV's Science Editor for *Good Morning America*, arrived with the most immediate solution to my dilemma with his *Five Equations that Changed the World: The Power and Poetry of Mathematics*. Now I have to say that, while taken by Guillen's choice of equations and his chatty historical introduction to them, on the other hand, his popularization upsets me greatly in terms of my own expectations for expository mathematics. In Guillen's (1983) prior book, *Bridges to Infinity: The Human Side of Mathematics*, he "did it all without subjecting the reader to a single equation (1995)." Why is that "the" human side? Are equations not human constructions? Why are there no references in the current text? Are we to presume that mathematicians are polymaths who are both completely self-sufficient and have an incredible memory? Amongst sources, I am particularly curious whether Guillen had read Harald Fritzsche's (1994) book entitled *An Equation That Changed the World: Newton, Einstein, and the Theory of Relativity* (which had appeared initially in German in 1988 as *Eine Formel verändert die Welt: Newton, Einstein und die Relativitätstheorie*). Have we really accomplished the handshake that we extend if we do not overcome deep suspicions about mathematical formulations? In contrast to Guillen, consider John L. Casti's (1996)

⁵(<http://www.life.uiuc.edu/micro/lazarow.html>)

⁶(<http://www.math.utk.edu/~gross/quant.lifesci.html>)

⁷([gopher://merlot.gdb.org:70/00/Math-In-Biology/math/](http://merlot.gdb.org:70/00/Math-In-Biology/math/))

recent book, *Five Golden Rules: Great Theories of 20th-Century Mathematics - and Why They Matter* which is full of equations and is also highly readable. However, not only Guillen, but other popularizers of mathematical beauty also completely avoid the use of equations. For example, compare the mathematical richness of D'Arcy Wentworth Thompson's *On Growth and Form* (1917) with a recent popularization by Delta Willis (1995) who wrote *The Sand Dollar and the Slide Rule*. In deep contrast, Sand⁸ gives Guillen's (1995) *Five Equations ...* high praise for pedagogical purposes: "Dr. Guillen takes famous equations we all learned in high school science classes and turns them inside out. Slowly, delicately, he explores the history of the experimenter/scientist. Each discovery reaches a crescendo that culminates in examples of how they shaped the modern world. For those who fell asleep in science class this is a refreshing look at the mystery and excitement of discovery." Hence, despite my reservations, I set out to identify equations that have had tremendous impact on biological research and which have been publically acknowledged.

The ten equations presented here were selected upon the basis of wide-spread recognition of the value of the models as indicated by their: (1) being cited in common undergraduate (admittedly sophomore or above levels) biology textbooks, (2) being the subject of biographies of the names associated with these equations, (3) appearance in historical monographs on biology, and/or (4) receipt of public awards such as Nobel prizes and British Knighthood. Why ten, when three authors could write a whole book on one equation or five equations? I believe that in order to convince biologists, one has to show the importance of

mathematics across a variety of subdisciplines in biology to avoid the oft stated claim: "Oh, that may apply to population genetics, but it doesn't apply to my area of biology." Are ten sufficient? Probably not. Partly I respect the reader's endurance. Partly I do not have the temerity nor the intelligence to emulate David Hilbert (1862-1943) who opened the twentieth century (at the International Congress of Mathematics in 1900) by posing twenty-three problems which have been the subject of much mathematical investigation ever since. Nor do I believe that displaying 49 equations in a light hearted manner as Salem, Testard, and Salem's (1992) *The Most Beautiful Mathematical Formulas* would convince my colleagues.⁹

Hence, this short list of equations represents an historical thread of mathematical contribution to fundamental questions of twentieth century biology. Henry Oliver Lancaster (1994) states that: "it could be concluded that mathematics enters into biology as an adjunct to measuring and counting problems, that is, in most cases, as an aid to the technology of, rather than the science of, biology" (p.16). In contrast, in each of my essays I have tried to illustrate scientific, as opposed to mere mechanistic, importance of each historical example and at least one additional opportunity for understanding some social, cultural, political, philosophical, or ideological aspect associated by various interpreters of an equation. In reading them, I ask you to re-ask Steen and Albers's (1981) questions: "What role should applications play in mathematics curricula? Is the traditional division between mathematics and science instruction still valid? How can mathematical topics be related to cultural issues that are relevant to students?"

I. Fisher's "Fundamental Theorem of Natural Selection"

Sir Ronald A. Fisher along with Sewall Wright and J. B. S. Haldane are usually credited by Anglo-American biologists for synthesizing two, then warring, major disciplines in twentieth century biology: namely, genetics and evolution. This integration is usually referred to as the neo-Darwinian Synthesis. "In 1930 *The Genetical Theory of Natural Selection* represented the most substantial contribution to the synthesis of Mendelism, Darwinism, and biometrics yet published" (Provine, 1971, p.154). Biographies exist for each of the three luminaries. Since population genetics has been called the most successful application of mathematics to biology, there are far too many equations to privilege just one; however, Frisman (1978) states: "One of the most interesting results of the mathematical theory of natural selection is known as Fisher's Fundamental Theorem of Natural Selection." According to Price (1972), Fisher believed that his "Fundamental Theorem" was as important to biology as the second law of thermodynamics was to chemistry. While nearly every population geneticist qualifies the contemporary importance of this equation, Ewens (1979), as a representative of this cautionary group, says: "it so beautifully quantifies in genetic terms the main theme of the Darwinian theory." If controversy is the lifeblood of science, students could not appreciate the fullness either of the Mendelian-Darwinian debate nor its resolution without some understanding of the mathematics of population genetic theory in neo-Darwinian syntheses.

⁸(in an electronic book review - ssand@ionet.net)

⁹(In order to make this manuscript cohere as well as possible, references for the non-equation portion of this article are placed conventionally at the end of the article; however, references that relate directly to a particular equation are at the end of each section.)

II. Cormack: Computer Assisted Tomography

Computer Assisted Tomography (CAT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and ultrasonography have revolutionized noninvasive visualization in medical practice in just twenty years (Sochurek 1988.). While the developers were largely ignored in their early years (see PBS special in the New Explorers series called "Doctors with X-Ray Vision"), most hospitals are currently considered underequipped without these instruments and/or without physicians educated well in interpreting them. In particular, Raymond V. Damadian (see Schneider 1997) experienced heavy resistance to his innovation of magnetic resonance imaging (MRI). Cormack shared the 1979 Nobel Prize for his design of CAT scanners with a source and sensor across from one another on an apparatus that could be rotated around a patient to visualize a thin slice by sweeping through a region and which could use attenuated X-rays. He solved the traditional phase problem which so plagues other arenas in biological imaging such as in X-ray crystallography of biopolymers. His scanning process looked at small three dimensional points (voxels) which could then be stacked into a full three dimensional image of the portion of the individual being examined. Cormack (1963) was even surprised by the originality of his own insight because: "One would think that this problem would be a standard part of the nineteenth century mathematical repertoire, but the author has found no reference to it in standard works." In 1983, he reviewed the work on Radon's (1917) problem of reconstructing densities from their projections which was not generally known as well as citing his own pleasure in pursuing solutions to this problem. Robert Ledley, another mathematical biology pioneer who published a book in 1965 entitled *Use of Computers in Biology and Medicine*, received the 1997 National Medal of Technology for his development of the automatic computed transverse axial (ACTA) scanner which "revolutionized the fields of radiology and medical imaging and set the standard for all subsequent CT [and MRI and PET] scanners" [announced in *Scientific American*, June 1997]. Shepp (1983) noted the lack of appreciation of such major work not just by biologists, but by mathematicians as well:

The central technology in CT is unquestionably recognized to be mathematics, not only in the medical community but in the physics and engineering areas of CT as well. It is unfortunate that the mathematical community itself has less of an appreciation and understanding of this important application of mathematics. The reason for this is the usual one, that mathematicians are often content to work on questions 'of intrinsic interest', and there are always plenty of these around which do not have to deal with the realities of a real-world problem such as CT" (p. ix) and "... to illustrate the frequent characterization of the mathematician as one who ignores the real world and prefers to be imbedded in axiomatics and idealized abstract models. Nevertheless, the advantages of the mathematical approach, based on a well-defined model, to a real problem are manifold: clarity, computability, elegance, to name a few" (p. 1).

From a personal point of view, I have seen the transformation that these technologies, especially ultrasonography, have had on couples expecting a child. When my son and daughter-in-law brought home the ultrasonography videotape to show grandpa (me) the movie of their developing fetus, I appreciated deeply how this application of mathematics has modified our understanding of and personal interpretation of ethical issues involved in embryogenesis as discussed by feminists considering the new technologies (Sandelowski, 1994).

Equation from Cormack (1963):

$$g(r, \theta) = \sum_{n=-\infty}^{+\infty} g_n(r) i^n$$

where the line integral is

$$g_n(r) = \frac{1}{2\pi} \int_0^{2\pi} g(r, \theta) C^{-in\theta} d\theta$$

"Suppose for now that X-ray absorbancy has a well defined value [g] at each point in the patient's cross section. Then ... the value at a point ... is approximately equal to the line integral between the source and the detector of the X-ray absorbancy of the patient's tissue. ... In order to reconstruct the values of [g] at individual points in the patient's cross section, we need to estimate its line integrals for many different lines L. ... In a modern CT scanner this number is of the order 10^5 to 10^6 [lines]." (Herman, 1986)

References:

Bousquet, J. C. (1994). "Tomodensitometrie: technique actuelle et perspectives" [Translation of French: Tomodensitometry: current technique and perspectives]. *Prog Urol (BRV)* 4 (5 Suppl 2): 48-58 (October). (A review.)

Cormack, A.M. (1963). "Representation of a function by its line integrals, with some radiological applications. *J. Applied Physics* 34: 2722-2727.

Cormack, A.M. (1983). "Computed tomography: Some history and recent developments. In Lawrence A. Shepp, editor. *Computed Tomography*. Proceedings

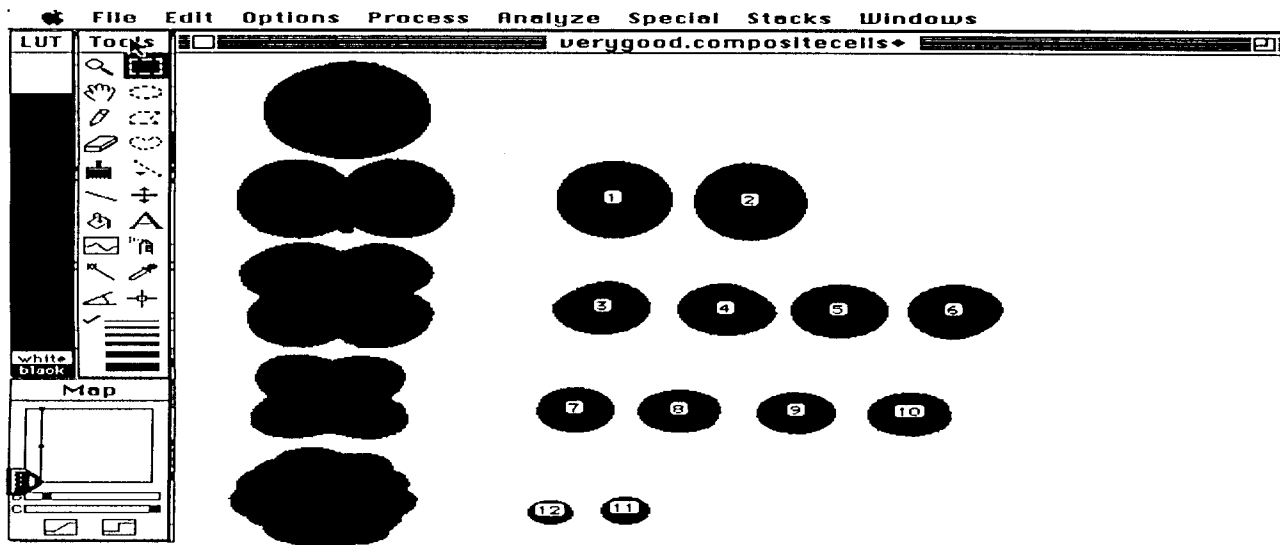


Figure 3. Screen shot of *Image Analysis* (starfish embryos) in *NIH Image*.

- of Symposia in Applied Mathematics, Volume 27. American Mathematical Society: Providence, Rhode Island, p. 35-42.
- Herman, Gabor T. (1986). "Computerized reconstruction and 3-D imaging in medicine." *Annual Review of Computer Science* 1:153-179.
- Kevles, Bettyann Holtzmann. (1997). *Naked to the Bone: Medical Imaging in the Twentieth Century*. Rutgers University Press: New Brunswick, New Jersey.
- Kurtis, Bill. (1997). "Doctors with X-Ray Vision." The New Explorers Series. PBS Video.
- Mannella, C.A., M. Marko, P. Penczek, D. Barnard and J. Frank. (1994). "The internal compartmentation of rat-liver mitochondria: Tomographic study using the high-voltage transmission electron microscope." *Micros. Res. Tech.* 27:278-283.
- McGowan, A. (1989). "The Ichthyosaurian tailbend: A verification problem facilitated by computed tomography." *Paleobiology* 15:429-436.
- Natterer, Frank. (1986). *The Mathematics of Computerized Tomography*. John Wiley and Sons: Chichester, Great Britain.
- Radon, von Johann. (1917 [reprinted 1983]). Über die Bestimmung von Funktionen durch ihre Integralwerte längs gewisser Mannigfaltigkeiten ("On the determination of functions from their integrals along certain manifolds"). Reprinted in Lawrence A. Shepp, editor. *Computed Tomography*. Proceedings of Symposia in Applied Mathematics, Volume 27. American Mathematical Society: Providence, Rhode Island, p. 71-86.
- Romans, Lois E. (1995). *Introduction to Computed Tomography*. Williams & Wilkins: Baltimore, Maryland.
- Sandelowski, Margarette. (1994). "Separate, but less unequal: Fetal ultrasonography and the transformation of expectant mother/fatherhood." *Gender and Society* 8(2):230-245 (June).
- Schneider, David. (1997). "Profile: Raymond V. Damadian: Scanning the Horizon." *Scientific American* 276(6):32, 34.
- Shampo, M. A., and R. A. Kyle. (1996). "Cormack—codeveloper of computed tomographic scanner." *Mayo Clin Proc (LLY)* 71(3):288 (March).
- Shepp, Lawrence A., editor. (1983). *Computed Tomography*. Proceedings of Symposia in Applied Mathematics, Volume 27. American Mathematical Society: Providence, Rhode Island.
- Sochurek, Howard. (1988). *Medicine's New Vision*. Mack Publishing Company: Easton, Pennsylvania.
- Webb, Steve. (1990). *From the Watching of Shadows : The Origins of Radiological Tomography*. Adam Hilger: Bristol, United Kingdom.
- Relevant web sites:**
- Dale Alvin Walters (1996) has a nice visualization of a CAT set-up: <http://casual1.enci.ucalgary.ca/~dawalter/Cat.html>
- Beth Israel Hospital has an introduction to CAT Scanning for patients to help them prepare for an exam. It also includes photographs of patient in a CAT scanner, and CT scans of a head and kidneys, as well as illustrations of what is going on: <http://www.bih.harvard.edu/radiology/Modalities/CT/CT.html>
- Computed tomography of forest canopies (Dave Vieglaiss) : <http://ze.ke.kbs.ukans.edu>
- Relevant BioQUEST modules:**
- Blystone, Robert and Richard Cooper. (1996). "Image Analysis." *The BioQUEST Library IV*:(First Review Folder): University of Maryland - College Park.
- Rasband, Wayne. (1996). "NIH Image" *The BioQUEST Library IV*:(Support Materials Archive): University of Maryland - College Park.

III. Genetic Mapping (The Haldane Function)

Thomas Hunt Morgan won the 1933 Nobel Prize for his "Theory of the Gene" which presented chromosomes as linear maps. Students should be able to easily relate to this achievement because the first genetic map published was calculated by an undergraduate named A. H. Sturtevant in Morgan's lab in 1913. The unit of measurement for genetic distance is named after Morgan. In 1919, J. B. S. Haldane published the first equation for relating the observed % of crossing-over between two loci (recombination rate) with the physical distance between two loci on a chromosome (see Wimsatt (1992) for a history of controversies about several models of linkage). While this equation does not include multiple crossing-overs, interference, synteny, or special biological features associated with particular taxa, it captured several features of the functional relationship between the empirical measurements and the inferred map including a maximal distance of 50 centiMorgans because any longer distance would represent no linkage (Mendel's independent assortment) and the nonlinear form of this correlation. We could see all of contemporary work in genomic analysis: sequencing genomes, restriction maps, contig assemblies, complementation maps, deletion maps, transcription maps, cytogenetic FISH (fluorescent *in situ* hybridization) or chromosome painting, etc. as derivative of this pioneering work. Wimsatt (1992) reviews two approaches which he believes "are indicative of the problems theorists and experimentalists have in talking to each other everywhere, and I suspect that many or most of the reasons are generalizable."

Relationship between recombination frequency and mapping distance (Haldane function):

$$C_{AB} = \frac{1}{2}(1 - e^{-2x_{AB}})$$

C_{AB} = recombination fraction between loci A and B

x_{AB} = map distance between loci A and B

References:

- Allen, Garland E. (1978). *Thomas Hunt Morgan: The Man and His Science*. Princeton University Press: Princeton, New Jersey.
- Haldane, J. B. S. (1919). "The combination of linkage values and the calculation of distances between loci of linked factors." *J. Genetics* 8:299-309.
- Keats, Bronya J. B., Newton E. Morton, D. C. Rao, and Wick R. Williams. (1979). *A Source Book for Linkage in Man*. The Johns Hopkins University Press: Baltimore, Maryland.
- Morgan, T. H. (1919). *The Physical Basis of Heredity*. J. P. Lippincott Company: Philadelphia, Pennsylvania.
- Ott, Jurg. (1985). *Analysis of Human Genetic Linkage*. The Johns Hopkins University Press: Baltimore, MD.
- Shine, Ian B. and Sylvia Wrobel. (1976). *Thomas Hunt Morgan: Pioneer of Genetics*. University Press of Kentucky: Lexington, Kentucky.
- Stahl, F. W. (1979). *Genetic Recombination: Thinking About It in Phage and Fungi*. W. H. Freeman and Co.: San Francisco, California, p. 9-18.
- Terwilliger, Joseph Douglas and Jurg Ott. (1994). *Handbook of Human Genetic Linkage*. The Johns Hopkins University Press: Baltimore, MD.
- Thompson, Elizabeth A. (1986). *Pedigree Analysis in Human Genetics*. The Johns Hopkins University Press: Baltimore, MD.
- Weir, B. S. (1990). *Genetic Data Analysis: Methods for Discrete Population Genetic Data*. Sinauer Associates, Inc.: Sunderland, Massachusetts, p. 210-221.
- Wimsatt, William C. (1992). "Golden generalities and co-opted anomalies: Haldane vs. Muller and the *Drosophila* group on the theory and practice of linkage mapping." In Sahotra Sarkar, editor, *The Founders of Evolutionary Genetics*, Kluwer Academic Publishers: Netherlands, p. 107-166.

Relevant WWW pages:

- MendelWeb (conceived and constructed by Roger B. Blumberg):
<http://www.netspace.org/MendelWeb/>
- Microbial Genetics problems (for 2 and 3 point crosses):
<http://www.life.uiuc.edu/micro/316resources/problems/recombination/3factor-crosses/>
- Online Mendelian Inheritance in Man:
http://www.ornl.gov/TechResources/Human_Genome/vl.html#omim
- Mapping sites: Gateways To Other Resources: <http://www.ornl.gov/hgmis/links.html#mapping>
- Science Human Linkage Maps:
<http://www.chlc.org/ScienceData.html>

Three relevant historical papers on-line:

- Mendel's Paper in English. Experiments in Plant Hybridization (1865):
<http://hermes.astro.washington.edu/mirrors/MendelWeb/Mendel.html>
- Morgan, Thomas, H. (1909). What are "factors" in Mendelian explanations? *American Breeders Association Reports*, 5:365-369: <http://www.gdb.org/rjr/history/thm-09.pdf>
- Bridges, Calvin B. (1914). Direct proof through non-disjunction that the sex-linked genes of *Drosophila*

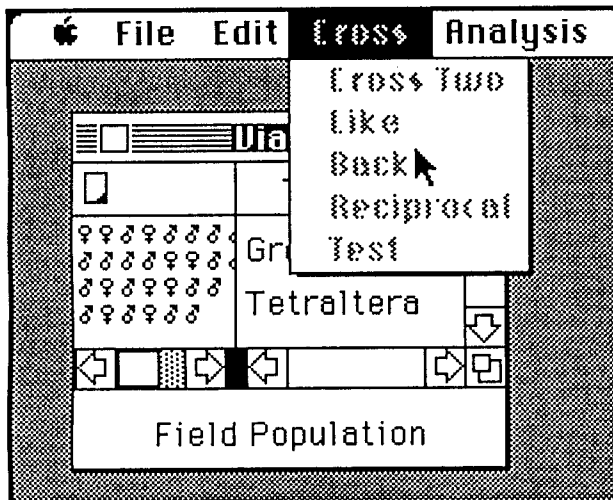


Figure 4. Screen shot of GCK.

are borne on the X-chromosome. *Science, NS vol. XL:107-109*: <http://www.gdb.org/rjr/history/cbb-14.pdf>

Relevant BioQUEST modules:

Calley, John N. and John R. Jungck. (1996). "Genetics Construction Kit." *The BioQUEST Library IV*:(The BioQUEST Core Collection): University of Maryland - College Park.
 Calley, John N. and John R. Jungck. (1996). "Microbial Genetics Construction Kit (GCK)." *The BioQUEST Library IV*:(Candidate Collection): University of Maryland - College Park.

Other Software: Map Manager is a program for a Macintosh personal computer which helps analyze the results of genetic mapping experiments using backcrosses, intercrosses, or recombinant inbred (RI) strains. It is a specialized database proplay of information from such mapping experiments, but it also has tools for statistical analysis of the experimental results. Map Manager was created and is maintained by Kenneth F. Manly, Robert Cudmore, Jr, and Greg Kohler in the Department of Molecular and Cellular Biology at Roswell Park Cancer Institute. To contact the developers of Map Manager: mapmgr@mcbio.med.buffalo.edu

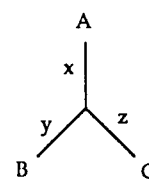
IV. Fitch-Margoliash Little Maximum Parsimony Algorithm for Phylogenetic Tree Construction

The availability of amino acid sequences of proteins with similar functions from many different species excited systematicists and geneticists in the mid-1960's. Emile Zuckerkandl and Linus Pauling (1965) are usually credited for the fundamental reasoning behind molecular evolutionary research; namely, proteins and nucleic acids are better molecules for building phylogenetic relationships than are secondary metabolites which do not reflect sequential information transferred between generations. Cavalli-Sforza and Edwards (1967) stated an additive hypothesis for converting distances between molecular sequences into phylogenetic trees. However, the first development of an algorithm that was employed in building a tree of proteins that was fairly congruent with classical taxonomy was widely publicized in Walter Fitch's and Emanuel Margoliash's (1967) analysis of

cytochrome C's. While the combinatorial explosion of topologies ($\bar{X} = \sum_{i=1}^{n-2} (2i - 5)!$ or over Avogadro's number for just 22 taxa) makes an exhaustive search computationally prohibitive, they circumvented many complications by collapsing nodes after each new sequence was added. By using a known topology, they only had to solve for distances using three equations with three unknowns. Four taxa trees have three different topologies and a series of over-determined equations. So Fitch and Margoliash collapsed the two closest taxa into the tip of a single branch in each iteration and then added each taxon successively. They overcame the problem of the order of entry of taxa by randomizing the order until a particular topology was well supported (such as minimizing total distances over a tree). Since their publication, revolutions in cladistics, resampling statistics (bootstrapping and jackknifing), maximum likelihood techniques, multiple sequence alignment algorithms, and general computer science have led to a proliferation of powerful alternative techniques (Huelsenbeck and Rannala 1997). Nonetheless, the Fitch-Margoliash algorithm is still employed and its historical importance is indelible because of its language of minimal mutational distances, invariant residues, and inferring function from homologous molecular sequence alignments. Furthermore, I agree wholeheartedly with Clegg (1984) when he stated: "Much of what is occurring today (in molecular biology especially evolution) could not have been anticipated by a logical extension of population genetic theory, no matter how inspired."

Distance Matrix		A	B	C
	A	∅	d _{AB}	d _{AC}
	B	d _{AB}	∅	d _{BC}
	C	d _{AC}	d _{BC}	∅

Tree



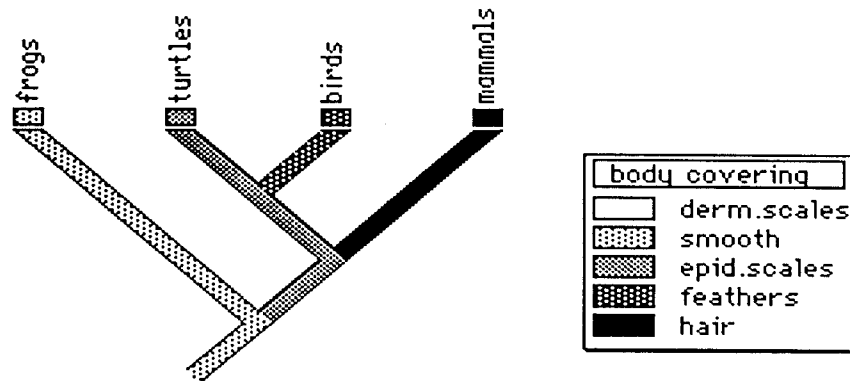


Figure 5. *MacClade* tree with trace of character states

Equations from Nei (1987), p. 56:

$$x = (d_{AB} + d_{AC} - d_{BC}) / 2$$

$$y = (d_{AB} - d_{AC} + d_{BC}) / 2$$

$$z = (-d_{AB} + d_{AC} + d_{BC}) / 2$$

References:

- Cavalli-Sforza, L. L., and A. W. F. Edwards. (1967). "Phylogenetic analysis: Models and estimation procedures." *Amer. J. Hum. Genet.* **19**:233-257.
- Clegg, M. T. (1984). "Molecular Evolution: The coming of age." *Evolution* **38**:459-461.
- Fitch, Walter M. and Emmanuel Margoliash. (1967). "A method for estimating the number of invariant amino acid coding positions in a gene using cytochrome c as a model case." *Biochem. Genet.* **1**: 65-71.
- Fitch, Walter M. and Emmanuel Margoliash. (1967). "Construction of phylogenetic trees." *Science* **155**: 279-284.
- Fitch, Walter M. (1996). "Uses for evolutionary trees." In Paul H. Harvey, Andrew J. Leigh Brown, John Maynard Smith, and Sean Nee, editors, *New Uses for New Phylogenies*. Oxford University Press: Oxford, United Kingdom.
- Huelsenbeck, John P., and Bruce Rannala. (1997). "Phylogenetic methods come of age: Testing hypotheses in an evolutionary context." *Science* **276**(5310):227-232.
- Maddison, Wayne and David Maddison. (1996). *MacClade 3.0* (Professional version), Sinauer: Sunderland, Massachusetts.
- Nei, M. (1987). "Fitch and Margoliash's Method." *Molecular Evolutionary Genetics*. Columbia University Press: New York, New York, p. 298-302.
- Hendy, Michael D. and David Penny. (1986). "How the theory of evolution could be disproved, but isn't." P. 173-182 in Richard J. Groom, Gregory C. Arnold, Thomas H. Hassard, and Robert M. Pringle, editors, *The Fascination of Statistics*. Marcel Dekker, Inc.: New York, New York.
- Zuckerlandl, Emile and Linus Pauling. (1965) "Molecules as documents of evolutionary history." *Journal of Theoretical Biology* **8**:357-366.

Relevant WWW sites:

David and Wayne Maddison's "Tree of Life" and their *MacClade* homepage: <http://phylogeny.arizona.edu/tree/phylogeny.html>
<http://phylogeny.arizona.edu/macclade/macclade.html>

TREEBASE, a searchable data base of phylogenies from various papers. It's in its early days yet so it has almost entirely angiosperm phylogenies in it: <http://phylogeny.harvard.edu/treebase/>

Joe Felsenstein's course syllabus, references, and PHYLIP software:

<http://weber.u.washington.edu/~genetics/courses/genet590/genet590.html>

<http://weber.u.washington.edu/~genetics/courses/genet554/genet554.html>

<http://evolution.genetics.washington.edu/phylip.html>

PAUP homepage: <http://phylogeny.arizona.edu/tree/programs/programs.html#PAUP>

Computational Molecular Evolution: <http://dexter.gnets.ncsu.edu/lab/moleevol.html>

Good site for links on evolution: <http://golgi.harvard.edu/biopages/evolution.html>

Relevant BioQUEST modules:

Maddison, Wayne and David Maddison. (1996). *MacClade 2.1* (student use only), *The BioQUEST Library IV*:(Support Materials Archive).

Peterson, Nils S. (1996). "Taxonomic Features Data Manager." *The BioQUEST Library IV*:(Extended Learning Resources).

Brewer, Steve "Phylogenetic Investigator." (1996). *MacClade 2.1* (student use only), *The BioQUEST Library IV*:(First Review Folder).

<http://141.218.91.93/docs/PIGuide/piguide.html>

V. Lotka-Volterra Interspecific Competition Logistic Equations

Israel (1985) describes a critically important transition in the way that biology is done: "The 1920's were a period of rapid growth and change in modern biomathematics. ... The first of these was a kind of *invasion* [emphasis his] of biology by mathematics; mathematics was no longer used merely as a technical aid but as a conceptual tool for investigation purposes. It was no longer a question of using a few formulae for carrying out an occasional calculation, but of bringing into action the whole vast array of sophisticated theorems of mathematical analysis." While the notion of exponential population growth has been discussed throughout much of recorded history, most of us credit the Reverend Thomas Malthus for calling attention to the idea of a finite carrying capacity. In other words, exponential ($N_t = N_0 e^{rt}$) models do not adequately mimic the actual growth of species with finite space and nutrients (such as bacteria in a chemostat or flour beetles in a granary) because populations asymptotically approach a maximal equilibrium value. If we increase the complexity by adding biotic factors such as the existence of species which may compete for the same food or exist in some well-recognized co-evolutionary relationship: predator-prey, host-parasite, plant-pollinator, commensalism, mutualism, proto-cooperation, or amensalism, we need a more sophisticated model. In the era discussed by Israel above, Lotka (1925) and Volterra (1931) independently modelled two species interactions with a pair of simultaneous differential equations. While many challenges to the field validity of their assumptions and many modifications have been added to these equations to account for time lags and other complexities, the Lotka-Volterra equations still serve as a cornerstone of much population ecology. Historically, students could also learn much about priority disputes as a part of science through a closer look at this example (Kingsland 1985). An even more fascinating historical twist is that the utilization of these equations have been elaborated with a strong political interpretation (Wilson and Bossert 1971) based on r- and K-selection. Haraway (1997) states these implications thusly: "Careful parents with solid family values versus vermin and weeds: That seems to be the gist of the story in this reading of an equation. ... In the U.S. imperialist imaginary, societies 'down there' relative to the United States, in the warm and sordid regions of the planet, seem to have lots of human beings who act like r-strategists. The colder, more cerebral, less genital climes to the north - if one discounts immigrants of color and other nonprogressive types common in racist imagery - are replete with good K-strategists."

Lotka-Volterra Interspecific Competition Logistic Equations from Hedrick (1984) pp. 231-232.

$$\frac{dN_1}{dt} = r_1 N_1 \left(\frac{K_1 - N_1 - \alpha N_2}{K_1} \right)$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(\frac{K_2 - N_2 - \beta N_1}{K_2} \right)$$

N_i = population size of species i

T = time

r_i - instantaneous or intrinsic rate of increase

K_i = carrying capacity

References:

- Gaylord, Richard J., and Kazume Nishidate. (1996). "Predator-Prey Ecosystems: Behaviors of predators and prey are modeled using a cellular automaton implemented in Mathematica." *Mathematica in Education and Research* 5(1):29-35.
- Haraway, Donna J. (1997). *Modest_Witness@Second_Millennium. FemaleMan[®]_Meets_OncoMouse[™]: Feminism and Technoscience*. Routledge: New York, New York. (Quote from page 204.)
- Hedrick, P. W. (1984). *Population Biology: The Evolution and Ecology of Populations*. Jones and Bartlett Publishers: Boston, Massachusetts.
- Israel, Giorgio. (1985). "On the contribution of Volterra and Lotka to the development of modern bio-mathematics." Paper presented at the XVIIth International Congress of History of Science, University of California, Berkeley, 31 July - 8 August 1985. (Dipartimento di Matematica, Università degli Studi di Roma "La Sapienza, P. le A. Moro, 5-00185 ROMA, Italy).
- Keddy, Paul A. (1989). *Competition: Population and Community Biology Series*. Chapman and Hall: London, U.K., p. 50-56, "The Lotka-Volterra Models."
- Kingsland, Sharon. (1985). *Modeling Nature: Episodes in the History of Population Ecology*. University of Chicago Press: Chicago, Illinois.
- Lotka, A. J. (1925). *Elements of Physical Biology*. Williams and Wilkins: Baltimore, Maryland.

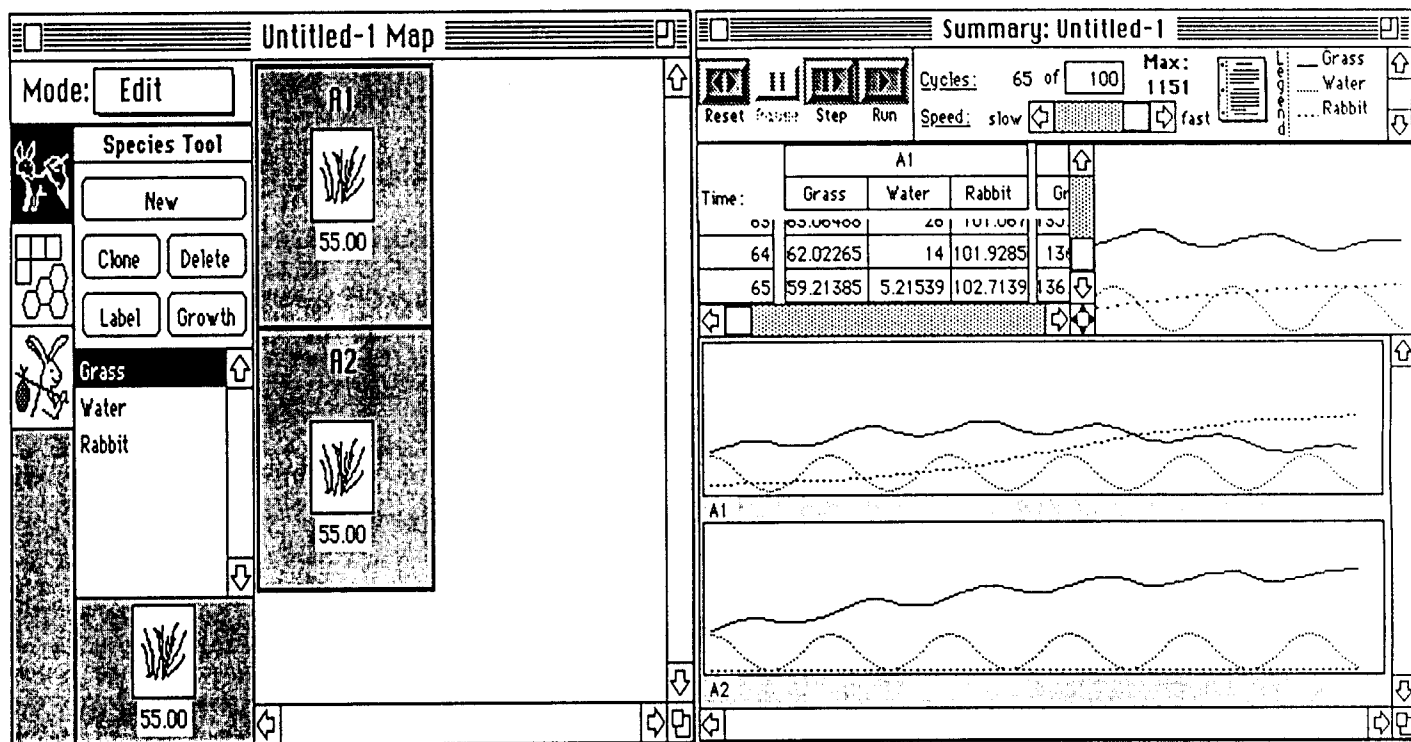


Figure 6. Two windows from *Biota*.

Swartzman, Gordon L. and Stephen P. Kaluzny. (1987). *Ecological Simulation Primer*. Macmillan: New York, New York.

Thompson, J. M. T. (1979). "An evolution game for a prey-predator ecology." *The Journal of Mathematics and Its Applications* 15:162-167 (July).

Volterra, V. (1931). Variazioni e fluttuazioni del numero d'individui in specie animal conviventi. *Mem. Acad. Lincei*. 2:31-113. Translated as an appendix to Chapman, R. N. (1976). *Animal Ecology*. McGraw-Hill, Inc.: New York, New York.

Wilson, E. O. and W. H. Bossert. (1971). "The Lotka-Volterra equations." "Volterra's principle." "r and K Selection." *A Primer of Population Biology*. Sinauer: Sunderland, Massachusetts, p.129-138, 110-111.

Relevant WWW sites for Lotka-Volterra Equations and mathematical approaches to solving them:

Lotka-Volterra Model (Quantitative Population Ecology: Dept. of Entomology, Virginia Tech, Blacksburg, VA):
<http://www.gypsymoth.ento.vt.edu/~sharov/PopEcol/lec10/lotka.html>

Stability in Random Lotka-Volterra Webs:
<http://www.santafe.edu/~tkeitt/papers/foodweb/node3.html>

Applications of Systems of Differential Equations; Predator-Prey Problems; The Lotka-Volterra system (Mathematica): <http://mac205.sjcdcc.ca.us/ODE/7-B-1/7-B-1-ma.html>

The dynamical game. The Lotka - Volterra equations

for taxa: <http://www.iiasa.ac.at/~muellers/these/node29.html>

Mathematical Modelling of Lotka-Volterra Predator-Prey (Department of Mathematics and Statistics University of South Alabama):

<http://www.mathstat.usouthal.edu/~hitt/courses/590/population/population09.html>

Lotka-Volterra Dynamics (Russell K. Standish). EcoLab Documentation. EcoLab is a system that implements an abstract ecology model:

<http://parallel.acsu.unsw.edu.au/rks/docs/ecolab temp/note/node3.html> node3.html

Oscillating Chemical Reactions Simulated by Molecular Dynamics : A particular example: MD simulations of the modified Volterra-Lotka reaction:

<http://virgil.ruc.dk/~kneht/csp/node3.html>

Interactive Text BRE 471/571 - Nonlinear Systems BRE 471/571 - Biosystems Modeling Techniques. Topic: Nonlinear Systems. Cellular Automata: <http://biosys.bre.orst.edu/bre571/mech/nonlin1.ht>

Systems of Differential Equations; Population Dynamics; Two Species Model: http://spam.maths.adelaide.edu.au/jdenier/dyn_mod/

Second-order differential equations. Solution to the set of...: http://dept.physics.upenn.edu/courses/gladney/mathphys/java/sect3/subsection3_1_5.html

XPP Tutorial: Basic Idea and Introduction. Dynamical systems theory provides the language and the machinery for the analysis ...: <http://www.cnd.mcgill.ca/computing/doc/xpptut/xpptut.html>

An interactive predator-prey model using PERL from Sweden: http://fisher.teorekol.lu.se/simulation_server/
 Pollination model from the same source: <http://fisher.teorekol.lu.se/cgi-bin/pollination.pl>
 Chrisitan V. Forst. A general system of high-order differential equations describing... Chaotic Interactions of Self-Replicating RNA.
<http://www.santafe.edu/sfi/publications/Abstracts/95-10-093abs.html>

Relevant BioQUEST modules:

Danbury, Jim, Ben Jones, John Kruper, Eric Nelson, William Sterner, Jeff Schank, Jim Lichtenstein, Joyce Weil, and William Wimsatt. (1996). "Biota." *The BioQUEST Library IV*: (The BioQUEST Core Collection): University of Maryland - College Park.
 Schank, Jeff and William Wimsatt. (1996) "Modelling Tools: Logistic Growth," *The BioQUEST Library IV*: (Collection Candidates): University of Maryland - College Park.

VI. Hodgkin-Huxley (Goldman) Equations for Neural Axon Membrane Potential

Membranes have served to define many biological systems from the boundary condition of closure that separates inside from outside or a biological organism from its environment. Yet these membranes are semi-permeable. This border of exchange mediates communication between a cell and its neighbors, interactions with other species, chemical signals (hormones, neurotransmitters, antigens, drugs, pheromones, etc.) or various physical factors (mechanical, electrical, thermal, etc.). Hence, models that could capture much of the qualitative and quantitative behavior of membrane systems have been an important theme of cell, plant, and animal physiology and biophysics. Given the anthropocentric bias that confers special status toward vertebrate brains, it is not surprising that neural membranes receive even greater attention. Paradoxically an invertebrate model has historically been associated with the most well known model of neural behavior: namely, the Hodgkin-Huxley equations for squid axons' action potentials. The model is used to model mammalian nerves as well as the mechanical responsiveness of some plant membranes. Hodgkin and Huxley won the 1963 Nobel Prize in Physiology and Medicine "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane." For students who are interested in model organisms, historical investigation of squid axons would be enormously beneficial.

Equations from Edelstein-Keshet (1988): "The Hodgkin-Huxley equations consist of four coupled ODEs with highly nonlinear terms. For this reason they are quite difficult to understand in an analytic mathematical way."

$$\frac{dv}{dt} = \frac{-1}{c} [g_{Na}(V)(V - V_{Na}) + g_K(V)(V - V_K) + g_L(V - V_L)]$$

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

where $g_{Na} = \bar{g}_{Na} m^3 h$ and $g_K = \bar{g}_K n^4$

"In assessing the Hodgkin-Huxley model, we should keep in mind that all but one of its equations were tailored to fit experimental observations. Part of the surprisingly great success of the model lies in its ability to predict fairly accurately the results of many other observations not used in formulating the equations" (Edelstein-Keshet, 1988). The equations have also been the focus of a great deal of mathematical exploration and competition amongst software developers to tame the complexities of these equations. Furthermore, models were extended to excitable media in two dimensions and applied to cardiac arrhythmias.

References:

Aidley, David J. (1989). *The Physiology of Excitable Cells, third edition*. Cambridge University Press: Cambridge, United Kingdom.
 Cole, K. S. (1972). *Membranes, Ions, and Impulses*. University of California Press: Berkeley, California.
 Cronin, Jane. (1981). *Mathematics of Cell Electrophysiology*. Marcel Dekker, Inc.: New York, New York.
 Edelstein-Keshet, Leah. (1988). *Mathematical Models in Biology*. Random House: New York, New York, p. 314-346.

- Friesen, W. Otto, and Jonathan A. Friesen. (1994). *NeuroDynamix: Computer Models for Neurophysiology*. (Includes DOS disk). Oxford University Press: New York, New York.
- Hodgkin, A. L. and A. F. Huxley. (1952). "A quantitative description of membrane current and its application to conduction and excitation in nerve." *J. Physiol.* **117**:500-544.
- Kandel, Eric R., James H. Schwartz, and Thomas M. Jessell. (1991). *Principles of Neural Science, third edition*. Elsevier: New York, New York.
- Nicoholls, John G., A. Robert Martin, and Bruce G. Wallace. (1992). *From Neuron to Brain, third edition*. Sinauer Associates: Sunderland, Massachusetts.
- Oakley, Bruce and Rollie Schafer. (1978). *Experimental Neurobiology: A Laboratory Manual*. The University of Michigan Press: Ann Arbor, Michigan.
- Peskin, Charles S. (1976). *Partial Differential Equations in Biology*. Courant Institute of Mathematical Sciences: New York University. Chapter IV: "Equations of the Nerve Impulse."
- Riggs, Douglas Shepard. (1963). *The Mathematical Approach to Physiological Problems*. MIT Press: Cambridge, Massachusetts.

Relevant WWW sites:

Hodgkin and Huxley Equations (equations scanned from original):

<http://152.3.161.11/neurolab/hhequat.htm>

A Brief history of Computational Neuroscience (John W. Moore @ Duke Univ. - see wife of Steven E. Fox, Department of Physiology, SUNY Health Science Center at Brooklyn):

<http://theta.hippo.hscbklyn.edu/fox/Neuron.User.Manual/2/pioneer.html>

The Hodgkin-Huxley Equations under Voltage Clamp (Yong-Nam Jun @ CalTech):

<http://www.klab.caltech.edu/~yongjun/cns221/homeworks/haus1/node2.html>

Models and Math pages (Lance Hahn @ UPenn):

Hodgkin-Huxley model:
http://retina.anatomy.upenn.edu/~lance/modelmath/hodgkin_huxley.html

Software simulation from (Yoram Etzyon @ Department of Physiology Faculty of Health Sciences, Ben Gurion University, POB 653, Beer-Sheva, Israel):
<http://medic.bgu.ac.il/mededu/software/hh/hh.html>

Hodgkin Huxley Equation (University of Stirling, U.K.): <http://www.students.stir.ac.uk/biology/membpot/hodhux.htm>

Relevant BioQUEST modules:

Bergland, Mark. (1996). "Action Potential Experiments." *The BioQUEST Library IV*: (Extended Learning Resources Folder): University of Maryland - College Park.

Macey, Robert and John N. Calley. (1996). "Axon." *The BioQUEST Library IV*: (The BioQUEST Core Collection): University of Maryland - College Park.

Meir, Eli. (1996). "Spike Studio." *The BioQUEST Library IV*: (Support Materials Archive): University of Maryland - College Park.

Roy, Marc M. (1996). "Real-Time Data Acquisition." *The BioQUEST Library IV*: (First Review Folder): University of Maryland - College Park.

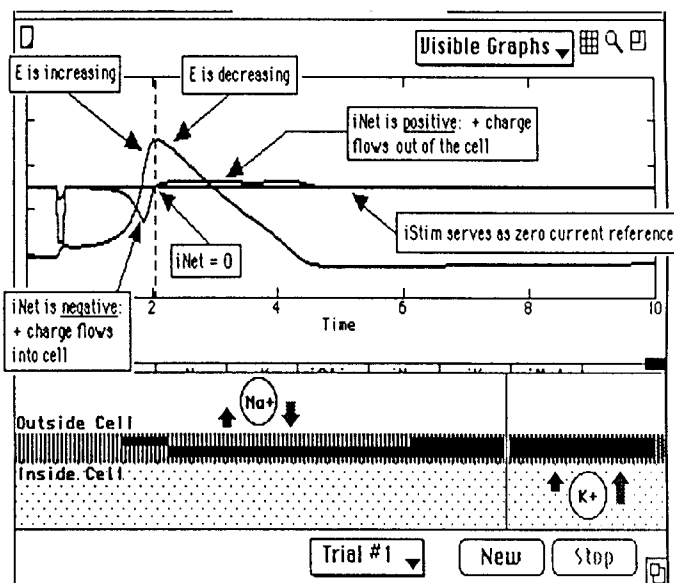


Figure 7. Axon window.

VII: Michaelis-Menten Equation for Enzyme Kinetics

Enzyme catalyzed reactions occur so fast that they have often been used as equivalents for life itself such as in the vitalism (Pasteur) - materialism (Büchner) debate of the previous century. In order to understand these rapid reactions, most models have focused on the initial rate of these reactions as a function of substrate concentration. Leonor Michaelis and Maude Leonora Menten (1913) collaborated on developing a basic equation that has served to describe the qualitative behavior of thousands of enzymes, many with only minor modification. Since then, their model has been modified to handle steady state conditions rather than at equilibrium (Briggs-Haldane) and to account for temperature and pH differences. The linear transforms of their equation are also so famous that they too bear their developers' names: Scatchard, Eadie-Hofstee, Wolff-Augustinson, Lineweaver-Burke (usually the worst way to plot one's data despite the popularity of this double reciprocal plot - see Dowd and Riggs 1965), and in other disciplines such as in plant physiology (Classen and Barber 1974.). Since today we could directly do a nonlinear fit to the original Michaelis-Menten equation, there would seem little benefit in

continuing to use these linear transformations especially when they do not robustly test the validity of the underlying assumptions of the kinetic model. Segel (1984) provides a thorough mathematical development of the Michaelis-Menten model. Fantini (1988) describes the French school's approach to regulation which developed exponential versions of the equation to deal with allosterity and feedback inhibition as well as conformational shifts in repressors regulating operons. Cornish-Bowden (1995) has developed software named "Leonora" to celebrate this woman's (Smith 1979) important contribution to quantitative biology.

Michaelis-Menten equation:

$$v = \frac{V_{max} [s]}{k_m + [s]}$$

v = velocity

V_{max} = maximal velocity

$[s]$ = substrate concentration

k_m = kinetic constant

References:

- Cleland, W. W. (1979). "Statistical analysis of enzyme kinetic data." *Methods in Enzymology* **63**:103-138.
- Cornish-Bowden, Athel. (1995). *Fundamentals of Enzyme Kinetics*, 2nd edition. Portland Press: London, United Kingdom.
- Dowd, J. E. and D. S. Riggs. (1965). "A comparison of estimates of Michaelis-Menten kinetic constants from various linear transformations." *Journal of Biological Chemistry* **240**:863.
- Fantini, Bernardino. (1988). *Jaques Monod: Pour une éthique de la connaissance*. (Histoire des sciences series). La Decouverte: Paris, France.
- Fruton, Joseph S. (1972). *Molecules and Life: Historical Essays on the Interplay of Chemistry and Biology*. Wiley-Interscience: New York, New York.
- Jack, R. Cecil. (1995). *Basic Biochemical Laboratory Procedures and Computing*.
- Laszlo, J. A. (1987). "Determination of stoichiometric association constants by a non-iterative computational method." *Computer Applications in the Biosciences* **3**:351-357.
- Michaelis, Leonor and Maude Leonora Menten. (1913). "Die Kinetik der Invertinwirkung." *Biochim. Z.* **49**: 333-369.
- Nimmo, I. A. and G. L. Atkins. (1979). "The statistical analysis of non-normal (real?) data." *Trends in the Biochemical Sciences* **4**:236-238.
- Rudolph, F. B. and H. J. Fromm. (1979). "Plotting methods for analyzing enzyme rate data." *Methods in Enzymology* **63**:138-159.
- Segel, Lee A. (1984). *Modeling Dynamic Phenomena in Molecular and Cellular Biology*. Cambridge University Press: Cambridge, U.K.

- Smith, D. B. (1979). "The Menten of the Michaelis-Menten equation." *Trends in the Biochemical Sciences* **4**: N150.
- Washington, Clive, Neena Washington, and Clive Wilson. (1990). *Pharmacokinetic Modelling using Stella on the Apple™Macintosh™*. Ellis Horwood Limited: Chichester, West Sussex, England.
- Zierler, K. (1989). "Misuse of nonlinear Scatchard plots." *Trends in the Biochemical Sciences* **14**:314-317.

Relevant WWW sites:

- Mathcad for Computers in Chemistry course at <http://www.pmf.ukim.edu.mk/PMF/Chemistry/wmc-rmm1.html>
- Kinetics of Enzymatic Reactions: The Michaelis-Menten Equation: <http://www.pmf.ukim.edu.mk/PMF/Chemistry/wmc-rmm1.html>
- Fitting Michaelis-Menten parameters to nutrient uptake data (Mineral Nutrition of Plants, SoilScience/Botany/Horticulture 626, Phillip Barak and Edgar Spalding, Instructors, University of Wisconsin-Madison): <http://www.soils.wisc.edu/~barak/soilscience626/mm3.htm> (based on: A method for characterizing the relation between nutrient concentration and flux into roots of intact plants. N. Classen and S.A. Barber. (1974.) *Plant Physiol.* **54**:564-568.

<http://esg-www.mit.edu:8001/esgbio/eb/kinetics/MandM.html>
<http://oac1.oac.tju.edu/CWIS/OAC/biochemistry/kinetics/HTML/PAGE3A.HTML>
http://www.chem.ufl.edu/~chapo/gepasipage/gepasi_intro.html (metabolic modeling)
<http://www.geotrans.com/bio1d.html> (Anaerobic Biodegradation)
<http://www.micromath.com/pklib2.html> (Micromath: Pharmacokinetics)
<http://www.denison.edu/fipse/chem/sokolik.html> (Maple programs)
<http://www.chem.ualberta.ca/courses/plambeck/p102/p02175.htm>
<http://www.liv.ac.uk/~jse/abouthyp.html> (Windows: Hyperbolic Regression Analysis)
<http://www.engr.umd.edu/~nsw/ench485/lab13.htm> (Chemical Engineering Experiment)
<http://www.biochemtech.uni-halle.de/molmod/subkin.html> (in German - nice graphics)

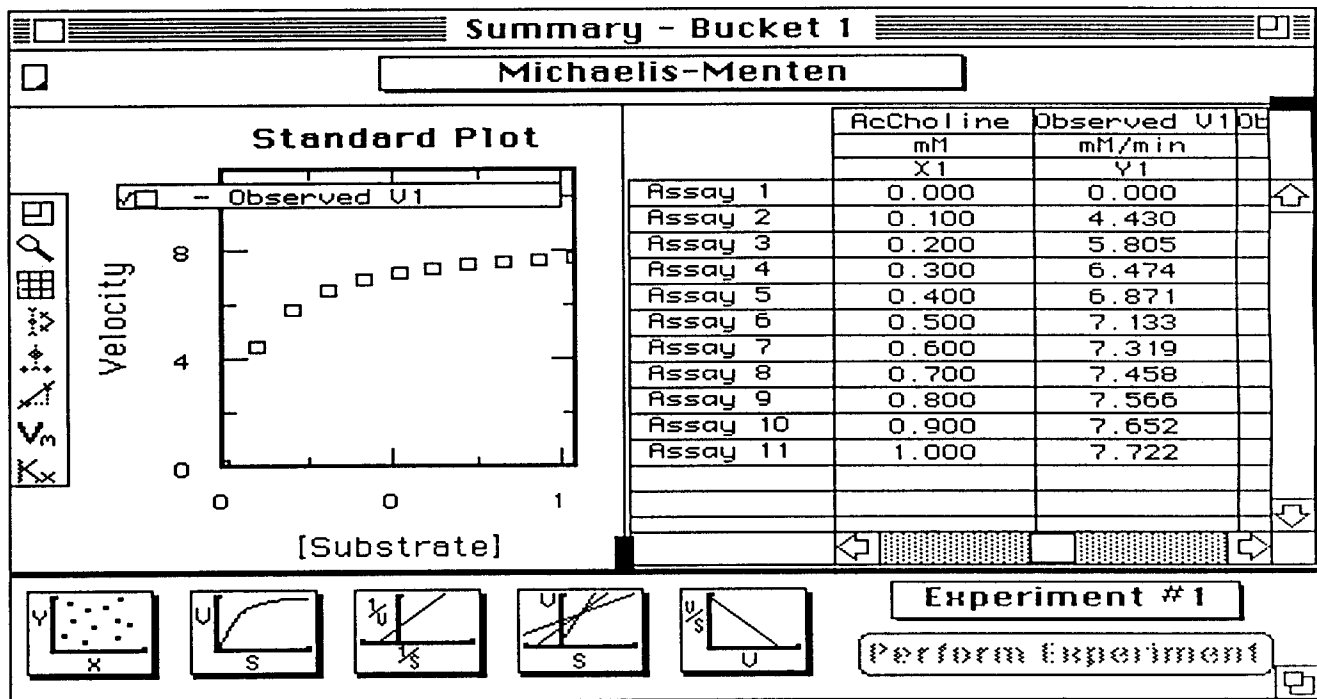


Figure 8. Screen shot of RateIt!

Pharmacokinetic Software: listing & links:

<http://www.cpb.uokhsc.edu/pkin/soft.html>

Models and Math pages (Lance Hahn @ UPenn):

Michaelis-Menten Function:

<http://retina.anatomy.upenn.edu/~lance/modelmath/michaelis.html>

Relevant BioQUEST modules:

Gilbert, Don. (1996). "Enzyme Kinetics." *The BioQUEST Library IV*:(Support Materials Archive): University of Maryland - College Park.

Place, Allen and Tom Schimdt. (1996) "RateIt!" *The BioQUEST Library IV*:(Candidate Collection): University of Maryland - College Park.

Other Software: The software package "Lenora" for IBM PC compatible computers is designed expressly for fitting enzyme kinetic data. It is included on a disk in: Athel Cornish-Bowden. (1995). *Analysis of Enzyme Kinetic Data*. Oxford University Press: Oxford, United Kingdom.

VIII: Allometry: e.g., MacArthur-Wilson Theory of Island Biogeography Species-Area Law

The relationship between size and shape is perhaps the simplest of all equations to have had a major importance in biology and has been commented upon since Galileo, who argued that if you enlarged a mouse to the size of an elephant, it would not have skinny legs like a mouse but stout legs like an elephant to support the mass because mass increased according to the cube of the linear dimensions. D'Arcy Thompson's *On Growth and Form* (1917) and J. B. S. Haldane's (1928) essay *On Being the Right Size* are two of the most famous examples of the biological application of this concept. In the 1930's and 1940's Huxley and others popularized the investigation of allometry in embryonic growth. More recently Niklas (1994) has made an industry of understanding allometric relationships in the biomechanical constraints on plants. Most recently, West, Brown, and Enquist (1997) have developed "a general model for the origin of allometric scaling laws in biology" based on fractal geometry (Williams 1997). However, after the suggestion of Ethel Stanley, I'll stress a different allometric relationship which has received considerable attention as a level above the individual organism, namely, ecology. Robert H. MacArthur and Edward O. Wilson developed a theory of island biogeography in 1967 which simply stated an allometric relationship between the diversity of species that could survive in a region with the size of that region. They plotted this relationship for the disappearance of habitat in various archipelago and the famous recolonization of the Krakatau Islands. Earth First and other environmental activist organizations have widely adopted this hypothesis in their arguments to preserve much larger habitats than the small regions where "charismatic megafauna" are sighted. Even much of the professional biodiversity literature has maintained the theory of island biogeography while modifying it with fractal measures of areas in order to understand the effects of rough edges which may be more conducive to "weedy species" and whether corridors of many small islands (metaphorically understood as well as literally: forests in cattle lands of the Amazon, mountain islands in the sky, meadows surrounded by tilled land, oases in deserts, etc.) work as well as one large region. David Quammen's

The Song of the Dodo: Island Biogeography in an Age of Extinctions (1996) is one of the best and most recent popularizations of this theory. While Gilbert (1980) had argued that it was premature to base nature conservation on the theory of island biogeography, Harris (1984) pioneered "the use of this theory as an alternative to current practices of timber harvesting" and won the 1986 Wildlife Society Publication Award for his case study.

Allometry Equation: E.g., MacArthur-Wilson Theory of Island Biogeography Species-Area Law

$$S = CA^z$$

S = species

A = area

C = constant

z = allometric exponent

References:

- Bonner, John Tyler. (1988). *The Evolution of Complexity: by means of natural selection*. Princeton University Press: Princeton, New Jersey.
- Brown, J. H., and A. C. Gibson. (1983). *Biogeography*. C. Mosby Co.: London, United Kingdom.
- Brown, J. H., and M. V. Lomolino. (1989). Independent discovery of the equilibrium theory of island biogeography." *Ecology* 70(6):1954-1957
- Calder, III, William A. (1984). *Size, Function, and Life History*. Harvard University Press: Cambridge, Massachusetts.
- Campbell, Paul Jude. (1988). "Growth and form: Logarithmic plots and allometry," in Solomon Garfunkel and Lynn A. Steen, editors, *For All Practical Purposes: Introduction to Contemporary Mathematics*. W. H. Freeman and Company: New York, New York, p. 281-283.
- Gilbert, F. S. (1980). "The equilibrium theory of island biogeography: fact or fiction?" *Journal of Biogeography* 7: 209-235.
- Goldman, Corey A., Richard R. Snell, Jeffrey J. Thomason, and David Bartholomew Brown. (1990.) "Principles of allometry." In Corey A. Goldman, editor, *Tested Studies for Laboratory Teaching: Proceedings of the Eleventh Workshop/Conference of the Association for Biology Laboratory Education (ABLE)*. Carolina Biological Supply Company: Burlington, North Carolina.
- Goss, Richard J. (1964). *Adaptive Growth*. Logos Press, Limited: London, England.
- Haldane, J. B. S. (1928). [1985 (reprint edition)]. *On Being the Right Size*. John Maynard Smith, editor. Oxford University Press: Oxford, Great Britain.
- Harris, Larry D. (1984). *The Fragmented Forest: Island Biogeography Theory and the Preservation of Biotic Diversity*. University of Chicago Press: Chicago, Illinois.
- Huxley, Julian. (1972). *Problems of Relative Growth*. Dover Publications, Inc.: New York, New York.
- Jolicoeur, P. (1963). "The multivariate generalization of the allometry equation." *Biometrics* 19: 497-499.
- Levin, Simon A. (1993). "The Problem of Scale in Ecology." AMS-MAA Joint Lecture Series (Videotape), the American Mathematical Society: Providence, Rhode Island. ISBN 0-8218-8081-0.
- MacArthur, R. and E. O. Wilson. (1967). *The Theory of Island Biogeography*. Princeton University Press: Princeton, New Jersey.
- McMahon, Thomas A. and John Tyler Bonner. (1983). *On Size and Life*. Scientific American Books, Inc.: New York, New York.
- Niklas, Karl J. (1994). *Plant Allometry: The Scaling of Form and Process*. University of Chicago Press: Chicago, Illinois.
- Quammen, David. (1996). *The Song of the Dodo; Island Biogeography in an Age of Extinctions*. Scribner: New York, New York.
- Ransom, Robert. (1981). *Computers and Embryos: Models in Developmental Biology*. John Wiley & Sons, Ltd.: Chichester, Great Britain.
- Reiss, M. J. (1991). *The Allometry of Growth and Reproduction*. Cambridge University Press: Cambridge, Great Britain.
- Rosenzweig, Michael L. (1995). *Species Diversity in Space and Time*. Cambridge University Press; Cambridge, United Kingdom.
- Sarkar, Sahotra. (1996). "Ecological theory and anuran declines." *BioScience* 46(3): 199-207.
- Shafer, Craig L. (1991). *Nature reserves: Island theory and conservation practice*. Smithsonian Institution Press: Washington, D.C.
- Schmidt-Nielsen, Knut. (1984). *Scaling: Why Is Animal Size So Important?* Cambridge University Press: New York, New York.
- Thompson, D'Arcy Wentworth. (1942, 1917 [Reprinted Dover, 1992 unabridged]). "On Growth and Form. The Complete Revised Edition." Dover Publications, Inc.: New York, New York.
- Villa, F., O. Rossi, and F. Sartore. (1992). "Understanding the role of chronic environmental disturbance in the context of island biogeographic theory." *Environmental Management* 16:653-666.
- Villa, F., F. Sartore, and O. Rossi. (1991): "Ecological factors and the shape of the species-area relationship: a simulation study." *Atti della Società Italiana di Ecologia (S.It.E.)* 12: 891-896.
- West, Geoffrey B., James H. Brown, and Brian J. Enquist. (1997). "A general model for the origin of allometric scaling laws in biology." *Science* 276(5309):122-126 (4 April).

- Williams, Nigel. (1997). "Fractal geometry gets the measure of life's scales." *Science* 276(5309):34 (4 April).
- Wilson, E. O. and W. H. Bossert. (1971). "Biogeography: Species Equilibrium Theory." *A Primer of Population Biology*. Sinauer: Sunderland, Massachusetts, p.166-184.
- Zimmerman, B. L., and R. O. Bierregaard. (1986). "Relevance of the equilibrium theory of island biogeography and species-area relations to conservation with a case from Amazonia." *J. Biogeography* 13:133-143.

Relevant Web Pages:

Ferdinando Villa, Department of Environmental Sci-

ences, University of Parma, Viale delle Scienze, 43100 Parma, Italy, villa@eagle.bio.unipr.it, also has a nice web write-up on island biogeography: <http://eagle.bio.unipr.it/cv/cv.villa/node10.html>

Galapagos and Island Biogeography web tak:

<http://erasmus.biol.csufresno.edu/isbio.txt>

Bibliography on island biogeography:

<http://erasmus.biol.csufresno.edu/isbib.txt>

Relevant BioQUEST module:

Center for Polymer Studies, Boston University. (1996) "Fractal Dimension." *The BioQUEST Library IV: (Candidate Collection)*; University of Maryland - College Park.

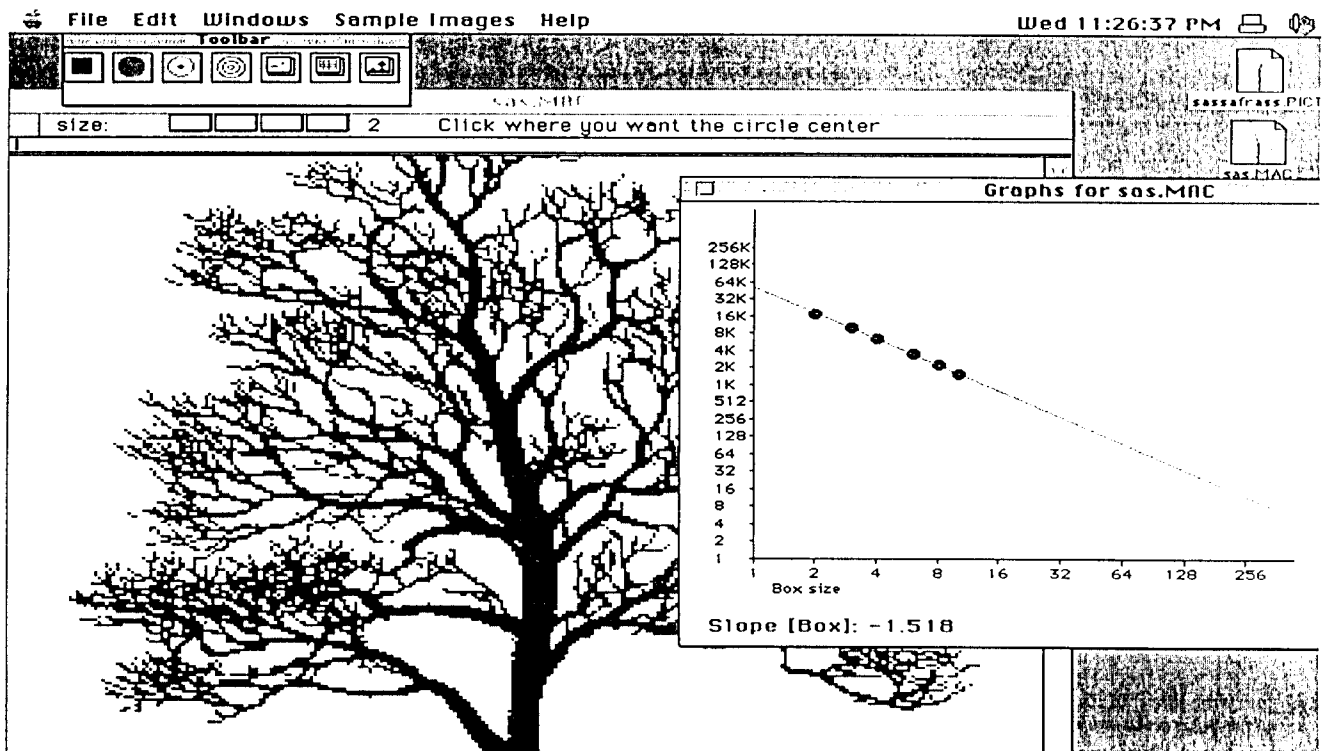


Figure 9. Fractal Dimension of a Tree Image.

IX: Hypothesis Testing: Luria-Delbrück Fluctuation Test for Mutations in Viruses

Perhaps no more normative practice of twentieth century biology exists than the notion of hypothesis testing within the context of statistical fiducial levels set ahead of time; e.g., a 5% level or less chance that the results would be expected on the basis of chance alone. While statistics often has an uneasy home in some mathematics departments, most biologists see statistics as one of the most crucial aspects of their students' education. However, when you try to pin biologists down, many are uneasy with statistical tests as the final arbiter of crucial hypotheses unless the chance of a hypothesis being rejected is beyond the level of belief (e.g. 10^{-20}). In an extended analysis of Fisher's statistical reasoning, Howson and Urbach (1989) conclude:

that one cannot derive scientifically significant conclusions from the type of information which the Fisher and Neyman-Pearson theories regard as adequate. We shall also see that in order to match significance testing with scientific practice, extra principles need to be imported, and that these involve the personal judgment of the experimenter or statistician. Hence, the much-vaunted objectivity of the classical approach is spurious ..." (p. 130).

On the other hand, my personally favorite experiment in twentieth century biology is the Luria-Delbrück Fluctuation Test of teleology in evolutionary biology. It applied the Poisson distribution to rule out Lamarckian premises and to estimate mutation rates quantitatively. Luria and Delbrück shared the 1969 Nobel Prize in Physiology and Medicine. I was delighted to see that the popular general biology textbook author, George Johnson (1996) of Washington University in Saint Louis, also identified it in his list of most significant experiments. In an obituary for Delbrück (*Trends in Biochemical Sciences* May 1981), an anonymous editor reinforced the importance of this classic paper:

“Just as the birth of genetics is considered to have taken place in 1865 upon the appearance of Gregor Mendel’s paper reporting the conclusions he had drawn from his crosses of the garden pea, so the birth of bacterial genetics can be dated as of 1943, when Luria and Delbrück published a joint paper in which they showed that the variants in cultures of phage-resistant variants in cultures of phage-sensitive bacteria represented the selection of spontaneous bacterial mutants. This conclusion was contrary to the then current teachings of bacteriology, which, according to Luria, were ‘the last stronghold of Lamarckism.’ Luria and Delbrück were not the first to study bacterial mutation, any more than Mendel was the first to cross plants for the study of heredity. But with their paper Luria and Delbrück did for bacterial genetics what Mendel had done for general genetics - namely, showed for the first time what kind of experimental arrangements, what kind of data analysis, and, above all, what kind of sophistication was needed for obtaining meaningful and unambiguous results.”

The Luria-Delbrück Fluctuation Test has recently been the subject of further mathematical exploration as well as being under attack by a new round of “neo-neo-Lamarckians” who have argued that mutagenesis can be directed and advantageous for a population under stress. Richardson (1994), Keller (1992), and Sarkar (1991b) provide accounts of the controversy between Darwinists like Lenski, Levin, and Stahl with challengers like Cairns, Shapiro, Rosenberg, and Hall. With stakes the likes of Darwin and Lamarck, this revived controversy is great fun for students to follow and learn why controversy is often considered the lifeblood of science. Also, this example illustrates well how experiments are reinterpreted much later in light of new theories and experiments.

Luria-Delbrück Fluctuation Test Equation for Poisson Process:

$$p \text{ (proportion of zero class)} = e^{-\mu n}$$

μ =mutation rate

n =population size

References:

- Armitage, P. (1952). “The statistical theory of bacterial populations subject to mutation.” *J. Roy. Stat. Soc. B.* 4:1-40.
- Armitage, P. (1953). “Statistical concepts in the theory of bacterial mutation.” *J. Hygiene* 51:162-184.
- Cairns, J., J. Overbaugh, and S. Miller. (1988). “The origin of mutants.” *Nature* 335:142-145.
- Galitski, T., and J. Roth. (1995). “Evidence that F plasmid transfer replication underlies apparent adaptive Mmutation.” *Science* 268:421-423.
- Howson, Colin, and Peter Urbach. (1989). *Scientific Reasoning The Bayesian Approach*. Open Court: La Salle, Illinois.
- Johnson, George. (1996). *How Scientists Think: Twenty-One Experiments that Have Shaped Our Understanding of Genetics and Molecular Biology*. _____? _____
- Keller, Evelyn Fox. (1992). “Between language and science: The question of directed mutation in molecular genetics.” *Perspectives in Biology and Medicine* 35(2):292-306.
- Kimmel, M. and D.E. Axelrod. (1994). “Fluctuation test for two-stage mutations: Applications to gene amplification.” *Mutation Res.* 306:45-60.
- Koch, A. L., (1982). “Mutation and growth rates from Luria-Delbrück fluctuation tests.” *Mutation Research* 95:129-143.
- Lea, D. E. and C. A. Coulson. (1949). “The distribution of the numbers of mutants in bacterial populations.” *J. Genetics* 49:264-285.
- Levin, B.R., D. M. Gordon, and F. M. Stewart. (1993). “The origin of mutations: mundane processes can account for departures from Luria-Delbrück expectations.” [in preparation]
- Luria, S. and M. Delbrück. (1943). “Mutations of bacteria from virus sensitivity to virus resistance” . *Genetics* 28:491-511.
- Ma, W.T., S. Sarkar, and G. vH. Sandri. (1992). “Analysis of the Luria-Delbrück distribution using discrete convolution power.” *J. Applied Probability* 29: 255-267.
- Radicella, J., P. Park, and M. Fox. (1995). “Adaptive mutation in *Escherichia coli*: A role for conjugation.” *Science* 268:418-420.
- Richardson, Sarah. (1994). “Survival of the mutable: In which the ghost of that oft-reviled ancestor, Jean-Baptiste Lamarck, returns to trouble the sleep of neo-Darwinian evolutionists.” *Discover* 15(4): 27-228 (September).

Sarkar, Sahotra. (1991). "Haldane's solution of the Luria-Delbrück distribution." *Genetics* 127: 257-261.

Sarkar, Sahotra. (1991). "Lamarck contre Darwin, reduction versus statistics: Conceptual issues in the controversy over directed mutagenesis in bacteria." In A. I. Tauber, editor, *Organism and the Origin of Self*. Princeton University Press: Princeton, NJ.

Sarkar, S., W.T. Ma, and G. vH. Sandri. (1992). "On fluctuation analysis: a new, simple and efficient method for computing the expected number of bacterial mutants." *Genetica* 85:173-179.

Stewart, Frank M. (1994). "Fluctuation tests: how reliable are the estimates of mutation rates?" *Genetics* 137(4):1139-1146 (August).

Stewart, Frank M., David M. Gordon, and Bruce R. Levin. (1990). "Fluctuation analysis: the probability distribution of the number of mutants under different conditions." *Genetics* 124:175-185.

Stewart, Frank M. (1992). *DataFit (Macintosh software for analyzing Luria-Delbrück fluctuation tests)*. Department of Mathematics, Brown University, Providence, Rhode Island.

Thompson, W. A. (1988). *Point Process Models with Applications to Safety and Reliability*. Chapman and Hall: London. See p. 83: "The Luria-Delbrück Model" and problem set on p. 88.

Relevant WWW sites:

Luria and Delbruck/ Benzer/ Poisson:
<http://www.life.uiuc.edu/micro/316resources/problems/mutations/poisson/>
 "Important Experiments in Life Science Field"
http://life.nthu.edu.tw/~mjhsieh/Biology/experiment/fluct_test.html

References on adaptive mutation:

http://helix.biology.mcmaster.ca/4d3/direct_mut.html
 The Poisson Distribution in Biology: ABC '95, a Biological Sciences Web Page, W. R. McClure, wm0p+@andrew.cmu.edu, Department of Biological Sciences, Carnegie Mellon University
<http://info.bio.cmu.edu/courses/abc/ABC95Poisson/ABC95PoissonPage.html>
 The Impact of Biology on Mathematics:
<http://www.gdb.org/Dan/mathbio/1.html>

Relevant BioQUEST modules:

Calley, John N., and John R. Jungck. (1996). "Microbial Genetics Construction Kit (μ GCK)." *The BioQUEST Library IV*: (Candidate Collection): University of Maryland - College Park.

Hornbach, Daniel. (1996). "Biometrics." *The BioQUEST Library IV*: (Candidate Collection): University of Maryland - College Park.

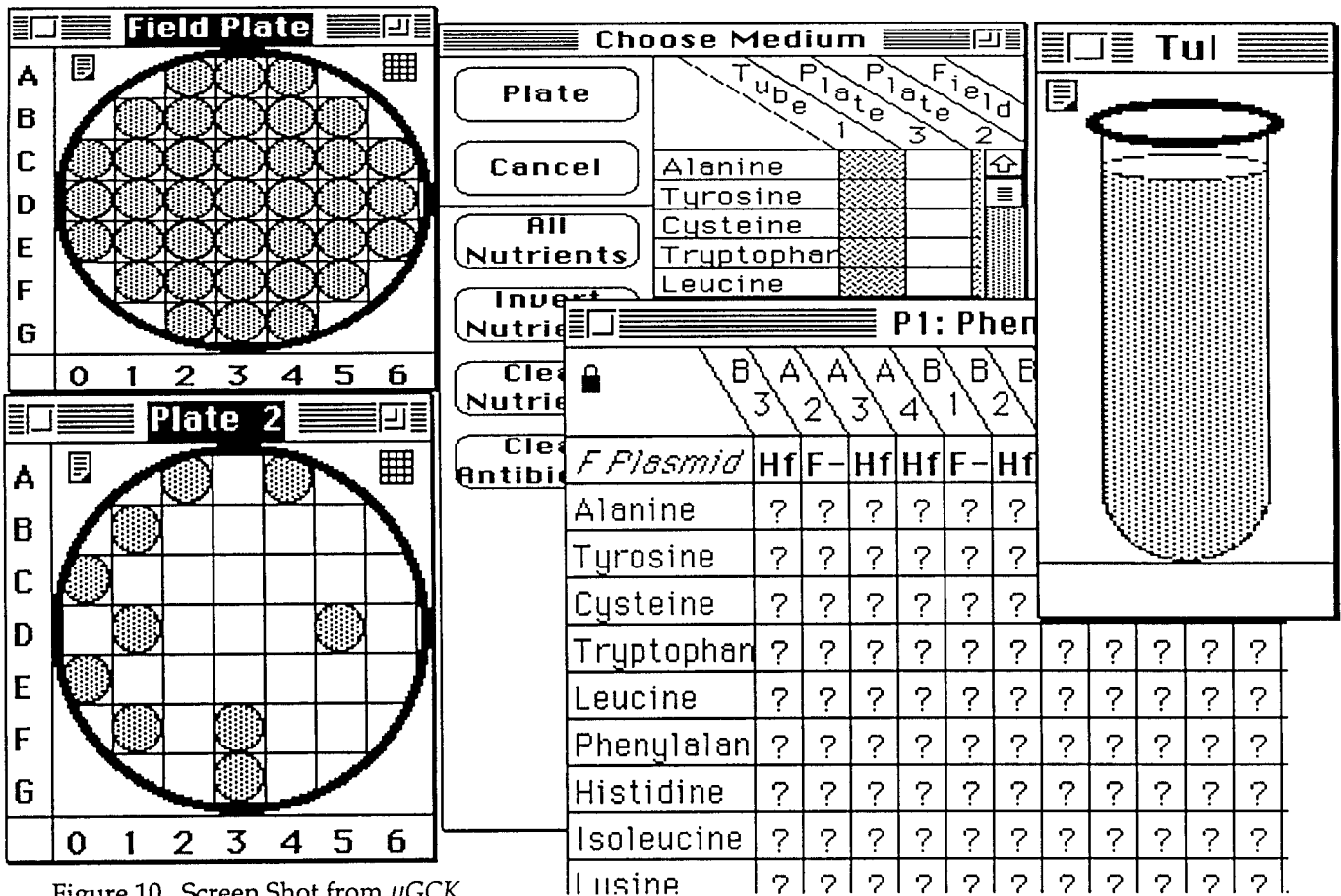


Figure 10. Screen Shot from μ GCK.

X. Genetic Coding: Crick-Griffith-Orgel Comma-free Coding Theory for the Adaptor Hypothesis

One of the greatest ironies of scientific exploration is generating a significant hypothesis based on improper inference or invalid data. For example, Stephen Jay Gould (1996) noted that Charles Darwin's development of the theory of natural selection had made an improper inference:

For those who still cherish the myth that fact alone drives any good theory, I must point out that Darwin, at his key moment of insight - making his analogy from geography to time and evolution - was quite wrong in his example. *Macrauchenia* is not, after all, an ancestor (or even a close relative) of guanacos, but a member of a unique and extinct South American mammalian group, the Litopterna.

This is not only a phenomena of the past century, but our own as well. In their contribution to generating a theory of genetic coding, Crick, Griffith, and Orgel (1957) made a critical mistake of fact: there are not twenty amino acid words (codons) because the maximal number of comma-free code words is twenty because genetic coding does not use a comma-free mechanism; however, for the wrong reasons they predicted that genetic coding is dependent upon an adaptor molecule of nucleic acid that carries an amino acid and is recognized by a three nucleotide site in messenger RNA. We now know this adaptor molecule as transfer RNA and their work ascribed a function to a series of heterogeneous molecules heretofore referred to simply as "soluble RNA." "Poor analogy, good idea." Crick *et al.* (1961) corrected themselves in an important theoretical paper in which they asserted that the standard genetic code is commaless rather than comma-free, has sixty four not twenty codons, is degenerate, starts from a fixed point and then reads a contiguous and continuous sequence. Their second paper explained frameshift as well as point mutations and made suggestions for the elucidation of genetic coding. However, even here, their enthusiasm exceeded reality because they predicted that: "If the coding ratio is 3, as our results suggest, and if the genetic code is the same throughout Nature [sic], then the genetic code may well be solved within a year." Most historians would argue that it took until 1966 before sufficient words were exhaustively scrutinized such that all sixty-four codons were assigned with textbook certainty and we now know that "the genetic code is [NOT] the same throughout Nature." Crick, Griffith, and Orgel (1957) contributed critically to our understanding by generating a hypothesis that enabled us to interpret and design a large number of experiments that was respected even by geneticists and biochemists skeptical of mathematics. Interestingly, both biochemists (Hoagland 1996) and philosophers (Sarkar 1996) have tried to trivialize the role that theory played and in so doing express deep concerns about the expectations of "theory" by both. Personally, I have been concerned with genetic codes as codes for a long time and have shown how Crick, Griffith, and Orgel's (1957) work can be used to understand another problem (Jungck, 1984), namely, the origins of genetic codes, and Shepherd (1981) has developed a pragmatic set of tools based on comma-free codes that are commonly used in nucleic acid sequence analysis packages to predict reading frame.

Equation for comma-free codes:

$$W_k(n) \leq \frac{1}{k} \sum_{d/k} \mu(d) n^{k/d}$$

$W_k(n)$ = number of comma-free
code k-letter words with alphabet n
 $\mu(d)$ = Möbius function
summation is extended over all divisors d of k

References:

- Bertman, Martha O., and John R. Jungck. (1977). "Some unresolved mathematical problems in genetic coding." American Mathematical Society Symposium: Some Mathematical Questions in Biology, American Association for the Advancement of Science annual meeting, Washington, D.C., Abstract No. 184; also, *Notices of the American Mathematical Society* 25(1): A-174 (Bio 78-3), (January, 1978).
- Bertman, Martha O., and John R. Jungck. 1979. "Group graph of the Genetic Code." *Journal of Heredity* 70: 379-384.
- Cedergren, Robert and Pedro Miramontes. (1996). "The puzzling origin of the genetic code." *Trends in the Biochemical Sciences (TIBS)* 21(6): 199-200.
- Crick, Francis H. C., J. S. Griffith, and Leslie E. Orgel. (1957). "Codes without commas." *Proceedings of the National Academy of Sciences US* 43: 416-421.
- Crick, Francis H. C., Leslie Barnett, Sydney Brenner, and R. J. Watts-Tobin. (1961). "General nature of the genetic code for proteins." *Nature* 192(4809): 1227-1232 (December 30).
- Gould, Stephen Jay. (1996). "Why Darwin?" *The New York Review of Books* XLIII (6): 12 (April 4).
- Hoagland, Mahlon. (1996). "Biochemistry or molecular biology? The discovery of 'soluble RNA'." *Trends in the Biochemical Sciences (TIBS)* 21: 77-80.
- Jimenez-Montano, Miguel A., Carlos R. de la Mora-Basanez, and Thorsten Pöschel. (1995). "On the hypercube structure of the genetic code." In Hwa

A. Lim and Charles R. Cantor, editors, *Bioinformatics and Genome Research*. World Scientific: Singapore, p. 445.

Jimenez-Montano, Miguel A., Carlos R. de la Mora-Basanez, and Thorsten Pöschel. (1997). "The hypercube structure of the genetic code explains conservative and non-conservative amino acid substitutions *in vivo* and *in vitro*." *BioSystems* (in press).

Jungck, John R. (1977). "Complementarity and Coding." *Journal of College Science Teaching* 7: 27-28.

Jungck, John R. (1978). "The genetic code as a periodic table." *Journal of Molecular Evolution* 11: 211-224.

Jungck, John R. (1984). "The adaptationist programme in molecular evolution. The origins of genetic codes." Pp. 345-364 in K. Matsuno, K. Dose, K. Harada, and D. L. Rohlfsing, eds., *Molecular Evolution and Protobiology*, Plenum Press: New York.

Jungck, John R. (1985). "Mendel, Mendeleev and Me: Teaching's Impact Upon Research." *American Biology Teacher* 47(4): 197-201.

Jungck, John R., and Robert M. Friedman. (1984). "Mathematical Tools for Molecular Genetics Data: An Annotated Bibliography." *Bulletin of Mathematical Biology* 46(4): 699-744.

Osawa, Syozo. (1995). *Evolution of the Genetic Code*. Oxford University Press: Oxford, UK.

Ratner, Vadim A., Andrey A. Zharkikh, Nikolay Kolchanov, Sergey N. Rodin, Viktor V. Solovyov, and Andrey S. Antonov. (1996). *Molecular Evolution*. Biomathematics Volume 24. Springer-Verlag:

New York. See chapter 3.2: "Noise immunity of the genetic code and texts," pp. 44-50.

Sarkar, Sahotra. (1996). "Decoding 'coding' - information and DNA." *BioScience* 46(11): 857-864.

Shepard, J. C. (1981). "Method to determine the reading frame of a protein from the purine/pyrimidine genome sequence and its possible evolutionary justification." *Proceedings of the National Academy of Sciences USA* 78:1596-1600.

Relevant WWW sites:

The Impact of Mathematics on Cellular and Molecular Biology:
<http://www.gdb.org/Dan/mathbio/2.html>
in silico biology: Computational Molecular Biology and Molecular Bioinformatics (contains many links and bibliographies):
<http://juno.ucsd.edu/~sje/thailand.html>
 Computational Biology in the UW-Madison CS Dept.:
<http://www.cs.wisc.edu/~shavlik/uwcompbio.html>

Relevant BioQUEST modules:

Bergland, Mark. (1996). "DNA Electrophoresis." *The BioQUEST Library IV*:(Extended Learning Resources): University of Maryland - College Park.

Gilbert, Don. (1996). "SeqApp, SeqPup, Dotty Plotter, GelFragSizer, GenBank Search, and LoopDLoop/LoopViewer" *The BioQUEST Library IV*:(Support Materials Archive): University of Maryland - College Park.

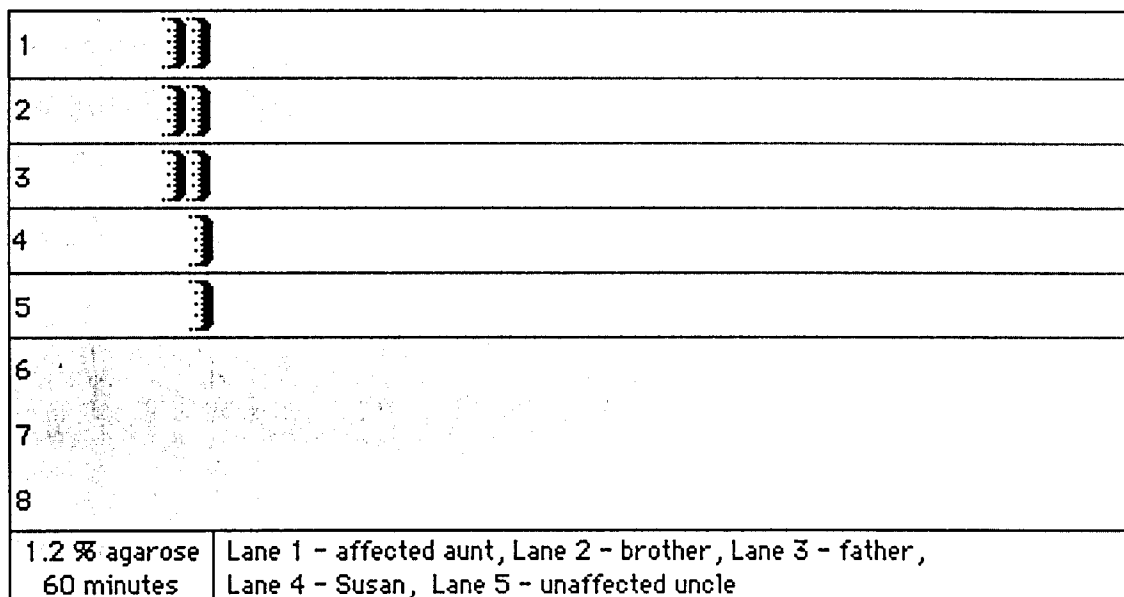


Figure 11. DNA Electrophoresis screen shot.

Conclusions:

The best aspect of these ten equations in terms of their roles in the foundations of twentieth century biological research is that it was so difficult narrowing the list to ten. If I have made the case for any one of these equations' importance to an area of biology that you teach or an area about which you strongly feel that twenty-first century biology students should know something about, then I hope that you will help us address the need for much more mathematics in general biology education. Not only do I believe that students deserve the respect that this curricular move would make, but I believe that it would be a fun challenge for ourselves in terms of professional and personal growth. Please revisit Steen and Albers's (1981) questions quoted herein on page 15 and see whether you agree that: (1) applications should play a role in mathematics curricula, (2) that the traditional division between mathematics and science instruction is invalid, and (3) that mathematical topics can be related to cultural issues that are relevant to students. If I have not convinced you that these are appropriate responses to their questions, then I urge you to read Simon A. Levin's introduction to the one hundredth volume in the series of books that he has edited on mathematical biology:

Mathematical biology has changed a great deal in the last decade, mainly for the better. Whereas twenty years ago, it was peripheral to many subdisciplines of biology, its success is marked today by ever increasing integration into areas of application. Mathematical biologists, who once found in each other the most eager listeners and constructive critics, now see their work guiding experiments, and shaping the conceptual foundations of almost all areas of biology. Indeed, in some areas, the integration is so complete that there are no clear distinctions between theoretician and experimentalist: every respectable researcher must be a little of each. And in areas where that is not yet true, it will be so within a decade more. (Levin 1994)

As we enter the next century, can we afford to continue to offer biology curricula so distinctly removed from contemporary research practices, from important historical foundations, and cultural issues that all would be so much better informed by greater familiarity with mathematical beauty, utility, and robustness?

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General Bibliography:

- Blystone, Robert and Rick Cooper. (1996). Presentation at Iowa State University, May; transcript available from the authors.
<http://www.math.iastate.edu/mbconf/>
- Casti, John L. (1996). *Five Golden Rules: Great Theories of 20th-Century Mathematics – and Why They Matter*. Wiley-Interscience: New York, New York.
- Changeux, Jean-Piere and Alain Connes. (1995). *Conversations on Mind, Matter, and Mathematics*. (Translation from the French by M. B. DeBevoise). Princeton University Press: Princeton, New Jersey.
- Edelstein-Keshet, Leah. (1988). *Mathematical Models in Biology*. Random House: New York, New York.
- Fritzsche, Harald. (1994). *An Equation That Changed the World: Newton, Einstein, and the Theory of Relativity* (which had appeared initially in German in 1988 as *Eine Formel verändert die Welt: Newton, Einstein und die Relativitätstheorie*, R. Piper GmbH & Co., KG: München). University of Chicago Press: Chicago, Illinois.
- Gross, Louis J. (1994). "Quantitative training for life-science students," *BioScience* 44(2):59.
- Gross, Louis J. (1996). Presentation at Iowa State University, May; transcript available from the author.
<http://www.math.utk.edu/~gross/quant.lifesci.html>
- Guillen, Michael. (1983). *Bridges to Infinity: The Human Side of Mathematics*. Jeremy P. Tarcher, Inc.: Los Angeles, California.
- Guillen, Michael. (1995). *Five Equations that Changed the World: The Power and Poetry of Mathematics*. Hyperion: New York, New York.
- Hughes-Hallett, Deborah, Andrew M. Gleason, Daniel E. Flath, Sheldon P. Gordon, David O. Lomen, David Lovelock, William G. McCallum, Brad G. Osgood, Andrew Pasquale, Jeff Tecosky-Feldman, Joe B. Thrash, Thomas W. Tucker, and Otto K. Bretscher. (1994). *Calculus* (Produced by the Consortium based at Harvard and funded by a National Science Foundation Grant). John-Wiley and Sons: New York, New York.
- Jungck, John R. (1997). "BIOLOGICAL AFTERMATH: What can we learn from contemporary mathematics reform?" *BioQUEST Notes* 2(2):1, 8-13 (Spring).
- Jungck, John R., Virginia Vaughan, Patti Soderberg, Ethel Stanley, John Calley, Jim Stewart, and Nils Peterson. (1996). *The BioQUEST Library Volume IV*. ePress Project: University of Maryland, College Park, Maryland.
- Keller, Evelyn Fox, and Lee A. Segel. (1970). "Initiation of slime mold aggregation viewed as an instability." *Journal of Theoretical Biology* 26:399-415.
- Keller, Evelyn Fox, and Lee A. Segel. (1971). "Traveling bands of chemotactic bacteria: a theoretical analysis." *Journal of Theoretical Biology* 30:235-248.
- Lancaster, Henry Oliver. (1994). *Quantitative Methods in Biological and Medical Sciences: A Historical Essay*. Springer-Verlag: New York, New York.
- Levin, Simon A. (1994). *Frontiers in Mathematical Biology*. Lecture Notes in Biomathematics Volume 100. Springer-Verlag: Berlin, Germany, p. ix.
- Salem, Lionel, Frédéric Testard, and Coralie Salem. (1992). *The Most Beautiful Mathematical Formulas*. John Wiley and Sons: New York, New York.
- Smith, David and Lawrence C. Moore. (1996). *Calculus: Modeling and Application*. Houghton Mifflin Company: Boston, Massachusetts.
- Steen, Lynn Arthur and Donald J. Albers, editors. (1981). *Teaching Teachers, Teaching Students: Reflections on Mathematical Education*. The Fourth International Congress on Mathematical Education. Birkhäuser: Boston, Massachusetts, p. viii.
- Thompson, D'Arcy Wentworth. (1917). *On Growth and Form*. Reprint 1961: Cambridge University Press: London, United Kingdom.
- Willis, Delta. (1995). *The Sand Dollar and the Slide Rule: Drawing Blueprints from Nature*. Addison-Wesley: Reading, Massachusetts.
- Wilson, Robin. (1997). "A decade of teaching 'Reform Calculus' has been a disaster, critics charge." *The Chronicle of Higher Education* XLIII(22):A12-A13

Sources on Mathematics Reform:

Project CALC (Smith and Moore, 1996),

<http://www.math.duke.edu/faculty/moore/pcalc.html>

<http://141.224.128.4/pkal/resources/ptw/duke.html>

<http://www.math.duke.edu/researchd/smith/smith.html>

<http://www.mathsource.com/cgi-bin/MathSource/Applications/Education/Calculus/0202-745>

Harvard-Calculus Overview

<http://archives.math.utk.edu/projnext/summaries/harvardCalculus.html>

<http://www.mat.ufrgs.br/~portosil/harvard.html>

<http://alan.sewanee.edu:8080/sc/links.html>
(provides 18 links on this project)

Lazarowitz and Uhl have developed a course entitled BioCalc at the University of Illinois - Champaign-Urbana wherein they have almost completely done away with lectures and have a series of *Mathematica*TM notebooks with biologically informed calculus education projects

<http://www.life.uiuc.edu/micro/lazarow.html>

Calculus&Mathematica

<http://www-cm.math.uiuc.edu/>

<http://www-cm.math.uiuc.edu/people/authors/jerry.html>

<http://www.wolfram.com:80/education/colleges/courseware/uhl.html>

Gross' group at the University of Tennessee - Knoxville has collected an enormous set of world wide web resources for a quantitatively based biology curriculum: <http://www.math.utk.edu/~gross/quant.lifesci.html>

The Mathematics Association of America (MAA), led by Wayne Roberts, Project Director, published five volumes (and mailed to every mathematics department in the U.S.!) with copy-able materials for Calculus. These are:

1. A lab book (26 technology-based but platform-independent labs): *Learning by Discovery*, Anita Solow (ed), MAA Notes, volume 27, 1993

2. A book of concept-oriented problems: *Calculus Problems for a New Century*, Robert Fraga (ed), MAA Notes, volume 28, 1993

3. A volume of 18 project-length application based problems from different areas: *Applications of Calculus*, Phil Straffin (ed), MAA Notes, volume 29, 1993

4. A collection of student investigation problems (one page each, and thus shorter than the application problems): *Problems for Student Investigation*, Mike Jackson and John Ramsay (eds), MAA Notes, volume 30, 1993, and

5. A series of readings for Calculus. Resources for Calculus, 5 volume collection: *Readings for Calculus*, Woody Dudley (ed), MAA Notes, volume 31, 1993.

Leitzel, James R. C., and Alan C. Tucker, Editors. (1994). *Assessing Calculus Reform Efforts: A Report to the Community*. Series: MAA Notes. Mathematics Association of America: Providence, RI.

From one of the reviewers

(Jeff Schank - Indiana University):

I just read through the manuscript you sent me, and of course I completely agree with you. The main comment I have is that you have an extremely powerful argument regarding the use of statistics in biology that should be driven home even harder. First, there is virtually no research that can be published these days without the use of statistics, which means choosing one or more statistical models for the data. Every biologist must be able to model, have basic mathematical knowledge of the statistics he or she is using, and understand what assumptions must be satisfied to use the model. Thus, to avoid teaching mathematical ideas in biology is negligent. Second, mathematical modeling in statistics can be just like mathematical modeling biological mechanisms in that one starts with a basic model or linear equation ($Y = Xb + \text{epsilon}$) and then it is elaborated for different experimental designs. Third, by recognizing that using statistics is modeling, I think one can begin to see that there may be other strategies for modeling data (I mean other than standard models in Statistics textbooks) such as doing Monte Carlo simulations. ... Mathematical modeling in teaching is one of the newly emerging threads in the history of modeling in biology.