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Order from Chaos, Fuzzy Logic, and Multi-Valued Medicine

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So far as the laws of mathematics refer to reality, they are not certain. And so far as they are certain, they do not refer to reality.

Albert Einstein
Geometry and Experience

This is what it's all about,
There's always going to be a doubt.

What's up with that?
Rhythmeen, Z. Z. Top

This is to acknowledge that W. C. Yarbrough, MD has no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

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This protocol gives a short introduction to Chaos Theory (see ref. 1) and Fuzzy Logic (3), but does not deal with many examples due to space constraints. References are supplied which deal with specific examples of these concepts in medicine, many of which are discussed, but not shown in the protocol. Please refer to the references for further reading.

Order from Chaos

Nonlinear science is one of a number of emerging methodological and theoretical constructs that make up what is often called the "science of complexity." The popular name for this new science is "chaos theory." The chaos referred to in the theory is not a lack of organization or order but is, instead, a complex state in which apparent randomness of a system is really constrained by a type of order that is **nonlinear**. Chaos is defined as the quality of a **deterministic** mathematical system in which an extreme sensitivity to initial conditions exists.

While chaos is the study of how simple systems can generate complicated behavior; **complexity** is the study of how complicated systems can generate simple behavior. An example of complexity is the synchronization of biological systems, ranging from fireflies to neurons. **Complex systems** are spatially and/or temporally extended nonlinear systems characterized by collective properties associated with the system as a whole, and that are different from the characteristic behaviors of the constituent parts.

The critical principles of this new science are as follows:

- Nonlinear systems can, under certain conditions, display highly chaotic behavior.
- The behavior of a chaotic system can change drastically in response to small changes in the system's initial conditions.
- A chaotic system is deterministic.
- System output is not proportionate to system input.

Introduction to Dynamic Systems

A dynamic system is a set of functions (rules, equations) that specify how variables change over time. One example is shown below:

$x_{new} = x_{old} + y_{old}$

$y_{new} = x_{old}$

This example illustrates a system with two variables, x and y. Variable x is changed by taking its old value and adding the current value of y. And y is changed by becoming X's old value. This is a silly system, but it does show that a dynamic system is any well-specified set of rules.

There are some important distinctions, which are outlined here. Variables that change over time, or are self-referring can be seen as dimensions (see below). This is in contrast to parameters, which are constant through time and are not self-referring. Discrete variables are restricted to integer values. This should be distinguished from continuous variables, which can have non-integer values. Stochastic refers to our usual ideas of probability, one outcome out of many, while deterministic dynamic systems have no random aspect to them (one to one). In the past, stochastic models have been the mathematics of choice to describe the long-term status of dynamical systems.

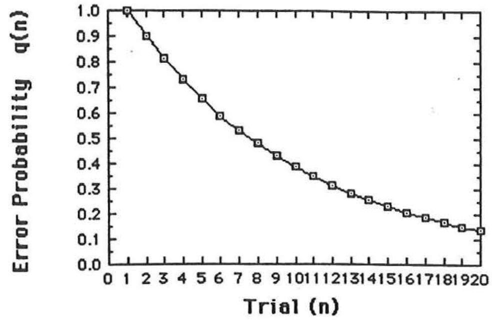
The current **state** of a dynamic system is specified by the current value of its variables, x, y, z, ... The process of calculating the new state of a *discrete(integer)* system is called **iteration**. To evaluate how a system behaves, we need the functions, parameter values, and **initial conditions** or **starting state.** *To illustrate*...Consider a classic learning theory, the *alpha model*, which specifies how q_n, the probability of making an error on trial n, changed from one trial to the next

$\mathbf{q_{n+1} = \beta\, q_n}$

The new error probability is diminished by ß (which is less than 1, greater than 0). For example, let the probability of an error on trial 1 be equal to 1, and ß equal .9. Now we can calculate the dynamics by **iterating** the function, and plot the results.

$q_1 = 1$

$q_2 = \beta q_1 = (.9)(1) = .9$
$q_3 = (.9)q_2 = (.9)(.9) = .81$, etc. ...



Error probabilities for the alpha model, assuming $q_1=1, \beta=.9$.

This "learning curve" is referred to as a time series. Certainly the idea that systems change in time is not new. Nor is the idea that the changes are probabilistic. As we will see, these systems give us:

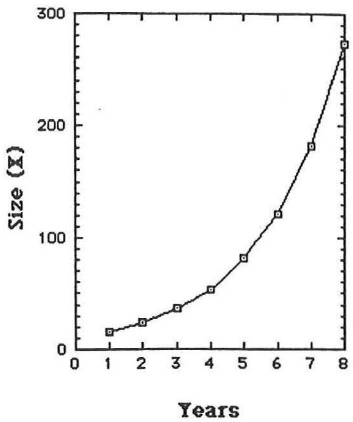
- A new meaning to the term *unpredictable*.
- A different attitude toward the concept of *variability*.
- Some new *tools* for exploring time series data and for modeling such behavior.
- And, some argue, a new *paradigm*.

Nonlinear Dynamic Systems

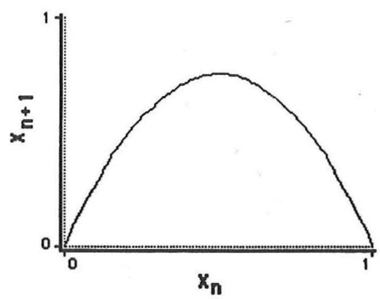
A linear function is one that can be written in the form of a straight line, as in the formula:
$y = mx + b$
where m is the slope and b is the y-intercept.

What's a nonlinear function?

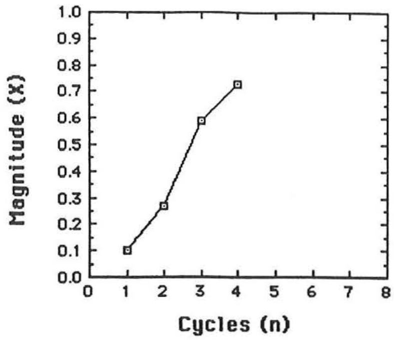
The Alpha model above is a linear model because q_{n+1} is a linear function of q_n. Just because its **output**, the plot of its behavior over time (Figure 1 earlier), is not a straight line doesn't make it a nonlinear system. What makes a dynamic system *nonlinear* is whether the function specifying the change is nonlinear. Not whether its behavior is nonlinear. And y is a nonlinear function of x if x is multiplied by another (non-constant) variable or by itself (that is, raised to some power). We can illustrate *nonlinear* systems using a logistic difference equation. This is a model often used to introduce chaos. The Logistic Difference Equation, or *Logistic Map*, though simple, displays the major chaotic concepts. We start with a model of growth (population, etc.):
$x_{new} = r\,x_{old}$
We can write this like a formula in terms of n:
$x_{n+1} = r\,x_n$.
This says x changes from one time period, n, to the next, n+1, according to r. If r is larger than one, x gets larger with successive iterations if r is less than one, x diminishes. If we set r to be larger than one, say 1.5, then we start year 1 (n=1), with a population of 16 [$x_1=16$], and since r=1.5, each year x is increased by 50%. So years 2, 3, 4, 5, ... have magnitudes 24, 36, 54, ... Our population is growing exponentially. By year 25 we have over a quarter million.



Iterations of Growth model with r = 1.5
Notice that this is a ***linear*** model that produces unlimited growth.
Limited Growth model - Logistic Map.
The Logistic Map can be made to prevent unlimited growth by inhibiting growth whenever it achieves a high level. This is achieved with an additional term, $[1 - x_n]$. The growth measure (x) is also re-scaled so that the maximum value x can achieve is transformed to 1. (So if the maximum size is 25 million, say, x is expressed as a proportion of that maximum.). Our new model is
$\mathbf{x_{n+1} = r\, x_n\, [1 - x_n]}$
[r between 0 and 4.] The $[1-x_n]$ term serves to inhibit growth because as x approaches 1, $[1-x_n]$ approaches 0. Plotting x_{n+1} vs. x_n, we see we have a nonlinear relation.



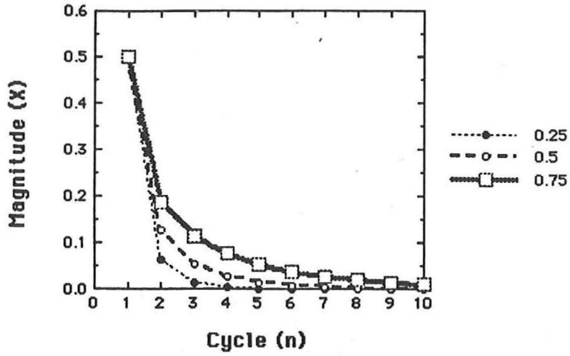
Limited growth (Verhulst) model. X_{n+1} vs. x_n, r = 3.
We have to **iterate this function** to see how it will behave.
Suppose: r=3, and x_1=.1
$x_2 = rx_1[1-x_1] = 3(.1)(.9) = .27$
$x_3 = r\, x_2[1-x_2] = 3(.27)(.73) = .591$
$x_4 = r\, x_3[1-x_3] = 3(.591)(.409) = .725$



Behavior of the Logistic map for $r = 3$, $x_1 = .1$, iterated to give x_2, x_3, and x_4

It turns out that the logistic map gives a very different appearance, depending on the control parameter r. To see this, **we next examine the time series produced at different values of r,** starting near 0 and ending at r=4. Along the way we see very different results, revealing and introducing major features of a chaotic system.

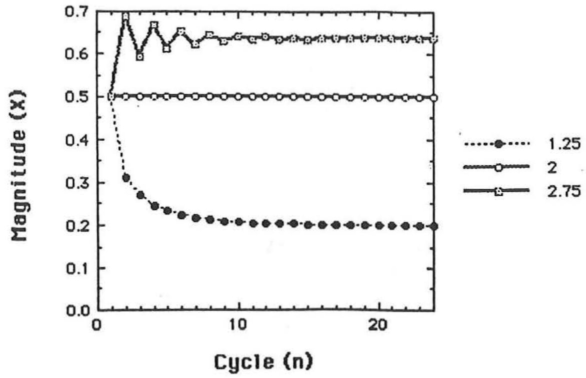
When r is less than 1



Behavior of the Logistic map for r=.25, .50, and .75. In all cases x_1=.5.

The same fate awaits any starting value. So long as r is less than 1, x goes toward 0. This illustrates a **one-point attractor.**

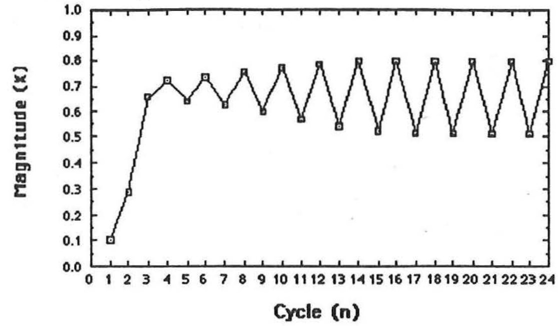
When r is between 1 and 3



Behavior of the Logistic map for r=1.25, 2.00, and 2.75. In all cases x_1=.5.

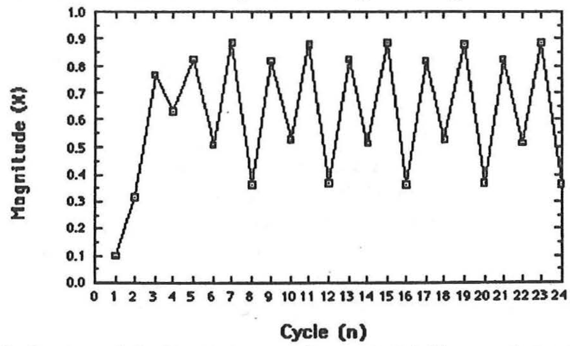
Now, regardless, of the starting value, we have what are called non-zero one-point attractors. In other words, the system settles down to a single value.

When r is larger than 3



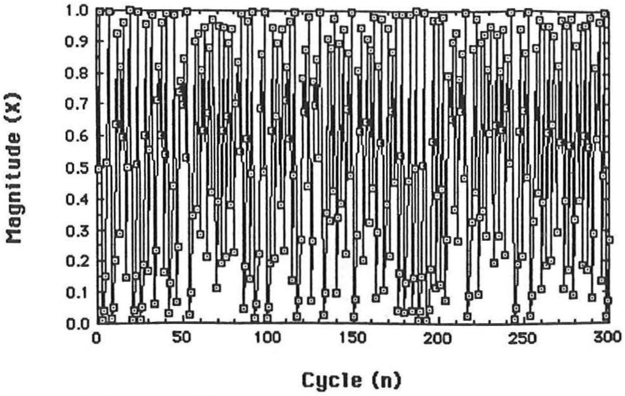
Behavior of the Logistic map for r=3.2.

Moving just beyond r=3, the system settles down to alternating between two points. This is called a *two-point attractor*. This illustrates the concept of a **bifurcation**, or **period doubling**. If we increase the control parameter again, we get another bifurcation.



Behavior of the Logistic map for r= 3.54. Four-point attractor

The concept: an **N-point attractor**. However, if we keep increasing the parameter, we will finally be unable to distinguish the pattern of the attractor. We then consider the map chaotic.

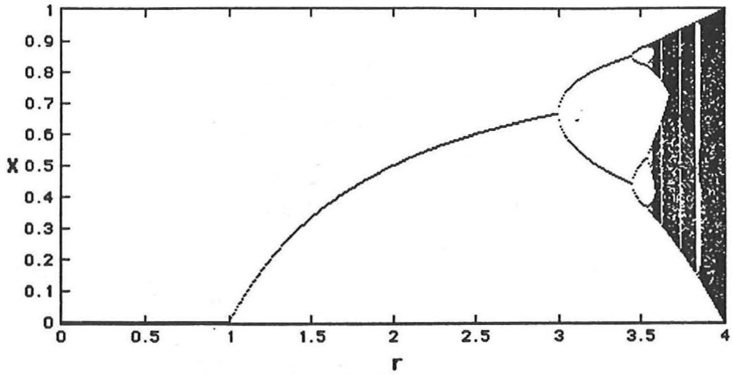


Chaotic behavior of the Logistic map at r= 3.99.

An **attractor** is whatever the system "settles down to". This is a very important concept from nonlinear dynamics: A system eventually "settles down". But what it settles down to, its attractor, need not have 'stability'; it can be very 'strange'.

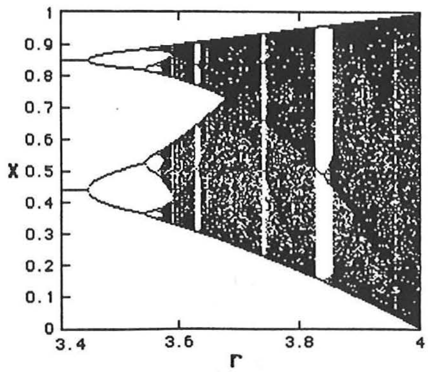
Bifurcation Diagram

A bifurcation is a period-doubling, a change from an N-point attractor to a 2N-point attractor, which occurs when the control parameter is changed, as above. A Bifurcation *Diagram* is a visual summary of the succession of period-doublings produced as r increases. The next figure shows the bifurcation diagram of the logistic map, r along the x-axis. For each value of r the system is first allowed to settle down and then the successive values of x are plotted for a few hundred iterations.



Bifurcation Diagram r between 0 and 4

We see that for r less than one, all the points are plotted at zero. Zero is the one point attractor for r less than one. For r between 1 and 3, we still have one-point attractors, but the 'attracted' value of x increases as r increases, at least to r=3. Bifurcations occur at r=3, r=3.45, 3.54, 3.564, 3.569 (approximately), etc., until just beyond 3.57, where the system is chaotic. However, the system is not chaotic for all values of r greater than 3.57. Let's zoom in a bit.

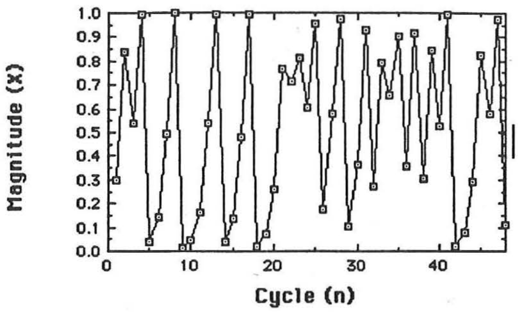


Bifurcation Diagram r between 3.4 and 4

Notice that at several values of r, greater than 3.57, a small number of x values are visited. These regions produce the 'white space' in the diagram. Look closely at r=3.83 and you will see a three-point attractor. In fact, between 3.57 and 4 there is a rich interleaving of chaos and order. A small change in r can make a stable system chaotic, and vice versa.

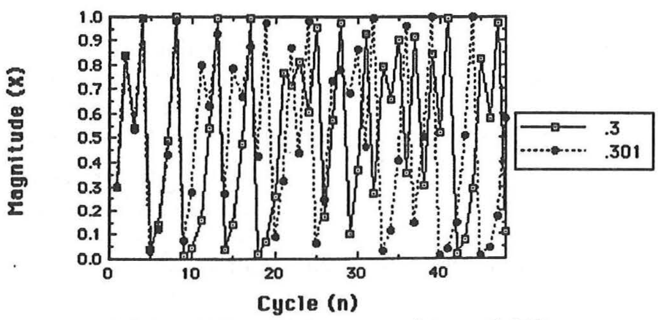
Sensitivity to initial conditions

Another important feature emerges in the chaotic region. To see it, we set r=3.99 and begin at x_1=0.3. The next graph shows the time series for 48 iterations of the logistic map.



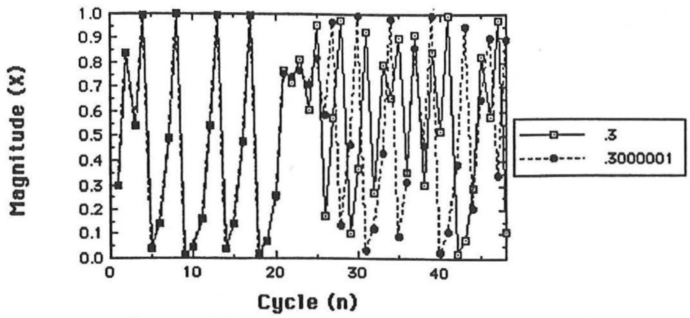
Time series for Logistic map r=3.99, x_1=0.3, 48 iterations.

Now, suppose we alter the starting point a bit. The next figure compares the time series for x_1=0.3 (solid) with that for x_1=0.301 (dashed).



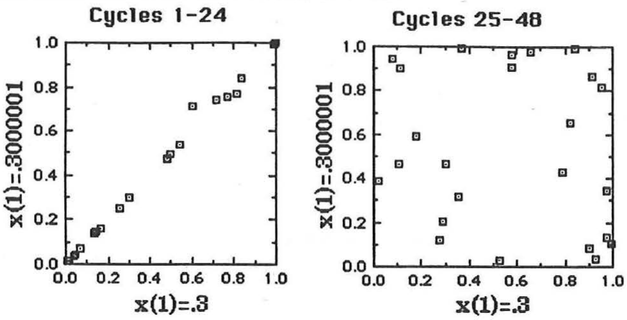
Two time series for r=3.99, x_1=0.3 compared to x_1=0.301

The two time series stay close together for about 10 iterations. But after that, they diverge and take their own paths. We next set the starting points orders of magnitude closer together. We compare starting at 0.3 with starting at 0.3000001.



Two time series for $r=3.99$, $x_1=0.3$ compared to $x_1=0.3000001$

This time they stay close for a longer time, but after 24 iterations they diverge. The curves stay together only twice as long despite the starting conditions being four thousand times closer together. To see just how independent they become, the next figure provides scatter-plots for the two series before and after 24 iterations.



Scatter-plots of series starting at 0.3 vs. series starting at 0.3000001.The first 24 cycles on the left, next 24 on the right.

The correlation after 24 iterations (right side), is essentially zero. Unreliability has replaced reliability. We have illustrated here one of the symptoms of chaos. A chaotic system is one for which *the distance between two trajectories from nearby points in its state space diverges over time*. The magnitude of the divergence increases *exponentially* in a chaotic system. This means that a chaotic system, even one determined by a simple rule, is in principle unpredictable. It is unpredictable, "in principle" because in order to predict its behavior into the future we must know its current value *precisely*. We have here an example where a slight difference (in the sixth decimal place) resulted in prediction failure after 24 iterations. And six decimal places far exceeds the kind of measuring accuracy we typically achieve with natural biological systems.

Symptoms of Chaos

This begins to sharpen our definition of a chaotic system. First of all, it is a *deterministic* system. If we observe behavior that we suspect to be the product of a chaotic system, it will also be difficult to distinguish from random behavior sensitive to initial conditions. We should note that neither of these symptoms, on their own, are *sufficient* to identify chaos. In a recent review, Rapp(13) listed the ways one can get a false impression about detecting chaos in biological systems. Uncontrolled shifts in the generator invalidate measures of the correlation dimension.

Furthermore, filter noise can be low-dimensional, have high determinism, and contain at least one positive Lyapunov exponent (see below). Over-sampling of data can produce spurious low-dimensional estimates due to the presence of too many near neighbors. Under-sampling can produce stroboscopic effects that also produce spurious results. The presence of noise, a high or low digitization rate, filter effects, nonstationarity, and short data epochs are all problems in data acquisition that can lead to spurious results. Because of these problems, Rapp claims that no single study has proven that chaos is actually in biological data.

Two- and Three-Dimension Systems

In order to investigate the distinction between variables (dimensions) and parameters, let us again consider the Logistic map

$x_{n+1} = r\, x_n[1 - x_n]$

Multiply the right side out,

$x_{n+1} = r\, x_n - r\, x_n^2$,

and replace the two r's with separate parameters, a and b,

$x_{n+1} = a\, x_n - b\, x_n^2$.

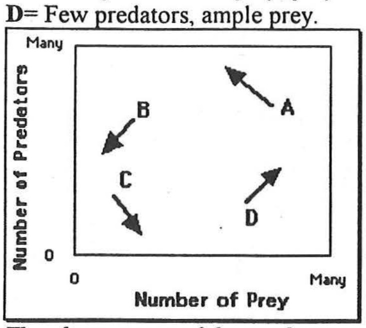
Now, **two** separate **parameters**, a and b, govern growth and suppression, but we still have only one **variable**, x. When we have a system with two or more variables:

- its current **state** is the current values of its variables, and is
- treated as a **point** in **phase (state) space**, and
- it has a **trajectory** or **orbit** in time.

Predator-prey system

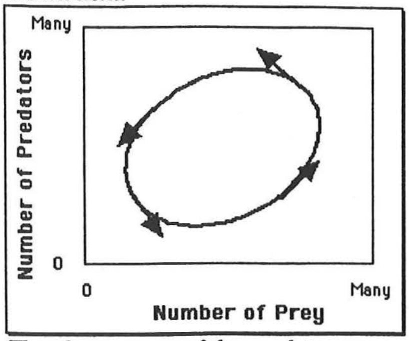
This is a two-dimensional dynamic system in which two variables grow, but one grows at the expense of the other. The number of **predators** is represented by y, the number of **prey** by x. We plot next the **phase space** of the system, which is a two-dimension plot of the possible states of the system.

A = Too many predators.
B = Too few prey.
C = Few predator and prey; prey can grow.
D= Few predators, ample prey.



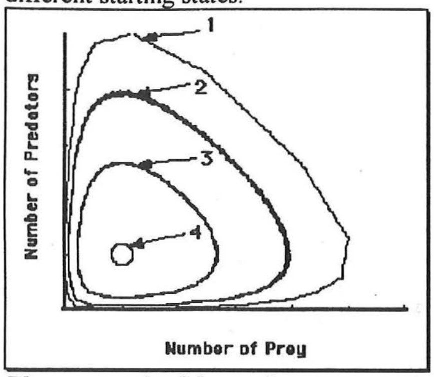
The phase-space of the predator-prey system.

Four states are shown. At **Point A** there are a large number of predators and a large number of prey. Drawn from point A is an arrow, or **vector**, showing how the system would change from that point. Many prey would be eaten, to the benefit of the predator. The arrow from point A, therefore, points in the direction of a smaller value of x and a larger value of y. At **Point B** there are many predators but few prey. The vector shows that both decrease; the predators because there are too few prey, the prey because the number of predators is still to the prey's disadvantage. At **Point C**, since there are a small number of predators the number of prey can increase, but there are still too few prey to sustain the predator population. Finally, at **point D**, having many prey is advantageous to the predators, but the number of prey is still too small to inhibit prey growth, so their numbers increase. The full **trajectory** (somewhat idealized) is shown next.



The phase-space of the predator-prey system.

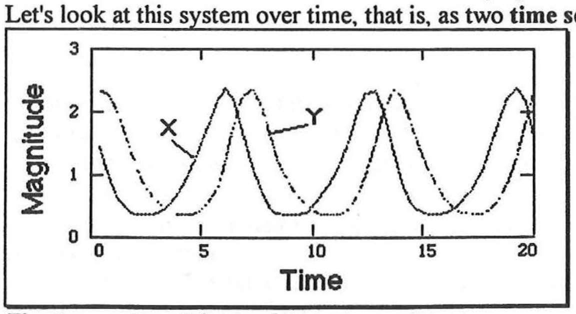
An attractor that forms a loop like this is called a **limit cycle**. However, in this case the system doesn't start outside the loop and move into it as a final attractor. In this system any starting state is already in the final loop. This is shown in the next figure, which shows loops from four different starting states.



***Phase-portrait** of the predator-prey system, showing the influence of starting state.*

Points 1-4 start with about the same number of prey but with different numbers of predators.

Let's look at this system over time, that is, as two **time series**.



The time series of the predator-prey system.

This figure shows how the two variables oscillate, out of phase.

Continuous Functions and Differential Equations

- Changes in discrete variables are expressed with **difference equations**, such as the logistic map.

- Changes in continuous variables are expressed with **differential equations.**

For example, the Predator-prey system is typically presented as a set of two differential equations:

dx/dt = (a-by)x

dy/dt = (cx-d)y

Although measles has nearly gone the way of smallpox in this country, it exhibited periodic epidemics prior to immunization. The dynamics were the same as the predator-prey example above. The infection was easily seen as deterministic. The recurrent epidemics occurred because measles infection during an epidemic immunizes individuals against further episodes. Measles has a short infectious period, so that a cohort of susceptible children had to build up before the next epidemic could occur. Epidemics occurred in two-year cycles, but showed bifurcations as well when viewed over time (see figure). The simplest description is the SEIR model (Susceptible, Exposed, Infectious, Recovered). This model can be expressed as a set of three nonlinear ordinary differential equations(64):

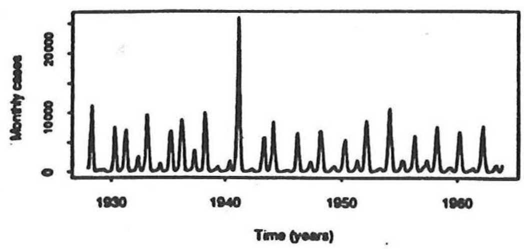
$$\frac{dS}{dt} = \mu N(1-p) - (\mu + \beta \frac{I}{N})S$$

$$\frac{dE}{dt} = \beta I \frac{S}{N} - (\mu + \sigma)E$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I$$

Where N is the size of the population. The average mortality rate from all causes is μ per year. During a measles epidemic, susceptible individuals move through the Exposed class at a rate of σ per year, and through the Infectious class at a rate of γ per year.

(a) New York, pre-vaccination



Types of two-dimensional interactions

Other types of two-dimensional interactions are possible:

- mutually supportive - the larger one gets, the faster the other grows
- mutually competitive - each negatively affects the other
- supportive-competitive - as in Predator-prey

Basins of attraction

For a given set of parameter values, the fate of the variable is determined entirely by where it starts, the initial values of x and y. In two dimensional phase space, each point can be classified according to its attractor. The set of points associated with a given attractor is called that attractors' **basin of attraction.**

Three-dimensional Dynamic Systems

The Lorenz System

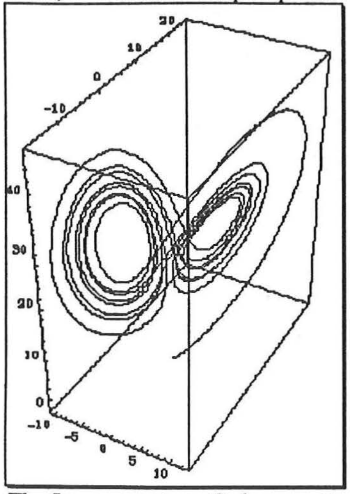
Lorenz's model of atmospheric dynamics is a classic in the chaos literature. The model nicely illustrates a three-dimensional system.

$dx/dt = a(y-x)$

$dy/dt = x(b-z) - y$

$dz/dt = xy-cz$

There are three variables reflecting temperature differences and air movement, but the details are irrelevant to us. We are interested in the trajectories of the system in its phase space for a=10, b=28, c=8/3. Here we plot part of a trajectory starting from (5,5,5).



The Lorenz system. Only a portion of one trajectory is shown.

Although the figure suggests that a trajectory may intersect with earlier passes, in fact it never does. Although not demonstrated here, the Lorenz system shows sensitivity to initial conditions. This is chaos, the first strange attractor, and it has become the icon for chaos.

Phase space - Limit Points

In order to discuss applications, some other entities need to be mentioned, however, they will not be discussed in detail. There are three kinds of limit points.

- **Attractors** - where the system 'settles down' to.
- **Repellors** - a point the system moves away from.
- **Saddle points** - attractor from some regions, repellor to others.

Fractals and the Fractal Dimension

The Concept of Dimension

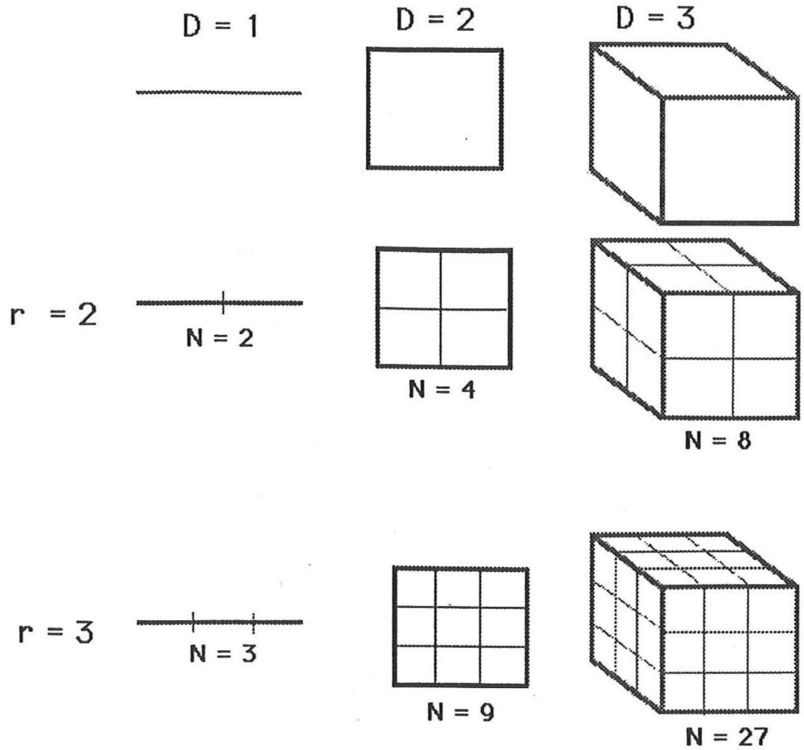
We have used "dimension" in two senses:

- The three dimensions of Euclidean space (D=1,2,3)
- The number of variables in a dynamic system

Fractals, which are irregular geometric objects, require a third meaning:

The Hausdorff Dimension

If we take an object residing in Euclidean dimension D and reduce its linear size by 1/r in each spatial direction, the measure (length, area, or volume) of the original object in terms of the new form would increase by $N = r^D$ times. This is pictured in the next figure.



$$N = r^D$$

Consider $N=r^D$, take the log of both sides, and get
$\log(N) = D \log(r)$.
If we solve for D.
$D = \log(N)/\log(r)$

If dimensions are examined this way, D need not be an integer, as it is in Euclidean geometry. It could be a fraction, as it is in fractal geometry. This generalized treatment of dimension is named after the German mathematician, Felix Hausdorff. It has proved useful for describing natural objects and for evaluating trajectories of dynamic systems. A strange attractor is a fractal, it is bounded to the phase space, the trajectory does not fill the phase space, and its fractal dimension is less than the dimensions of its phase space.

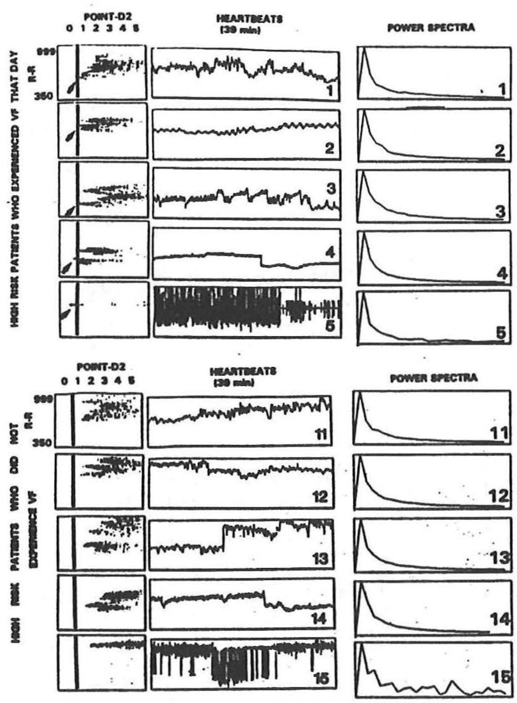
Low Dimensional Chaos in Biological Systems

This calculation of a correlation dimension is one of the ways to quantify a chaotic system. In other words, determine from the data how many independent variables are at work in the generator of the data points. If there is an exclusion of points on one or more of the continuous scales, then the dimension will be fractional, or fractal. All fractional dimensional systems are chaotic, giving data points that are aperiodic, complex, and seemingly unpredictable. These qualities are similar to what would be seen with noise, however there are important differences. A noise generator has an infinite number of variables and its calculated correlation dimension is extremely high. Chaotic systems with only a few variables will have a low correlation dimension that will be fractional (fractal)(6,14).

As discussed above, the phase or state space provides another way to quantify a chaotic system. If a system is deterministic, then its average trajectory in phase space will be more predictable than if its movement is random. A two-dimensional phase plot is made by plotting each data point in the series on the X-coordinate vs another data point on the Y-coordinate located a fixed number (Tau, τ) of data points away. Since the data is bounded between upper and lower limits, loops will form in the phase plot for all values of Tau. If two adjacent points on two different loops are marked, their distance from one another may continuously increase as the plot runs through the data. This divergence will occur in all chaotic systems and can be calculated by determining the Laypunov exponents(6), one of which will be positive if the points diverge in phase space.

Deterministic vs Stochastic Accuracy

Skinner, et. al.(5), performed experiments on serial heartbeats in patients at high risk for arrhythmia. They found a unique discrimination of outcome using the deterministic, chaos-based measure that was not present in several stochastic measures. The correlation dimension of the serial heartbeat intervals decreased in 24 of 24 high-risk patients that developed lethal ventricular fibrillation. This decrease in dimension occurred in the 24 hours prior to their arrhythmia, and did not occur in any of the equally high-risk patients that did not manifest the arrhythmia. The sensitivity and specificity of the measure as predictors of outcome were both very high. However, stochastic measures, such as the standard deviations of serial 5-minute heartbeat interval fluctuations and the power spectra of the entire intervals were unable to make significant predictions (5).



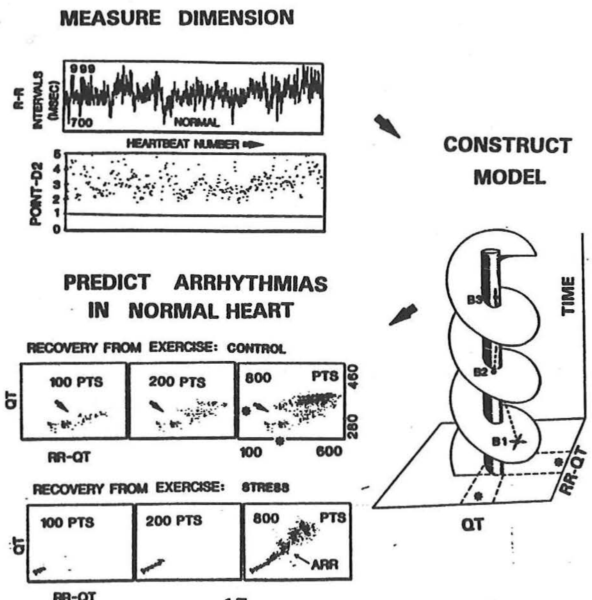
The real difference between these two methods can be seen in how predictions can be made from them. Both the standard deviations and the power spectra (stochastic measures) were significantly different when viewed in large groups of patients, however neither was specific. In other words, for any given individual patient, these measures had no real predictive value. They work in large groups without specificity. In contrast, the deterministic, chaos-based measure identified all patients that developed the lethal arrhythmia. It worked in small groups with individual specificity. It is more helpful to know that the individual patient will develop an arrhythmia than that the patient is in a high-risk group and may develop an arrhythmia.

Simplicity of Control

One of the hallmarks of chaotic systems is their sensitivity to initial conditions (see above). This attribute causes headaches when attempting to predict the course of the system. However, it can be used with facility to alter the present course of the system. Garfinkel, et. al., showed this for heartbeat dynamics(21). They injected an electrical impulse at the right time and place (a saddle point in the phase space, see above) to effect a change in the heart from a wildly shifting pattern to a stable rhythmic one and vice versa. Instead of using many pulses to entrain a simple oscillatory dynamics, a single pulse will do the same job. Also, the single pulse can produce very complicated long-lasting dynamics. This suggests that the control signal is amplified in intensity, from a low-energy input to a high-energy output.

Quantification of Determinism

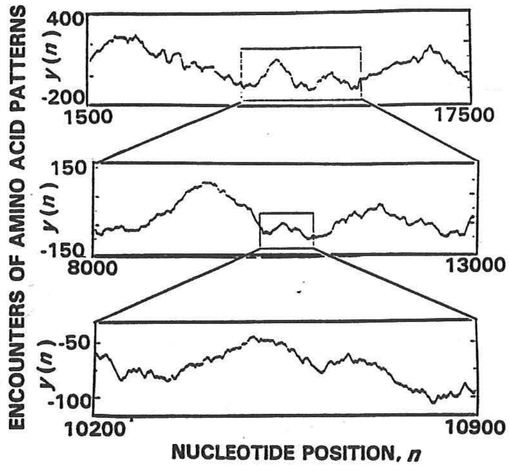
Deterministic systems provide information about the generator of the data. For example, rather than providing the familiar mean, standard deviation, or power distribution of the time series it can provide how many variables operate together to provide the data found. In the example of the heartbeat, one variable exists for each minute wave within the electrocardiogram. Classical descriptions of the conductance describe multiple, independent controllers of the same ion species, thus expanding the list of model variables to account for. In contrast, precise measurement of the correlation dimension of the heartbeat dynamics reveals that there are only a few variables in the generator. What this means is that while one can envision many variables interacting to produce the heartbeat, the system acts as though only a few are important (complexity theory).



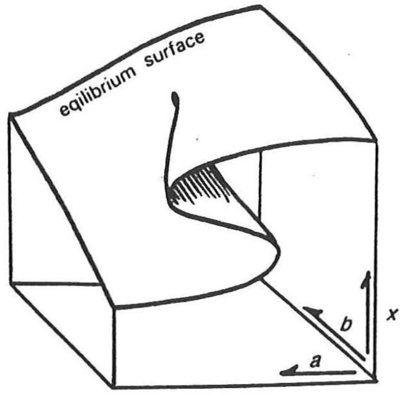
Skinner, et al. used this approach and found, on average, three variables at work in the heartbeat generator and that the system is completely deterministic (see above figure)(33). They arrived at a three dimensional deterministic model of the heartbeat, which accurately predicted a feature of the plot of heartbeat intervals not previously described. The model was able to explain how lethal ventricular fibrillation can be produced in a normal, healthy heart as a dynamical accident.

Goldberger, et al. used a simple-to-understand algorithm and suggested that shifts from moderately low dimensional dynamics to either higher dimensional noise or lower dimensional periodicity was a definitive sign of underlying pathology in many physiologic systems(23). Recently, a German research team, Lehnertz and Elger, demonstrated that a loss of complexity due to coordinated nerve firing is detectable in brain waves an average of 11 minutes before the onset of a seizure(66). Because of the sensitivity to initial conditions the team is already testing whether patients whose seizures originate in the hippocampus, a region associated with memory and learning, can avoid the seizure by means of mere remembrances or learning tasks(73).

Peng et al. used those algorithms to point to chaotic features in gene structure(60). Since the processes of gene expression and translation result from a series of dynamical interactions, their investigation with the tools of chaos theory could lead to novel ways of controlling protein production by introducing simple pulses at critical times or places. The figure below suggests the fractal character within the exon structures of DNA.



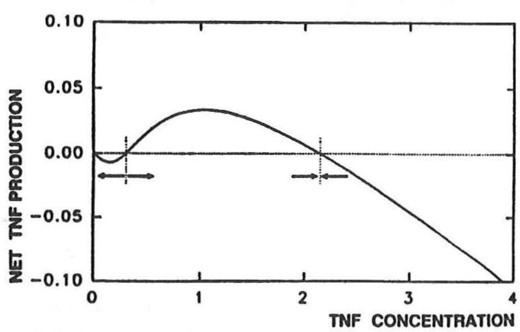
Cytokines are small peptide hormones secreted by cells for communication and recruitment. In normal, healthy individuals this cytokine network is in a state of stable equilibrium with low levels of most of the cytokines. Many of the cytokine molecules are active as dimers, and they often are autocrine, that is they induce their own synthesis. This allows their concentration to increase very fast. However, it also describes a deterministic system exquisitely dependent on initial conditions. Lewis et al. modeled cytokine synthesis which can be displayed graphically in the figure below and described the differential equation shown(76). All the points on the surface are in a steady state and most are stable. However, in the region of the fold there are three levels, the upper and lower are stable and the middle level is unstable.



$$\boxed{\frac{dV}{dt} = x^3 - ax + b}$$

Daames et al. demonstrated that a similar mechanism may exist for tumor necrosis factor, which is active as a trimer(77). The combination of the two equations gives a rather complicated system of two simultaneous differential equations that cannot be solved. By numerical analysis, however, they found that there were two stable points, one a concentration near zero, the other at a rather high concentration shown in the figure below. They suggest that the cytokine network is a chaotic system, normally behaving in a controlled manner. However, under special circumstances this system may acquire instability so that small fluctuations in the value of a parameter cause large changes in cytokine synthesis. This could have important implications for patients with diseases known to be associated with cytokine excesses, such as sepsis, ARDS, multi-organ failure, and even inflammatory arthritis. A small perturbation in the cytokine network appropriately timed could affect large lasting changes within the cytokine network due to the sensitivity to initial conditions.

Equations can model simple systems like a pendulum, and statistics can describe huge, disorganized systems like gas molecules in a jar. But math staggers with biological or humanistic systems. The problem has to do with the tremendous complexity of living organisms. This complexity is orders of magnitude greater than that of the most complex inanimate systems made or observed by man. Even though a deterministic equation can model very complex systems, if the number of variables is much above 10, then it is better to use a stochastic model.



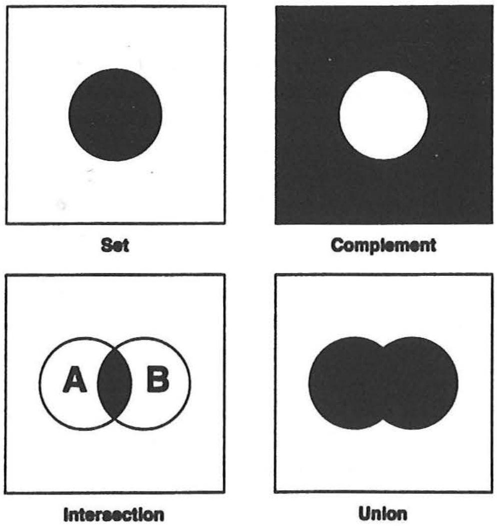
Binary Logic

Aristotle (384-323 B. C.), more than any other thinker, determined the orientation and the content of western intellectual history. He was the author of a philosophical and scientific system that through the centuries became the concepts and ideas of our western culture. Aristotle's intellectual range was immense, covering most of the sciences and many of the arts. He worked in physics, chemistry, biology, zoology, and botany; in psychology, political theory, and ethics; in logic and metaphysics; in history, literary theory, and rhetoric. He invented the study of formal logic, devising for it a finished system, known as Aristotelian syllogistic, that for centuries was regarded as the sum total of logic. Even though Aristotle's zoology is now out of date and his thoughts on the other natural sciences have long been left behind, his writings in metaphysics and in the philosophy of science are read and argued over by modern philosophers.

Aristotle's logic is binary and contains the law of the excluded middle. This logic was also the foundation for present day set theory. Simply stated, something either belongs to a set or does not belong to the set. There can be no middle ground.

Set Theory

Mathematicians and logicians depict classes with formal models. These formal models are built on set theory, which the German, Georg Cantor (1845-1918) developed in the later 19th century. Cantor sets are crisp. Each potential number either belongs or it doesn't belong and none straddle the line. Interactions between sets and relationships between sets are done or described through operations. Four such operations are shown in the figure below.



- Complement: The complement of a set is its opposite. Whatever is not in the set "A" is in its complement.
- Containment: Sets can contain other sets. The smaller set is called a subset.
- Intersection: If some members of set "A" belong to set "B" and vice versa, then those elements represent the intersection of the two sets A and B. This corresponds to the

Boolean logical operator “and”.

- Union: Union merges sets together. This would be all the elements of “A” along with all the elements of “B”. This corresponds to the Boolean logical operator “or”.

Trouble with Set Theory

Mathematicians were very fond of Cantor’s set theory, however it has always been associated with paradoxes. One of the famous paradoxes is called "sorites" often attributed to Zeno of Elea (490-430 B.C.), the "paradox of the heap." This paradox asks you to take a grain of sand from a heap and tell if you still have a heap. Take another grain from it and it remains a heap, and so on. Eventually, one grain is left. Is it still a heap? Remove it and you have nothing. Is that a heap? If not, then when did it cease being one? In Cantor’s theory, one resolves such dilemmas by dictating a break point. A certain number of grains constitute a heap. That number minus one is not a heap. Of course, in our every day speech we do not use the word so precisely, however we do precisely define it if we are speaking about logic, mathematics, and science, and in our case, medicine. If a heap has vague boundaries, the assumptions of set theory dissipate. We have, over a lifetime, simply drawn a line somewhere and pretended. We tolerate this tiny sacrifice for the convenience of thinking in crisp sets.

Vagueness

The first philosopher to grapple seriously with vagueness was Charles Sanders Peirce (1839-1914). Peirce held that everything exists on a continuum, and such continuums govern knowledge. For instance, size is a continuum as sorites shows. Peirce asserted that vagueness is a ubiquitous presence and not a mark of faulty thinking. He said, “vagueness is no more to be done away with in the world of logic than friction in mechanics”.

Bertrand Russell (1872-1970) also pursued the topic of vagueness. In 1923 he published a short paper discussing vagueness and precision in language and reality. However, Jan Lukasiewicz (1878-1955) made the first move toward a formal model of vagueness. In 1920 he published a brief paper describing early logic based on more values than true and false. This changed traditional propositional logic and led to the apparent absurdity of opposites equaling each other. In the paper, he let "one" stand for true and "zero" for false. However, in addition, "one-half" stood for possible. In logic, the operation called negation defines opposites. In true/false logic, the true (1) becomes false (0) and the false, true. This can be demonstrated in the following table.

Statement	Negation
1	0
0	1

Statement	Negation
1	0
1/2	1/2
0	1

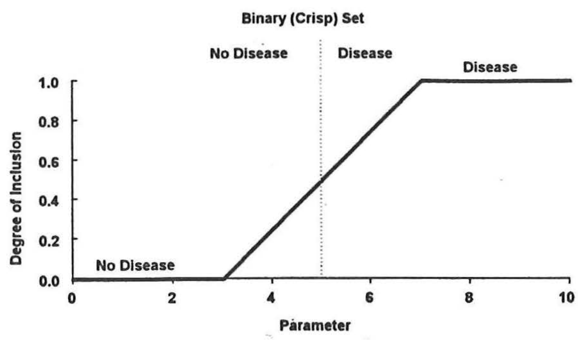
In the three valued logic of Lukasiewicz the table gains an extra line. The values for binary logic remain intact at the corners. Lukasiewicz saw no reason to insert just one extra value. He could have an infinite number of values strung out between zero and one with true and false at the extremes. The sliding scale yielded greater precision. Instead of merely acknowledging an intermediate value, multi-valued logic conveyed its size. It could, therefore, quantify degrees of truth. Max Black (1909-1989) published a paper in 1937 in which he described a continuum of degrees of usage of terms.

Bertrand Russell described a paradox, which literally removed the underpinnings of mathematics. The trouble with a paradox in mathematics is that it would then allow you to prove anything (or prove nothing). Russell's paradox had to do with set theory. The set of all apples does not contain itself, since it is a set and not an apple. However, as you might imagine some sets (of sets) do contain themselves as one of the sets. Russell's paradox concerned the set of all sets, which do not contain themselves as a member. Does this set contain itself? If it does not contain itself as a member, then by definition it must, since it is the set of all sets, which do not contain themselves as members. If it does contain itself as a member, then it can not. There is the paradox. This led to a crisis in mathematics. Russell himself suggested a solution, which was to do away with the *law of the excluded middle*, although this was too radical and was not generally accepted.

Fuzzy Sets

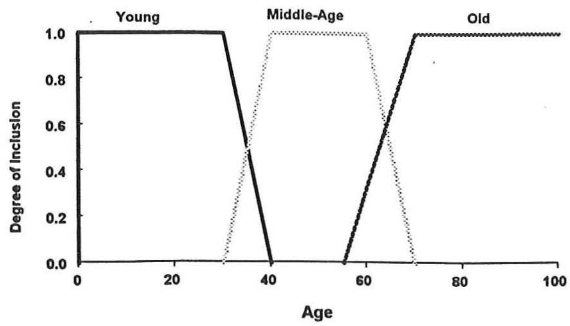
In 1965 Lotfi Zadeh, who was at the time Chairman of the University of California at Berkeley's electrical engineering department, published a paper called "Fuzzy Sets". In this paper, Zadeh set down formal logical operations on fuzzy sets and explained their importance. The key to Zadeh's paper was the concept of graded memberships. A set could have members who belonged to it partly, in degrees. Fuzzy sets discriminate much better and supply more information than "crisp" sets. They are, despite the name, more precise than crisp sets. The figure below demonstrates an example of a fuzzy set.

Fuzzy Set vs Crisp Set



In this instance there is a gradual progression from "no disease" to "disease." The parameter could be diastolic blood pressure for the disease Hypertension, or fasting blood glucose level for the disease Diabetes Mellitus. Most diseases can be expressed this way. The slope that indicates the degree of inclusion can be adjusted to span whatever distance of the parameter is necessary. If the slope is completely vertical, then you have a crisp set. From this, one can see that a crisp set is a special case of fuzzy sets (one with infinite slope). If there is more than one "linguistic variable" then there will be more than one sloping line and there can be overlap as well:

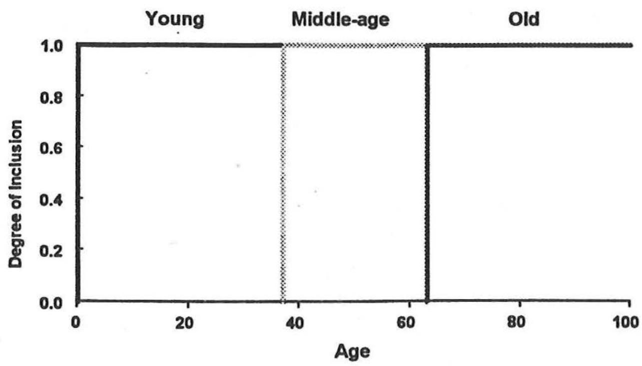
Fuzzy Age



"Young", "middle age", and "old" are sets where the variable (or parameter) is "age". The degrees of membership in each set ranges from zero, no membership, to 1.0, exclusive membership. A fundamental element of fuzzy logic is the "linguistic" variable that Zadeh introduced. A linguistic variable is a variable whose values are words instead of numbers. For example, "age" is a linguistic variable if the possible values are "young", "middle age", and "old". Each value refers to a membership function. A membership function assigns a degree of membership to any numerical age fitting the perception of "young", "middle age", and "old". Fuzzy sets appear to more closely reflect the way people naturally categorize the world. In this figure the membership functions overlap so that ages of 57 to 65 years are to a certain degree both "middle aged" and "old" at the same time. An age of 65 is comparatively less "middle aged" and more "old". The transition from "middle age" to "old" is gradual as age increases.

Membership functions are not the same as probabilities. An age of 60 is not "middle age" with a certain probability. Instead, it is both "middle aged" and "old" at the same time. The degree to which it is, "middle aged" and the degree to which it is "old" reflect the context and subjectivity underlying the membership functions. Increased precision in the specification of age or the membership functions would not alter the inherent fuzziness in classifying age.

Crisp Age



This figure demonstrates age-grouping using sets of binary logic. The shape of the membership functions is rectangular with a height of one. In comparison with the fuzzy set above, binary sets are a special case of the fuzzy sets. The differences lie at the boundaries between the sets. Membership functions of binary sets do not overlap, so that the transition between sets is abrupt. An age of 62 years is "middle aged" whereas an age of 63 is "old". In binary logic, people are either old or they are not old.

Fuzzy sets easily resolve the paradox of the heap. With each grain of sand removed, the heap has less membership in the set of heaps. It drops from 1.0 through 0.8 and 0.2 to, finally, 0. Fuzzy sets glide smoothly across the truth continuum. Estimating the memberships in fuzzy sets is a subjective task. However, the placement of the crisp or binary divisions is likewise a subjective task. Fuzzy sets, with their decimal values, yield better estimates than just 1 and 0. Fuzzy sets include crisp sets. A crisp set is just a fuzzy one with membership values of 1 and 0. Crisp sets imply that the crux of the argument is the ***existence*** of membership, while for fuzzy sets it is the ***extent*** of membership.

Fuzzy sets can be used by complex disciplines. Zadeh recognized the role of fuzziness in managing complexity and described a law of incompatibility(54):

> *As complexity rises, precise statements lose meaning and meaningful statements lose precision.*
>
> *"...as the complexity of a system increases, our ability to make precise yet significant statements about its behavior diminishes until a threshold is reached beyond which precision and significance (or relevance) become almost mutually exclusive characteristics".*

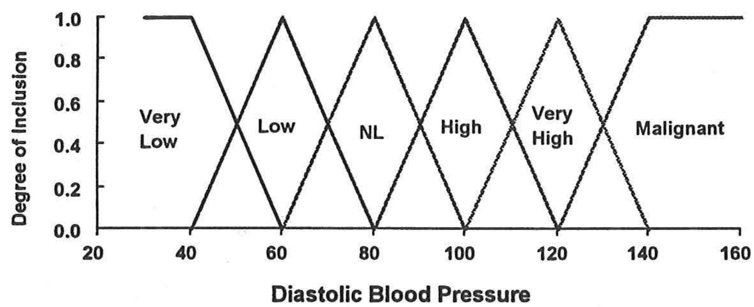
When people face complex information, they use the strategy of summarization. For example, a patient with bilateral amputations, proteinuria, characteristic retinopathy, and, an extremely elevated hemoglobin A_{1C} on large doses of insulin may be summarized as a "bad diabetic" on rounds, particularly if diabetes was not the primary reason for hospitalization.

The brain itself is constantly summarizing sense data. Television utilizes this summarization by transmitting only half of each image. If the television screen has 200 horizontal lines, then each image is transmitted as only 100 lines filling in every other line. Our brains fill in the rest of the image. This works well for moving pictures such as those that occur on television, however when people began to use computer monitors where most of the image does not change from second to second, people began to notice the flicker of the image and developed headaches and symptoms from this. This led to the development of what is called non-interlaced monitors for computers so that the entire image is refreshed each time, freeing the brain of its summarization task.

Anyone who has ever proofread a document understands the phenomenon of reducing massive detail to chunks of perception. Proofreading is very difficult because the mind normally races races over sentences, picking up just enough information to extract the meaning of the text. This also helps explain the fuzziness of words. Words centralize concepts that may have blurred bounds. Language is our ultimate shorthand, demonstrating our ability to summarize.

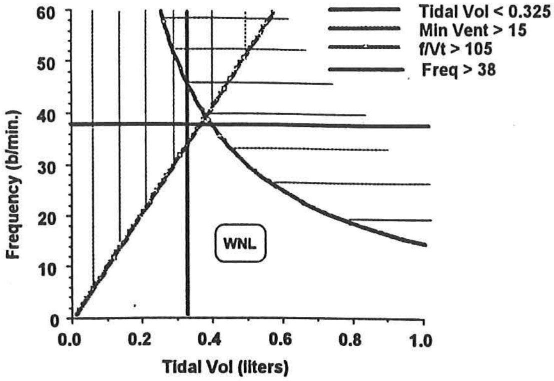
Zadeh felt fuzzy logic could handle complexity in a similar way. As members in a set grow, they eventually exceed human comprehension. The brain responds by summarizing the set into "chunks," labeled with words. For instance, it might divide the myriad hues of the spectrum into red, orange, yellow, green, blue, purple, violet, and other categories. Because each of these sub-classes is a fuzzy set with degrees of membership, members can describe them. By summing up words mathematically, fuzzy sets could help bring complex systems like the visual apparatus under control.

Fuzzy sets are representations of real-life groups. Binary logic (or formal logic or Aristotelian logic) calls for a division of absolute degree. It makes little sense to consider someone with a diastolic blood pressure of 89 as normal, and someone with a diastolic BP of 90 as hypertensive. This absolute division causes problems when we study diseases. Even though the patient with a diastolic BP of 89 is very close to our binary "Hypertension," he would not be considered to have that risk factor for coronary artery disease, since he was not labeled as such. On the other hand, the patient with the diastolic of 90 is labeled as "Hypertensive," and her insurance premiums will be higher because of this label. We lump patients into groups without accounting for the severity of the illness within the group. In the example below, I have drawn a fuzzy set of diastolic hypertension based solely on the severity of the blood pressure. Each category overlaps another category and the severity is graded. The terms are my own and the cut-off for normal, high, etc. are also my own and are only for illustrative purposes. I have still lumped patients together (all patients with a diastolic BP of 140 or higher). The fuzzy groups are drawn as equal in size and symmetrical and gradual, however there is no reason that they can not be S-shaped or asymptotic. I have also shown them as overlapping. Again, not all fuzzy sets would have to overlap. Some sets may be very narrow while others would be broad-based. This division is only important if the treatments at various levels are different. Differences in therapy might be diet, then diuretics and other mild drugs, then more potent drugs and combinations, then urgent hospital treatment, etc.



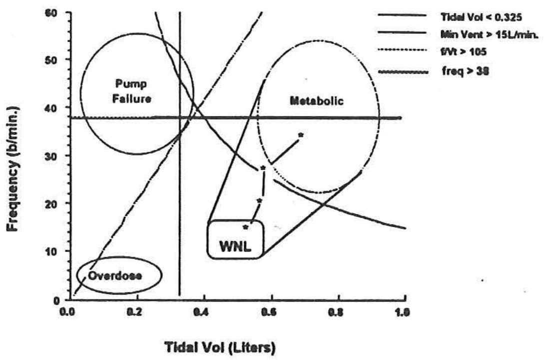
Attractors as Fuzzy Sets

Just as we looked at Attractors in Chaos theory, we can look at Fuzzy sets in a similar way. The Attractor keeps the system bounded to a certain region of phase space. This bounded region could be considered a "fuzzy" set of the system and include all of the region the system occupies. This would relieve us of having to know the deterministic equation that defines the attractor. It would also allow us to use easily understood variables and parameters.



This graph shows a "diagnostic space" using frequency and tidal volume. There are regions within the space which are physiologically difficult for patients to maintain without the help of mechanical ventilation. Studies have been performed (78) which show that there are boundaries to weaning patients off the ventilator.

Fuzzy Sets (Attractors) of Respiratory Failure



However, the space is not filled up randomly with patients. This graph shows that patients fall into areas on the graph. These areas can be considered as being around the location of attractors or they can be considered fuzzy sets of patients with different diseases. Considering the groups as fuzzy sets allows us to treat them with linear approximations. This fuzzy approximation is no different than the deterministic view when predicting, since the initial conditions can not be known close enough to predict more than a short time anyway.

Conclusion

We know deterministic mechanisms for many diseases. Those mechanisms will not change, although our ability to measure them and refine them and add to them will hopefully increase. But the vagueness will remain and that vagueness will only increase as our knowledge increases. It is to our benefit and the benefit of our patients to deal with this vagueness and include it in our understanding of medicine.

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