Time Concepts in Physics, Biology, and Pharmacokinetics

HAROLD BOXENBAUM

Received May 9, 1986 from the *Drug Metabolism Department, Merrell Dow Research Institute, Cincinnati, OH 45215-6300.*
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Abstract □ Three major types of time relativity are discussed: physical, biological, and psychological. Physical relativity illustrates how the same distant event may occur in the past of one observer and in the future of another. Moreover, space and time variables are not viewed in isolation from one another, but rather are blended together into a static, four-dimensional "block universe." Biological relativities arise through coordinate transformations of physical time-scales such that relevant processes become invariant in space–time. Because pharmacokinetic processes are integrated through a common, highly coordinated series of systems, relations between mammalian species may be probed through empiric allometric coordinate transformations. Psychological time relativity deals with a creature's awareness of its own duration and location within a restricted range of reality; it involves the transformation of perceived sequences (stimuli) into durations.

Introduction

The concept of time is the most vexing riddle confronting science; its mysteries permeate all things[1–10] (see Table I). For Newton and his followers, time was reduced to an absolute reality, an entity independent in its existence of anything external (Table I). In a universe devoid of physical or chemical change, the passage of time would still occur. Despite Newton's assertion, no formula of physics with time as a variable implies that time passes.[11]

Although an enthusiastic disciple of Newton, Immanuel Kant denied that time has any claim to absolute reality.[1,3,12–14] The basic premise of his "transcendental aesthetic" was that things are nothing more than representations of our sense perceptions (the form of which is space) and originate in our psychic apparatus. Time does not subsist of itself or inhere in objects or things as something objective, but rather pertains essentially to the functioning of the mind. Properties of things-in-themselves, the "noumena," can only be studied and known by their "phenomena," the reflection or images of the noumena in our sphere; namely, we cannot know the world as it really is, only our way of perceiving it. The projection of our awareness of time onto the external world transfers to physical systems a borrowed human logic, in particular a spatiotemporal pattern which is only human perception in disguise.[4] In Schrödinger's view,[15] experience is only a mental occurrence with each individual being isolated at the level of elementary perceptions. The notion of an external world has no meaning, and we may only speak of common elements in perceptions and judgments of collective individuals. Schrödinger believes this is suggestive of a single Mind (of which each of us is a temporary and fragmentary manifestation), a position characteristic of Indian philosophy (Vedanta classics).

A still unanswered question is whether the nerve cells of the brain invent space and time after perceiving impressions of "space and motion;" or if brain patterns and behavior might not be a creation of space and time.[4] Our perceived spatiotemporal spreading out of time may result from visual (electromagnetic) and auditory fractionation imposed by our sense organs.[4] When our conscious memory disappears, as when we sleep, our notion of time can take bizarre forms (dreams) or even disappear in some individuals. Whitrow[3] concludes that our conscious sense of time depends on the mechanism of attention and the coding and storage of information in the brain.

In the drift of evolution, Bergson argues that the central nervous system has been molded only for reasons that are of survival value; namely, the essential function of the intellect is to foresee and avoid destructive contingencies and entertain constructive possibilities.[16] Self-preservative action results from the perception of repetition and similarity, adaptive traits that require a Kantian filter to cut up time into clearly bounded intervals.

For Einstein, the passage of time was regarded merely as a feature of consciousness, with no objective counterpart.[3,17–20] In his special theory of relativity, he maintained that it is more useful to think in terms of a static, nonmoving picture of space and time, that is, a space–time continuum. In this continuum, events do not develop, they simply are. Sections connected by cause-and-effect relationships are either past or future, whereas those regions which cannot be so connected constitute the present. The world is a "block universe," to use the phase coined by William James, a sort of movie strip in which all the action already exists on individual frames of film; our lives consist of having the film strip exhibited to us.

Reiser[21] believes there are three major types of time relativity: (*1*) physical relativity, (*2*) biological relativity, and (*3*) psychological relativity. Although the third type is a special case of the second type, and this in turn is a special case of the first type, each form may be considered *sui generis*. Physical relativity does not rest upon anything peculiar to the organism. Einstein's special theory of relativity is a good example; despite the subjective appearance of the passage of time, the theory denies its existence. Biological relativity is based on how the observer senses and analyzes the object perceived; namely, it is concerned with the frame of reference from which properties of an object or system are deduced. For example, the terminal disposition half-life of hexobarbital in a 30-gram mouse can be expressed as 23.6 minutes, in which case the frame of reference would be chronological time, or as 1680 mouse gut beats, in which case the frame of reference employs a coordinate system based within the animal.[22] The advantage of the latter method is that the half-life is species invariant (among eutherian, terrestrial mammals), provided the gut beat duration (frame of reference) always corresponds to the same species to which the half-life refers. Psychological relativity refers to the manner in which the world appears as a function of the sensor–motor organization of the organism. Guy Pentreath put it in verse[3]:

"For when I was a babe and wept and slept, Time crept,
When I was a boy and laughed and talked, Time walked;
Then when the years saw me a man, Time ran,
But as I older grew, Time flew".

Our time sense apparently also depends on the number of

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Table I—Reflections on Time

Aristotle (384–322 B.C.)

Time is "the number of motion."[2,3]

Saint Augustine (354–430)

"What is time? If no one asks me the question, I know; if I must explain to someone who asks me, I do not know."[4]

Isaac Newton (1642–1727)

"Absolute, true, and mathematical time, of itself and by its own nature, flows uniformly, without regard to anything external."[5]

Jules Henri Poincaré (1854–1912)

"There is not one way of measuring time more true than another; that which is generally adopted is only more convenient. Of two watches, we have no right to say that the one goes true, the other wrong; we can only say that it is advantageous to conform to the indications of the first."[6]

Henri Bergson (1859–1941)

"Time is invention or it is nothing at all."[7]

Alfred North Whitehead (1861–1947)

"It is impossible to meditate on time and the mystery of the creative process of nature without an overwhelming emotion at the limitations of human intelligence."[3,8]

Albert Einstein (1879–1955)

"The non-mathematician is seized by a mysterious shuddering when he hears of 'four-dimensional' things, by a feeling not unlike that awakened by thoughts of the occult. And yet there is no more common-place statement than that the world in which we live is a four-dimensional space–time continuum."[9]

"Michele [Besso] has preceded me a little in leaving this strange world. This is not important. For us who are convinced physicists, the distinction between past, present, and future is only an illusion, however persistent."[10]

stimuli perceived and stored in our minds.[3] Following the 1908 Messina earthquake, three brothers were trapped in rubble for 18 days. After being dug out and freed, they thought they had only been trapped for about 4–5 days. Their severe sensory deprivation appeared to make the duration of their confinement shorter than it really was. When Einstein was lecturing on his theories of relativity, he sometimes would say to his audience[17]: "If you sit with a beautiful girl, two hours seem like two minutes. If you sit on a hot stove, two minutes seem like two hours. That's relativity."

Obviously, a multiplicity of times exist,[4] and some of these are listed in Table II. This paper will proceed by discussing the three forms of time relativity in greater detail. The rate of flow of time is operationally defined by monitoring any state variable undergoing change[23–25]; a clock is what does the monitoring. The meaning of time must therefore be sought in the operations through which the time at which events occur is determined.[26] As the choice of a clock determines our definition of time,[27] each of the three relativity sections will contain discussions on clocks which serve as the reference points about which the respective time functions are based.

Following this, the concept of pharmacokinetic time will be developed within the framework of biological time relativity. A final discussion will focus on the similarities and differences in philosophy and practice of allometric versus reductionist pharmacokinetic scaling. Empirically grounded allometric scaling relationships, which arise from the relations between the various subordinated systems and the systems which are superordinated to them, tacitly assume the concept of pharmacokinetic time. Reductionist scaling, with its primary emphasis on arrangement and mechanism, generally employs chronological time as its frame of reference. In the former, invariance is sought in terms of time, whereas in the latter, invariance is sought in terms of mechanism.

Physical Relativity

Imagine yourself in an automobile traveling at a speed of 20 miles per hour (mph). You are overtaken and passed by an automobile traveling at 60 mph. From your perspective, this second automobile will appear to have a velocity of 40 mph and, after 1.5 minutes, will have outdistanced you by a mile. However, had you been traveling at 50 mph, the velocity of the second automobile would only appear to be 10 mph, and you would have been outdistanced by a mile after 6 minutes. The second vehicle would always appear to have a velocity relative to your own. In this example, we assume the reference vehicle moves at a constant velocity relative to a stationary object, say, a sign post. But suppose the sign post was also in motion. If its direction of motion were the same as yours, your apparent velocity would decrease. However, if its motion were in the opposite direction of your own, your velocity would appear to increase. Next suppose that the clock you used to gauge your motion slowed down as your velocity increased (the same phenomenon would also occur with a clock attached to the reference system). Obviously, all velocity and time measurements would be relative to the frame of reference. In a much simplified fashion, this example illustrates a basic feature of Einstein's special theory of

Table II—A Multiplicity of Times[a]

Absolute Time	Lower Time
Abstract Time	Macroscopic Time
Aerodynamic Time	Man Time
All-embracing Time	Mathematical Time
Arbitrary Time	Measurable Time
Arithmetic Time	Mental Time
Astrological Time	Metric Time
Astronomical Time	Minimal Time
Atomic Time	Newtonian Time
Autistic Time	Objective Time
Automatic Time	Official Time
Autonomous Time	Old Time
Basic Time	Oniric Time
Biological Time	Ontic Time
Calendar Time	Ontological Time
Cerebral Time	Operational Time
Cerebrospinal Time	Ordinary Time
Chronological Time	Organic Time
Civil Time	Outside Time
Classical Time	Past Time
Clock Time	Perceptual Time
Conceptual Time	Personal Time
Conscious Time	Pharmacokinetic Time
Constitutive Time	Philosophical Time
Continuous Time	Physical Time
Coordinated Universal Time	Physiological Time
Cosmic Time	Possible Time
Creative Time	Present Time
Customary Time	Prime Time
Cyclical Time	Primordial Time
Derivative Time	Private Time
Determined Time	Probable Time
Dialectical Time	Proper Time
Dream Time	Psychical Time
Einsteinian Time	Psychological Time
Electromagnetic Time	Public Time
Electronic Time	Quality Time
Emotional Time	Rational Time
Ephemeris Time	Real Time
Extended Time	Reference Time
Exterior Time	Relational Time
External Time	Relative Time
Extrinsic Time	Relativistic Time
Fourth-Dimensional Time	Sensorimotor Time
Frozen Time	Sidereal Time
Functional Time	Single Time
Future Time	Social Time
Government Time	Societal Time
Great Time	Solar Time
Greenwich Mean Time	Space Time
Historical Time	Spatial Time
I-Time	Specific Time
Impersonal Time	Star Time
Individual Time	Statistical Time
Initial Time	Subatomic Time
Inner Time	Subjective Time
Inside Time	Terrestrial Time
Intensive Time	Thermodynamic Time
Interior Time	True Time
Internal Time	Unconscious Time
Intrinsic Time	Uniform Time
Inward Time	Universal Time
Kantian Time	Variable Time
Linear Time	Visceral Time
Living Time	World Time
Local Time	

[a] Entries were collected from the literature by the author.

relativity[9,12,19,20,28,29]; that is, if two systems are in relative motion with uniform straight-line velocity, time measurements made by observers in either system will not agree with one another (Einstein's general theory of relativity, which deals with nonuniform velocity and incorporates a new theory of gravitation,[29] will not be discussed here). In more general terms, the special theory of relativity applies to systems in which the observer moves at high speeds relative to the observed phenomena.[5] Under these circumstances, the concept of simultaneity does not exist.[3,4,9,12,19,20,24,28,30] Two events occurring at different places may appear to occur simultaneously to one observer and not to another. It is also possible for the same distant event to occur in the past of one observer and in the future of another; it all depends on the state of motion of the observer. Consider Einstein's example[9] of an individual traveling on a train of uniform velocity. Two bolts of lightning (A and B) occur simultaneously relative to the railway embankment. Mirrors on the embankment reflect the emitted light rays from the two lightning bolts to the train which was initially at their midpoint. If the train were stationary, the reflected light from A and B would be detected simultaneously. If, however, at the instant that the lightning bolts hit the embankment the train were traveling away from A and toward B, the observer would see the beam of light from B sooner than from A (remember that the speed of light has a finite value of about 186,000 miles per second). These events, which were simultaneous relative to the embankment, were not simultaneous relative to the train. Einstein's point was that every reference body (coordinate system) has its own proper time, and unless we know the system to which the event is referenced, there is no meaning in a statement of the time of an event; that is, concepts of "simultaneity," "time," and "now" are all relative to the reference system of the observer. The concept of simultaneity only makes sense for events happening at the same place.

Although the theory of relativity states that no body can travel as fast as the speed of light (*vide infra*), consider the following hypothetical example. You face a clock hanging on a wall and perceive its reflected light rays which tell you the time. Suppose that at exactly 12 midnight, you travel away from the clock at the speed of light. The reflected light rays, which transmit the 12 midnight face of the clock, will move with you. Light images corresponding to 12:01 a.m. on the clock will never reach you, and your time would always be frozen.[24] You would also have zero thickness and infinite mass.[19] To make time flow backward would require an infinite mass traveling faster than the speed of light overcoming an infinite entropy barrier.[19,24,31,32] In the movie "Superman I", the mythical hero circled the earth at a speed greater than that of light, making time flow backward and allowing ample opportunity to save Lois Lane, who had previously suffocated in an earthquake. Traveling at a speed faster than that of light is also the focus of an old limerick[28]:

"There was a young lady named Bright,
Who traveled much faster than light.
She started one day
In a relative way,
And returned on the previous night."

Another conclusion from the special theory of relativity is that the faster a system travels, the more slowly time passes within it (time dilation).[28,33] In an actual experiment, a sensitive atomic clock traveled the world in a jet plane (a seat had been reserved on a commercial carrier for the instrumentation). Compared to the clock on the ground, the one aboard the plane ran a trifle slower. Mathematically, a simple relationship exists between time in a stationary system and one that is moving:

$$\text{Time in a Stationary System} = \frac{\text{Time in a Moving System}}{[1 - (v^2/c^2)]^{1/2}} \quad (1)$$

where v is the constant velocity of the moving system and c is the speed of light. In a spaceship traveling at 86.6% the speed of light, the denominator on the right-hand side of eq. 1 equals 0.5. Four years spent on the spaceship, which has now become twice as heavy, corresponds to 8 years on stationary earth. (Note: this calculation neglects the earth's speed of 18.6 miles per second in its orbit around the sun.) A clock in an automobile also undergoes the effects of motion, but these time dilation effects are too small to matter.[34] For an automobile traveling at 60 mph, the denominator of the right-hand side of eq. 1 equals $[1 - (8.03 \times 10^{-15})]^{1/2}$ or 0.999999999999996. The most sensitive clock[27] is only reproducible to 1 part in 10^{11}.

Einstein's special theory of relativity also indicates that there is no such thing as space and time in the sense that we perceive them. Our feelings of past, present, and future are subjective illusions our weak minds are unable to overcome.[1,3,19,20] Two years after the special theory of relativity was published, Herman Minkowski developed the concept of space–time.[20,28] Einstein subsequently integrated the space–time concept to fit in with relativity theory. According to this view, it is improper to think of space and time as isolated from one another, but rather blended into a static, four-dimensional (4-D) continuum or manifold[18] (recent studies suggest space–time may have as many as seven extra dimensions[35]). In the space–time manifold, time is robbed of its independence; events do not happen, they simply are.[3,9,17,18,29,36] Every event in life already exists.[37] If we could observe the manifold, we would see all past, present, and future events as a block universe composed of space–time.[3,5,38] Not only had Einstein demonstrated the equivalence of matter and energy ($E = mc^2$), he also showed the indivisibility of space–time.[20] Just as space is made up of locations, space–time is made up of events; the feeling that time is elapsing is an illusion.[38] Only limited regions of space–time are accessible. Space–time locations (called points, slices, etc.), where you could travel to reach the here and now, constitute your past. Those events in space–time that you can still reach without traveling faster than the speed of light are your future.[38] The ensemble of events constituting your future actually exist prior to your knowledge of them.[5] Memory traces of an event occur at locations in space–time that have time coordinate values greater than those of the events themselves; this creates the illusion of the passage of time.[37] The history of each individual material particle in space–time is called its "world-line"; an individual could be thought of as a kind of long rubber bar extending in time from birth to death. In three dimensional terms, an individual is perceived as a conglomerate of matter changing in time (98% of the atoms on our bodies are replaced annually[17]). In terms of 4-D space–time, there is a form and image in which our physical bodies are molded, what Indian philosophers term the "Linga Sharira."[1] We can picture the Linga Sharira as consisting of all the features of a man from birth to death, stretched out in time as it were. Matter changes, but the Linga Sharira withstands this and remains intact.

In everyday experience and existence, these matters are of no concern to most individuals. With the exception of Einstein, there is little evidence that the physical concepts of time have affected the way physicists have ordered their lives.[5] In accordance with the entropy law, the direction of time moves from a more ordered universe (the past) to a less ordered one (the future). Time dilation is inconsequential, and activities are readily structured within the matrix of "local time." The latter is defined operationally by reference to clocks, which in turn regulate the flow of events in society.

Throughout history, man has always been interested in time. It was this interest that was the impetus for development of clocks.[39] The first clock was the sun.[40] As noted previously, the units of time are arbitrarily taken as the interval between the beginning and the end of any physical phenomenon (usually one that is uniform in terms of accepted physical theory). In one Indian culture, the temporal unit of time is taken as the duration required to boil rice.[3,17] The Chinese and Japanese have used fire and incense timekeepers since about the sixth century A.D. In one 200 year old clock displayed in a Tokyo department store, small pieces of different varieties of incense were burned sequentially, allowing those with sensitive noses to discern the time of day.[3] In antiquity, water clocks provided the chief method for time estimation. One clock consisted of a figure of a dog-headed ape with water being led out by a pipe through its penis; these creatures were renowned for urinating at precise intervals.[41] Most technological developments in clockmaking, however, were centered in Europe. For the Chinese, it was simply not important to tell time with any precision. However the monks in Europe believed their souls would be in jeopardy if they did not pray at proper times.[42] This and other stimuli resulted in the invention of various mechanical clocks containing three fundamental elements: (*1*) an instrument of motion; (*2*) an instrument of regulation; and (*3*) an escapement, namely, a device to divide up the motion.[24,28,43,44] Modern clocks have a device that produces a periodic phenomenon (resonator), a source of energy feeding the resonator (the combination of the resonator and energy source being termed the oscillator), and a detector to accumulate and display the tick or swings, that is, the hands of a clock.[24] In general, the faster the oscillations, the more accurate the clock.[39] In 1967, a second was defined as the duration of 9,192,631,770 periods of the radiation corresponding to the transition between two hyperfine levels of the fundamental (ground) state of the cesium-133 atom.[3,27] Prior to that,[40] the standard had been set in 1955; one second equaled 1/31,556,925.9747 of the year 1900. Going back further, it was around 1345 that the hour was divided into minutes and seconds.[28]

Biological Relativity

Biological or physiological time is one of the most significant characteristics of living animals[45]; it may be defined as a species-dependent unit of chronological time required to complete a species-independent physiological event.[46] Alternatively, "a physiological time-scale for a specified biological process is a time-scale obtained by transforming a physical time-scale so that the rate of change of the process becomes time-invariant in physiological [space] time."[47] Therefore, physiological time must be defined with reference to a specified biological process. Unlike local chronological time which is linked to oscillatory phenomena in physical systems (for example, the hundred thousand or so vibrations each second in quartz watch crystals[39]), biological time phenomena are linked to coordinate systems within the organism. An oscillatory system that could serve as the basis for a clock would be the resting heart rate (resonator) and ATP (resonator energy source). Mammalian heartbeat time (seconds) is characterized by the following allometric equation[48–51]:

$$\text{Heartbeat Time} = 0.2961\ B^{0.28} \qquad (2)$$

where B is body mass in kilograms. A 30-g mouse has a heartbeat (cardiochron) every 0.111 s compared with 0.973 s for a 70-kg human. These are equivalent biological times. Breath time (seconds) in mammalian species is similarly characterized by an allometric expression[48–51]:

$$\text{Breath (Pulmonary Cycle) Time} = 1.169B^{0.28} \quad (3)$$

A 30-g mouse has a resting respiratory cycle (pneumatochron) every 0.438 s compared with 3.841 s in a 70-kg human. Dividing breath time by heartbeat time in both rat and human gives a species-invariant value of 3.95. The same result is obtained through allometric cancellation:

$$\frac{\text{Breath Time}}{\text{Heartbeat Time}} = \frac{1.169B^{0.28}}{0.2961B^{0.28}} = 3.95 \quad (4)$$

There are numerous size-independent dimensionless group relationships among mammals[50]; for example, tidal lung volume over cardiac stroke volume is 9.4 and mass of kidneys over mass of liver is 0.26.

In general, the ontogenetic and phylogenetic increase in body size among mammals is associated with an increase in the duration of most periodic phenomena. This general trend can be formulated[52] by means of the empirical power law for biological time, t_b:

$$t_b = \text{constant} \times B^{0.25} \quad (5)$$

The relation between body size and biological timing processes may be related to energy or other turnover rates at the cellular level.[52] If one assumes that the allometric exponents for periodic phenomena remain relatively constant at about 0.25, it follows that many ratios of period times will be species invariant.[53]

As noted, many physiological periods or times have allometric mass exponents near 0.25. Most of the body organs that function volumetrically (heart, lung, spleen, gut, blood) scale to body mass essentially in a linear fashion[53]; that is, the allometric exponent is close to unity, and the system is said to be isometric.[54] Isometric systems maintain geometric similarity; namely, all dimensions of the small object may be multiplied by the same factor in designing the larger one.[55] Based either on elastic similarity (*vide infra*) criteria or empirical correlations, lung tidal volume and heart stroke volume are also isometric to body size.[45,54] The rate at which air flows through the lungs (volume per time) as well as cardiac output (volume per time) scale to body size with exponents near 0.75. It follows that breath time is equal to (tidal volume/air-flow rate) and heartbeat time is equal to (stroke volume/cardiac output). Hence,[45,53,54] these cycle lengths are approximately proportional to $B^{0.25}$. There are other examples[53] of mammalian biological period scaling with an allometric exponent of approximately 0.25, for example, 50% growth time, time to reproductive maturity, gestation period, time to metabolize fat stores, and gut beat duration. Additionally, the time required for animals to perceive and respond to their surroundings[53] also scales to $B^{0.25}$. Lindstedt and Calder[53] suggest that the fundamental unit of physiological time, $B^{0.25}$, is an inevitable consequence of the geometry of body size changes. Apparently, animals must have a circadian rhythm to help mesh a $B^{0.25}$ physiological time-scale with an indifferent environmental time-scale.[45]

If one initially assumes a $B^{0.25}$-based physiological time scale made inevitable by the evolution of body size, one can theoretically predict $B^{0.75}$ scaling variables, for example, basal metabolic rate. Conversely, if one initially assumes $B^{0.75}$ scaling, for example, based on elastic similarity, $B^{0.25}$ timing may be viewed as an inevitable consequence of an organism's metabolic needs.[45]

The principle of elastic similarity scaling deals with mechanical support of the body; it maintains that under loads, bone reconstructs itself to prevent too much bending.[54–58] With respect to each other, two organisms maintain elastic similarity if they have a similar threat of failing due to buckling or large-amplitude bending. According to this model, body and muscle cross-sectional areas, and consequently metabolically related variables, should scale to $B^{0.25}$.

As previously noted, the rate of flow of time is implied by the choice of a clock, just as the choice of a clock provides for the duration of time.[27] Physical time is generally defined in terms of standard cyclic processes considered uniform in terms of accepted physical theory.[59] Physiological clocks, of which there are at least two classes, are keyed to less uniform metabolic rhythms. The first type involves systems whose phases are reset or "entrained" by an external synchronizer, for example, by the daily cycles of light and darkness.[60] These clocks schedule biological events at ecologically appropriate times.[61] The name circadian, which means about (circa) a day (diem), refers to clocks whose free-running period of rhythms is close to 24 hours (usually 22–26 hours).[61] Other clocks possess innate periodicities synchronized to lunar and seasonal changes.[60] The second class of clocks are those which regulate physiological function in a manner independent of cyclical environmental influences. These are associated with heart rate, respiratory cycles, et cetera. In the case of the heart, the regular succession of excitation, transmission, contraction and relaxation constitute a kind of timing device.[52]

Synchronization mechanisms, probably neurohumoral in nature, are postulated to coordinate different functions at the cellular, organ and organismic levels.[52] Metabolic rate, which influences turnover rate at the cellular level, may modulate the physiological timing process.[52]

Psychological Relativity

The conceptual notion of time is not something with which we are born. During the first 5 to 7 years of life, children are at a sensory and motor perceptual stage of temporal organization in which they cannot separate time from spatial structures.[4] The child under the age of 4 is an image-chaser, capable of reminiscences but without the ability to localize in time and space. At about 8 to 12 years of age, he begins to liberate himself from the present and can direct his thoughts beyond the actual train of events. This transition from a perceptual to a conceptual image of time occurs as the brain (via the sense organs) becomes progressively more programmed by the outside world. The relative variation of time sensed from within provokes the sensation of before and after. Past and future become mythical representations activated if the brain decides to play or replay them. Externalization of this internal temporal function is a fundamental characteristic of man[4]; namely, it appears it is we who invest the world with the properties of space and time.[1] Having created names and symbols for space and time, we mistakenly believe we have discovered the "noumena" or things-in-themselves.[4]

The four essential characteristics of psychological time are that[4] (*1*) it may pass in a non-linear fashion; (*2*) its flow may be perturbed by either internal or external influences; (*3*) it may become detached from the past, affirming persistence within the present; and (*4*) it may function in a manner unrelated to external causality. In short, psychological time is a heterogeneous discontinuum.[30] Unlike physical time, psychological time represents a creature's awareness of its own duration and location within a restricted range of reality; it is the transformation of perceived sequences (stimuli) into durations.[4] Consequently, the intensity of stimuli can greatly influence psychological time.[3] In general, the more one is submerged in living, the more one exists in psychological time.[30]

Cultural and social variances also affect attitudes toward time. The Hopi Indian language contains no words implying that time passes in a linear fashion. Because they live in a kind of perpetual present constituting everything that ever happened, their verbs have no tenses.[17,19] Had they been scientifically oriented, their physics would no doubt have been considerably different from ours.[19] Just how time is perceived and reacted to (collective-ego-space–time) is even different within social classes in the United States.[62] The lower-lower classes build most of their meaningful behavior on the present (major admonishment to a child: "Stop that right now or I'll hit you"). The middle classes build behavior sequences on the basis that present conduct affects future events (major admonishment to a child: "Stop that or you will never get into college, get married, get a good job, etc."). The upper-upper classes build behavior sequences on the basis that the past directs much of how the present and future are to be treated (major admonishment to a child: "Stop that, your grandfather (or 'original ancestor') wouldn't like it"). The first group eats when they are hungry; the second, at clock times; and the third, when tradition dictates it is proper.

Psychological (subjective) time is affected by the number of stimuli and/or perturbations. In pituitary and thyroid diseases, normal processes may be slowed down or speeded up, and patients notice a divergence between clock time and time sensed.[44] Physiologic and psychologic clocks run faster when metabolic rate is increased; clock time is overestimated, subjects arrive early to appointments, and physical time appears to pass slowly. In states of decreased metabolic activity, clock time is underestimated, subjects arrive late to appointments, and "time seems to fly like magic."[8] The former case, termed time contraction, can also produce a simultaneous "expansion of space." In a psilocybin induced mind state, handwriting space becomes enlarged; that is, letters and words are written larger (space expansion), and Morse-code tapping rates increase (time contraction). The opposite effect, that is, time expansion–space contraction, may occur following administration of some phenothiazine tranquilizers.

Acute suffering also induces a sort of time contraction; there is excessive data content (pain or distress), and time appears to pass slowly. This is in contrast to cancer patients, who, after being notified of their disease, feel a sense of time urgency. Many unconsciously reverse this feeling by taking up fishing.[17] There is little data entry when you're sitting on a boat waiting for a fish to bite, and time drags.

Although it is not yet possible to make definite conclusions, the alpha rhythm (from electroencephalograms) is thought to be closely associated with our sense of time.[3] Time perception, however, is a complex process, and there may be a large number of independent clocks. These clocks are not readily identifiable, and laboratory techniques designed to isolate and reveal their processes are more likely to destroy them.[3] Nonetheless, below our level of consciousness, biological clocks superimpose their rhythms on our social and psychologically conditioned cognitive time sense.[3] These clocks appear to be a fundamental characteristic of intact living systems.[3]

Pharmacokinetic Time

Allometric Cancellation—Pharmacokinetic time[46] is a species-dependent unit of chronological time required to complete a species independent pharmacokinetic event. Using the example of 50% elimination of hexobarbital from the body (postdistribution equilibrium), chronological time is ~23.6, 210, and 328 min in the 0.030-kg mouse, 16-kg dog and 63-kg human, respectively. The terminal disposition half-life ($t_{½,z}$, min) is given by[22,46]:

$$t_{½,z} = 80.0B^{0.348} \quad (6)$$

The equation for gut-beat duration (G, min) in mammals is[63]:

$$G = 0.0475B^{0.31} \quad (7)$$

Allometric cancellation gives:

$$\frac{t_{½,z}}{G} = \frac{80.0B^{0.348}}{0.0475B^{0.31}} \approx 1684 \quad (8)$$

Consequently, hexobarbital disposition half-life is approximately invariant. (Gut-beat duration was arbitrarily chosen for this example, because the allometric exponent in eq. 7 closely approximates that of eq. 6.)

Pharmacokinetic Systems Concepts—A summative property is one which is identical within and outside the system of which it is a part.[64] Constitutive or constitutional characteristics are dependent on the specific relations within the complex. Suppose you have exactly 100 grams each of absolute ethanol and water at 20 °C. The two are mixed and allowed to reequilibrate. Although the mass of the solution is strictly summative, the volume[65] is reduced by 3.6%. The volume characteristic is constitutive; that is, it is dependent upon the interactions occurring within the system, in this case the Keesom (dipole–dipole) forces between molecules of ethanol and water. Pharmacokinetic properties are also constitutional, genetically integrated with other physiologic and biochemical processes in a remarkably coordinated system. Such linkage places extraordinary restrictions on what can or is likely to occur. This leads to correlations between rates of physiologic and pharmacokinetic processes.[67]

When dealing with complexes of elements in pharmacokinetic systems, say, for example, the hepatic drug disposition system, three types of distinctions may be made[64]: according to types, according to quantities, and according to relations with other elements. Hepatic clearance will depend on the types of enzyme molecules present, their quantity, and the manner in which they are distributed and interact with other elements at or within their boundaries, for example, the circulatory system. Hepatic clearance will therefore depend on plasma protein binding, blood cell partitioning, and hepatic blood flow. Having close functional relationships to anatomical dimensions and physiological processes, these characteristics tend to correlate well with body size and rates of physiologic processes; this in turn provides much of the basis for pharmacokinetic scaling.

Pharmacokinetic Scaling—In the example of McMahon,[56] a small pendulum clock is scaled up to produce a larger one 64 times its size. The durations (T) of one period of the pendulums are:

$$T = 2\pi(L/g)^{½} \quad (9)$$

where L is the pendulum length and g is acceleration due to gravity. The 64-fold increase in L will produce only an 8-fold increase in T, causing the larger clock to produce fewer ticks per minute. To compensate for the change in scale, the larger clock might have a belt drive ratio 8 times greater, thereby causing both clocks to move through identical arcs for each unit of time.

Analogous changes occur in anatomical, physiologic, and pharmacokinetic characteristics of systems of varying sizes. Mammalian liver mass (L, kg) is given by[66]:

$$L = 0.035B^{0.89} \qquad (10)$$

A 0.030-kg mouse would have a liver representing 5.15% of its total body mass, whereas the liver is only 1.69% of the total mass of a 750-kg cow. Yet a gram of liver in each species has virtually the same capacity to metabolize antipyrine. (Note: antipyrine intrinsic clearance of unbound drug [CLu_{int}, well-stirred model] is ~0.22 $L \cdot min^{-1} \cdot kg^{-1}$ liver mass)[46]. The rat with a relatively larger liver will have an approximately 3-fold greater CLu_{int}, when the latter parameter is expressed in terms of total body mass. However, the scale change produced through variations in total body mass is compensated by expressing antipyrine CLu_{int} in terms of liver mass.

Allometric Collapsing—Development of models capable of abstracting relevant characteristics of pharmacokinetic systems falls within the framework of the methodological paradigm.[67,68] Over the past decade, the focus of this paradigm has become increasingly reductionist; that is, it is dominated by the belief that complex pharmacokinetic phenomena are best understood by reducing system elements to their basic building blocks and viewing their functional relationships in physicochemical terms. By eliminating factors that cannot strictly be controlled, the spatial and temporal ordering of the remaining parts are more easily studied. This is the primary reason why drug metabolism pharmacologists feel most at ease when the thing they are studying is no longer alive. Observing the immense complexities of these well-controlled systems (thousands of coupled chemical reactions power even a single cell[69]), the mechanisms through which the basic building blocks of pharmacokinetic systems interact are viewed as being far too complex for allometric simplification. Nonetheless, complex pharmacokinetic systems typically tend toward simplification. For example, the following equations[46] characterizing antipyrine disposition in various mammalian species (excluding humans) have been posited:

$$CLu_{int} = 0.00816B^{0.885} \qquad (11)$$

$$Q_H = 0.0554\ B^{0.894} \qquad (12)$$

$$Vd_\beta = 0.756\ B^{0.963} \qquad (13)$$

$$t_{½,z}\ \text{(minutes)} = \frac{0.693\ Vd_\beta}{CL_b} = \frac{0.693\ Vd_\beta}{\left(\dfrac{f_b\ CLu_{int}\ Q_H}{(f_b\ CLu_{int}) + Q_H}\right)} \qquad (14)$$

where CLu_{int} is the intrinsic clearance of unbound drug in liters per minute, Q_H is hepatic blood flow in liters per minute, Vd_β is the volume of distribution in liters during the terminal disposition phase (referenced to blood), CL_b is blood clearance in liters per minute, and f_b is free fraction of drug in blood (taken as unity for antipyrine). Upon substituting eqs. 11, 12, and 13 into eq. 14, combinations, cancellations, and removal of insignificant terms result in a major collapse, the final relationship being considerably simplified:

$$t_{½,z}\ \text{(minutes)} = 73.7\ B^{0.077} \qquad (15)$$

By comparison, the empirically determined relationship is:

$$t_{½,z}\ \text{(minutes)} = 74.5\ B^{0.069} \qquad (16)$$

Despite species differences in the relative contribution of antipyrine metabolic pathways[70], eqs. 11 and 15 are both valid. The summated rather than individual clearance parameters seem to have been the object of natural selection[67]: "the end [disposal] rather than the means [pathways] seems to be the important thing."[71]

Interestingly, the activation of molecules to carcinogens may not have been significantly affected by the force of natural selection.[67] The property maximized through natural selection is net reproductive advantage.[72] If the ill effects produced by the accumulation of maleficent genes in the genome are not manifested until late in life, for example, with xenobiotic-induced carcinogenesis, they will be virtually out of reach of natural selection, that is, selectively neutral.[72] Xenobiotic-induced carcinogenesis may therefore be an artifact of domestication and civilization. Sacher[73,74] is critical of this view (see also Hayflick[75]). It is argued that there is no functional role for senescence and death in species with iteroparous reproduction and that selective processes should act on mechanisms for increasing the stability of the organism. Long life is seen as the result of selection of genetic systems that assure physiologic performance for an extended period of time.

Pharmacokinetic Space–Time—As noted in the discussion of biological relativity, a primary objective of biological scaling is the transformation of physical time-scales into forms whereby relevant processes become invariant in space–time. This concept will be developed in the context of pharmacokinetic systems. Assume intravenous bolus injection of a drug with monoexponential disposition. (Pharmacokinetic systems employing alternative input functions and nonlinear disposition characteristics have not yet been studied by these methods.) The plasma concentration–time function is[76]:

$$C = (D/Vd)\ e^{-kt} \qquad (17)$$

where C is plasma concentration at time t, D is dose, Vd is volume of distribution, and k is the first-order elimination rate constant. Presume the following interspecies allometric relationships:

$$CL = aB^x\ BW^z \qquad (18)$$

$$Vd = bB^y \qquad (19)$$

where CL is total plasma clearance and BW is brain mass (the rationale for including BW as a variable will become apparent in the upcoming discussion of neoteny). Since $k = CL/Vd$, eq. 17 can be rewritten:

$$\frac{C}{(D/B^y)} = (1/b)\ e^{-(a/b)\ (B^{x-y}\ BW^z)(t)} \qquad (20)$$

A Naperian log–linear plot of $C/(D/B^y)$ versus $(B^{x-y}\ BW^z)(t)$ is linear (and superimposable across species) with a slope of $-(a/b)$ and intercept ln (1/b). Figure 1 illustrates this plot for antipyrine. The area under this syndesichron curve is (1/a). We define[67] one centi-syndesichron, expressed in chronological time units, as $B^{y-x}\ BW^{-z}$. The abscissa of the syndesichron plot represents cumulative elapsed centi-syndesichrons. Consider variables from two species:

Human	Dog
B = 70.0 kg	B = 10.0 kg
BW = 1.53 kg	BW = 0.0531 kg
t = 14.6 min	t = 3.84 min

where x = 1.30, y = 0.950, z = −0.600, a = 0.400

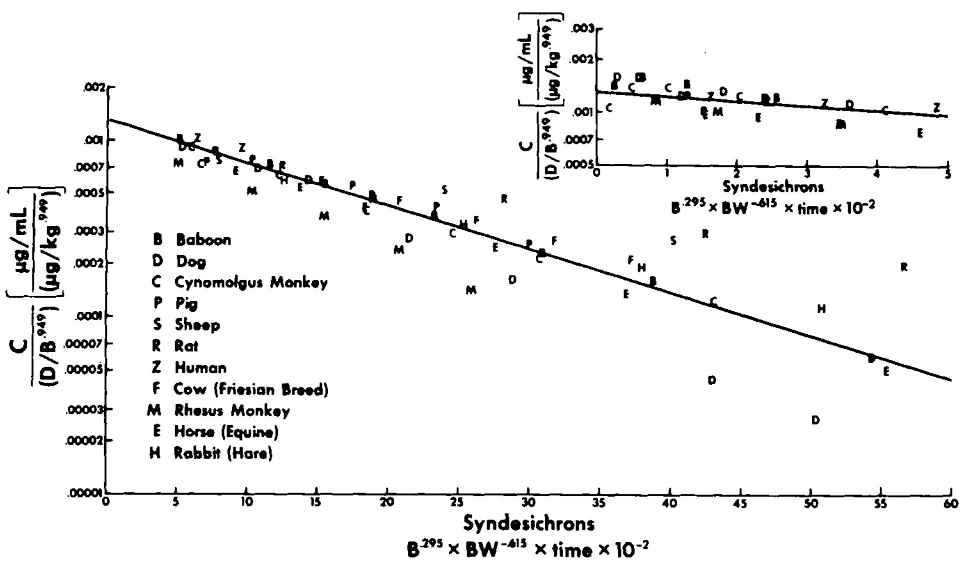

Figure 1—*Semilogarithmic syndesichron plot for antipyrine disposition in 11 mammalian species. Reprinted with permission from ref 67. Copyright 1984, Marcel Dekker, Inc.*

$mL{\cdot}min^{-1}{\cdot}kg^{-x}{\cdot}kg^{-z}$, and b = 0.750 $L{\cdot}kg^{-y}$. One-human and -dog centi-syndesichrons are equivalent to 0.292 and 0.0767 min, respectively. In each centi-syndesichron space–time unit, the two species will have eliminated the same fraction of dose from their bodies and cleared the same volume of plasma per kg^y body mass. In 14.6 min in the human and 3.84 min in dog (corresponding to 50 centi-syndesichrons in both species), 2.63% of the dose would be eliminated and a volume of 20 $mL/kg^{0.95}$ body mass would be cleared (the 0.95 exponent equals y).

In the special case where z = 0, $CL = aB^x$, and $Vd = bB^y$, the space–time unit is an apolysichron. If z = 0, y = 1, $CL = aB^x$, and $Vd = bB^{1.0}$, the space–time unit is a kallynochron. When clearance is expressed as a unique function of maximum lifespan potential (MLP), $CL = aB^x/MLP$, the fundamental unit becomes a dienetichron (see ref 67 for definitions and discussions of pharmacokinetic space–time units). As noted by Adolph[63]: "... no limitation is imposed by anything but the time and effort of investigation, upon the range of organisms and upon the array of properties that may be considered in interrelations." If, for example, the simple allometric expression does not suffice in characterizing volume of distribution, and this is due to variations in plasma free fractions, a free fraction term could be empirically incorporated into the mathematical relationship.

The aforementioned units result from the transformation of a physical time-scale (chronological time) to units in which the rate of change of the pharmacokinetic process becomes invariant in space–time. Historically, the search for order through comparisons of interspecies pharmacokinetic parameters using a single time frame has been a conspicuous failure. Measurement and evaluation of pharmacokinetic space–time phenomena offer a field of experimentation where a broad array of methodological operations and opinions may be evaluated heuristically. On the negative side, the empirical allometric approach has left us without confidence that we know what we are doing.[77]

Theory of Phase I Hepatic Pharmacokinetic Stuff—Wilkinson[78] noted that species which have successfully survived and developed in an often hostile chemical environment have done so in part because they evolved a variety of mechanisms which provided a measure of resistance (selective advantage) against potentially harmful chemical elements. The naturally occurring lipophilic xenobiotics represent the greatest threat, since their physicochemical properties impede easy removal in the aqueous media through which excretion occurs.

For drugs whose physicochemical properties foster phase I hepatic metabolism in a manner similar to that applied to naturally occurring xenobiotics, it is assumed that pharmacokinetic parameters characterize rate processes which evolved in the wild to rid the organism of these potentially toxic substances.[67] The theory of phase I hepatic pharmacokinetic stuff states that among terrestrial, eutherian mammalian species, the weighted, mean CLu_{int} for phase I hepatic metabolism of all naturally occurring xenobiotics ingested by a species, multiplied by MLP/B, is relatively invariant.[67] This association between lifespan and rates of phase I hepatic metabolism is obviously uninterpretable in terms of causation.[79–81]

Expressed in units of chronological time, short-lived species tend to have larger CLu_{int} parameters than longer-lived species of equal size. Not only is there a strong departure for human beings in the simple allometric relationships for brain size and lifespan, but also for many CLu_{int} parameters.[67,77,82] Yates and Kugler[77] view this as a manifestation of the effects of neoteny (the impact of neoteny on both brain mass and CLu_{int} is responsible for the empirical correlation between these two variables). Neoteny,[83] the retardation of somatic development for selected organs and parts, occurs in K-selected regimes, that is, for species characterized by a low reproductive effort, late maturation, greater size, longer life, and a tendency to invest a great deal of parental care in their offspring. Retardation of development provides a longer period of time for the amplification of enhanced morphologic complexity as well as better learning and social development. These features are adaptive traits in environments with dwindling resources.[83] K-selection occurs in ecosystems where density is high and competition for resources is intense. Under these conditions, channeling of resources into production and survival of a few offspring of high competitive ability is an optimal strategy. In contrast, r-selection occurs when populations can expand with no negative feedback on growth rate brought about by limiting resources. These strategists tend to channel all possible resources into production of numerous progeny; limited parental care and early maturation are characteristics tending to maximize the rate at which these progeny colonize an uncrowded environment. In reality, there is an r–K continuum where, under specific conditions, one selection regime might predominate.

Allometric versus Reductionist Scaling—Pharmacokinetic systems arise from multileveled structures in which each level consists of subsystems that are simultaneously wholes with respect to their parts and parts in relation to their larger wholes.[84] The dominant conceptual framework in pharmacokinetics today is to reduce organisms to constituent parts in order to study properties and mechanisms through which components interact. When necessary, adjustments in anatomical features, blood flows, partitioning characteristics, et cetera, are employed to extrapolate data and conclusions from one species to another (reductionist or physiological modeling paradigm).[85,86] The functional arrangement of these systems assumes that tissues and organs are neatly bounded compartments sequestered from the rest of the body, that is, from noncontiguous components. The success of reductive analysis in pharmacokinetics stems mainly from the fact that the properties that have been of most interest to the majority of investigators are exactly those which respond best to reductionist treatment. When taken to an extreme, phenomena which cannot be explained in reductionist terms are deemed by reductionists as unworthy of scientific investigation.

The more broadly based allometric paradigm treats separate objects of the reductionist paradigm as elements of dynamic whole. Its premise is that pharmacokinetic processes are genetically integrated in a remarkably coordinated system, and this linkage places extraordinary restrictions on what can or is most likely to occur. Explanation in terms of arrangement and mechanisms is forfeited in favor of characterization of relevant integrative features in terms of constitutional variables. Emphasis is placed on scale alterations, the goal of which is to manipulate variables of interest so they are unified (invariant) in their relation to one another (as in pharmacokinetic space–time). The organism itself frequently becomes the coordinate system upon which time scales are based; clock time is transformed into a form that becomes species invariant with respect to pharmacokinetic processes. The overall consistency of interrelations determines the structure of the network. Instead of concentrating on basic building blocks as in the reductionist paradigm, underlying principles of organization and function (especially in relation to their interactions with the environment) are emphasized. The reductionist and allometric approaches are complementary. Used in proper balance, they should help provide a deeper understanding of the evolution and functioning of drug absorption and disposition systems.

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