The Times of Time

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Time is such a complex universe that it requires much more exploration than these short insights. I/we shall take *time* to breathe, reflect, discuss, inquire, search select, cherry-pick or exclude, and if-and-when *time* allows, present a follow-up or a novel take on *time.*

In April 2018, in the Faraday Theatre at the Royal Institution in London, Carlo Rovelli gave an hour-long lecture on the nature of time (check it in the References and watch it!). A red thread spanned the stage, a metaphor for the Italian theoretical physicist's subject. "*Time is a long line,"* he said. To the left lies the past—the dinosaurs, the big bang—and to the right, the future—the unknown. "*We're sort of here*," he said, hanging a carabiner on it, as a marker for the present.

Then he flipped the script. "*I'm going to tell you that time is* not *like that,"* he explained.

Rovelli went on to challenge our common-sense notion of time, starting with the idea that it ticks everywhere at a uniform rate; in fact, clocks tick slower when they are in a stronger gravitational field. When you move nearby clocks showing the same time into different fields—one in space, the other on Earth, say—and then bring them back together again, they will show different times. "*It's a fact,"* Rovelli said, and it means "*your head is older than your feet*." Also, a non-starter is any shared sense of "*now."* We don't really share the present moment with anyone. "*If I look at you, I see you now—well, but not really, because light takes time to come from you to me,"* he said. "*So, I see you sort of a little bit in the* past*."* As a result, "*now*" means nothing beyond the temporal bubble "*in which we can disregard the time it takes light to go back and forth."*

Rovelli turned next to the idea that time flows in only one direction, from past to future. Unlike general relativity, quantum mechanics, and particle physics, thermodynamics embeds a direction of time. Its second law states that the total entropy, or disorder, in an isolated system never decreases over time. Yet this doesn't mean that our conventional notion of time is on any firmer grounding. Entropy, or disorder, is subjective: "*Order is in the eye of the person who looks*." In other words, the distinction between past and future, the growth of entropy over time, depends on a macroscopic effect— "*the way we have described the system, which in turn depends on how we interact with the system. A million years of your life would be neither past nor future for me. So, the present is not thin; it's horrendously thick*."

The equations for quantum gravity he's written down suggest three things, he said, about what "*clocks measure.*" First, there's a minimal amount of time—its units are not infinitely small. Second, since a clock, like every object, is quantum, it can be in a superposition of time readings. "*You cannot say between this event and this event is a certain amount of time, because, as always in quantum mechanics, there could be a probability distribution of time passing*." Which means that third, in quantum gravity, you can have "*a local notion of a sequence of events, which is a minimal notion of time, and that's the only thing that remains*." Events aren't ordered in a line "*but are confused and connected*" to each other without "*a preferred time variable—anything can work as a variable.*"

Even the notion that the present is fleeting doesn't hold up to scrutiny. It is certainly true that the present is "*horrendously short*" in classical, Newtonian physics. "*But that's not the way the world is designed*". Light traces a cone, or consecutively larger circles, in four-dimensional spacetime like ripples on a pond that grow larger as they travel. No information can cross the bounds of the light cone because that would require information to travel faster than the speed of light. "*In spacetime, the past is whatever is inside our past light-cone*. *So, it's whatever can affect us. The future is this opposite thing, So, in between the past and the future, there isn't just a single line—there's a huge amount of time.*" Now, imagine that you lived in Andromeda, which is two and a half million light years away. "*A million years of your life would be neither past nor future for me. So, the present is not thin; it's horrendously thick*."

"*Studying time is like holding a snowflake in your hands: gradually, as you study it, it melts between your fingers and vanishes*." (Carlo Rovelli, *The Order of Time*)

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Early November 2016 Jan W. Vasbinder, Director of the Para Limes Institute of NTU came to spend two days at my home, and he mentioned his intention to organize a major International Conference on Time –in its different aspects- in March 2018 in Singapore.

Jan is a physicist, and his professional approach to Time is somewhat different from mine. But he –again- sparked interest and thirst in me, and I delved into my usual sources of knowledge, i.e. Google, Wikipedia, and the myriad of tools available online.

The harvest was overwhelming, and the toughest order was the selection of concise, relevant, comprehensible (but not totally comprehensive), intelligible information.

This first essay is a draft of an attempt. I was caught between being pontifical and simplistic; this shows, and I failed to translate in accessible terms many highly technical jargons: I apologize. The list of references may help some to find more useful information and blame my guillotine.

Eternity is long. Especially towards the end…

Franz Kafka

(Part 1)

"Time brings all things to pass"

Aeschylus - The Libation Bearers

https://www.youtube.com/watch?v=wxMeu34o_jQ

As Wikipedia introduces '*Time is the indefinite continued progress of existence and events that occur in apparently irreversible succession from the past through the present to the future. Time is a component quantity of various measurements used to sequence events, to compare the duration of events or the intervals between them, and to quantify rates of change of quantities in material reality or in the conscious experience. Time is often referred to as the fourth dimension, along with the three spatial dimensions*.'

Defining time in a manner applicable to all fields without circularity has consistently eluded scholars. Nevertheless, diverse fields such as business, industry, sports, the sciences, and the performing arts all incorporate some notion of time into their respective measuring systems.

Two contrasting viewpoints on *time* divide prominent philosophers. One view is that time is part of the fundamental structure of the universe—a dimension independent of events, in which events occur in sequence. Isaac Newton subscribed to this realist view, and hence it is sometimes referred to as Newtonian time.

The opposing view is that *time* does not refer to any kind of "container" that events and objects "move through", nor to any entity that "flows", but that it is instead part of a fundamental intellectual structure (together with space and number) within which humans sequence and compare events. This view, e.g. for Gottfried Leibniz and Immanuel Kant, holds that time is neither an event nor a thing, and is not itself measurable nor can it be travelled.

In Physics, *time* is unambiguously operationally defined as "what a clock reads". Time is one of the seven fundamental physical quantities in both the International System of Units (SI) and International System of Quantities (ISQ). Time is used to define other quantities—such as velocity—so defining time in terms of such quantities would result in circularity of definition. An operational definition of time, wherein one says that observing a certain number of repetitions of one or another standard cyclical event (such as the passage of a free-swinging pendulum) constitutes one standard unit such as the second, is highly useful in the conduct of both advanced experiments and everyday affairs of life.

The operational definition leaves aside the question whether there is something called time, apart from the counting activity just mentioned, that flows and can be measured. Investigations of a single continuum called space-time bring questions about space into questions about time, questions that have their roots in the works of early students of natural philosophy.

Furthermore, there is a subjective component to time, but is time "felt" as a sensation, or is it a judgment, is still a matter of debate.

Measurement of time was a prime motivation in navigation and astronomy. Periodic events and periodic motion have long served as standards for units of time. Examples include the apparent motion of the sun across the sky, the phases of the moon, the swing of a pendulum, and the beat of a heart. Currently, the international unit of time, the second, is defined by measuring the electronic transition frequency of cesium atoms. Time is also of significant social importance, having economic value ("time is money") as well as personal value, due to an awareness of the limited time in each day and in human life spans.

Measuring Time

Chronometry takes two distinct forms: the calendar, a mathematical tool for organizing intervals of time, and the clock, a physical mechanism that counts the passage of time. In every day's life, the clock is consulted for periods less than a day whereas the calendar is consulted for periods longer than a day.

Now personal electronic devices display both calendars and clocks simultaneously.

The number (as on a clock dial or calendar) that marks the occurrence of a specified event as to hour or date is obtained by counting from a fiducial epoch—a central reference point.

Standards and Definitions

Originally the second was defined as 1/86,400 of the mean solar day, which is the year-average of the solar day, being the time interval between two successive noons,

i.e. the time interval between two successive passages of the sun across the meridian. In 1832 Carl-Friedrich Gauss introduced the CGS (centimeter/ gram/second system) combining fundamental units of length, mass and time. This second is "elastic", because tidal friction is slowing the earth's rotation rate. For use in calculating ephemerides of celestial motion, therefore, in 1952 astronomers introduced the "ephemeris second", currently defined as the fraction 1/31,556,925.9747 of the tropical year for 1900 January 0 at 12 hours ephemeris time.

The CGS system has been superseded by the *Système International* (SI). The SI base unit for time is the SI second.

The International System of Quantities, which incorporates the SI, also defines larger units of time equal to fixed integer multiples of one second (1 s), such as the minute, hour and day. These are not part of the SI, but may be used alongside the SI. Other units of time such as the month and the year are not equal to fixed multiples of 1s, and instead exhibit significant variations in duration.

The official SI definition of the second is as follows: the second is the duration of 9,192,631,770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the cesium 133 atom. At its 1997 meeting, the CIPM (Comité International des Poids et Mesures) affirmed that this definition refers to a cesium atom in its ground state at a temperature of 0 K. The current definition of the second, coupled with the current definition of the meter, is based on the special theory of relativity, which affirms our space-time to be a Minkowski space. The definition of the second in mean solar time, however, is unchanged. Atomic clocks do not measure nuclear decay rates -a common misperception- but rather measure a certain natural vibrational frequency of Cesium 133.

The concept of a single worldwide universal time-scale might have been conceived many centuries ago, but in practicality the technical ability to create and maintain such a time-scale did not become possible until the mid-19th century. The timescale adopted was Greenwich Mean Time, created in 1847. A few countries have replaced it with Coordinated Universal Time, UTC.

The Global Positioning System also broadcasts a very precise time signal worldwide, along with instructions for converting GPS time to UTC. GPS-time is based on, and regularly synchronized with or from, UTC-time.

Earth is split up into a number of time zones. Most (but not all, e.g. India) time zones are exactly one hour apart, and by convention compute their local time as an offset from UTC. In many locations these offsets vary twice-yearly due to daylight saving time transitions. While a few governments still legally define their national times as being based upon GMT, most major governments have now redefined their national times as being based directly upon UTC.

Sidereal time is the measurement of time relative to a distant star (instead of solar time that is relative to the sun). It is used in astronomy to predict when a star will be overhead. Due to the orbit of the earth around the sun a sidereal day is about 4 minutes (1/366th) less than a solar day.

The term *"time"* is generally used for many close -but different- concepts, including: instant; time interval; date; duration.

Chronology

We can also measure time by studying the past. Events in the past can be ordered in a sequence (creating a *chronology*), and can be put into chronological groups (periodization). One of the most important systems of periodization is the geologic time scale, which is a system of periodizing the events that shaped the Earth and its life. Chronology, periodization, and interpretation of the past are together known as the study of history.

Religion

Many cultures ancient and recent- such as Inca, Mayan, Hopi, and other Native American Tribes -plus the Babylonians, Ancient Greeks, Hinduism, Buddhism, Jainism, and others – have a concept of a wheel of time: they regard time as cyclical and quantic, consisting of repeating ages that happen to every being of the Universe between birth and extinction.

Conversely, the *Islamic and Judeo-Christian* world-view regards time as linear and directional, beginning with the act of creation by God. The traditional Christian view sees time ending, teleologically, with the eschatological end of the present order of things, the "end time".

In the Old Testament book Ecclesiastes, traditionally ascribed to Solomon (970–928 BCE), time -as the Hebrew word עדן, זמן `iddan (time) zĕman (season) is often translated- was traditionally regarded as a medium for the passage of predestined events. While another word, זמן "زمان " zamān, meant time fit for an event, and is used as the modern Arabic, Persian, and Hebrew equivalent to the English word "*time*" i.e. timing.

The Greek language denotes two distinct principles, Chronos (Χρόνος) and Kairos (καιρός) The former refers to numeric, or chronological, time. The latter, literally "the right or opportune moment", relates specifically to metaphysical or divine time. In theology, Kairos is qualitative, as opposed to quantitative.

In *Greek mythology*, Chronos is identified as the Personification of Time. His name in Greek means "time" and is alternatively spelled Chronus (Latin spelling) or Khronos. Chronos is usually portrayed as an old, wise man with a long, gray beard, such as "Father Time". Some English words whose etymological root is khronos/chronos include chronology, chronometer, chronic, anachronism, synchronize and chronicle.

According to *Kabbalists*, "time" is a paradox and an Illusion. Both the future and the past are recognized to be combined and simultaneously present.

Philosophy of Time Abridged

Philosophers also want to know which aspects of time we have direct experience of, and which we have only indirect experience of. Is our direct experience only of the momentary present, as Aristotle, Thomas Reid, and Alexius Meinong believed, or instead do we have direct experience of what William James called a "specious present," a short stretch of physical time? Among those accepting the notion of a specious present, there is continuing controversy about whether the individual specious presents can overlap each other and about how the individual specious presents combine to form our stream of consciousness. According to René Descartes' dualistic philosophy of mind, the mind is not in space, but it is in time.

Aristotle raised the issue of the mind-dependence of time when he said, "Whether, if soul (mind) did not exist, time would exist or not, is a question that may fairly be asked; for if there cannot be someone to count there cannot be anything that can be counted…" (Physics, chapter 14). He does not answer his own question because, he says rather profoundly, it depends on whether time is the conscious numbering of movement or instead is just the capability of movements to be numbered were consciousness to exist.

St. Augustine, adopting a subjective view of time, said time is nothing in reality but exists only in the mind's apprehension of that reality.

The 13th century philosophers Henry of Ghent and Giles of Rome said time exists in reality as a mind-independent continuum, but is distinguished into earlier and later parts only by the mind. In the 13th century, Duns Scotus clearly recognized both physical and psychological time.

In the 20th century, the philosopher of science Bas van Fraassen described time, including physical time, by saying, "There would be no time were there no beings capable of reason" just as "there would be no food were there no organisms, and no teacups if there were no tea drinkers."

The controversy in metaphysics between idealism and realism is that, for the idealist, nothing exists independently of the mind. If this controversy were settled in favor of idealism, then physical time, too, would have that subjective feature. However, like van Fraassen, one can be a realist in general but an idealist about certain specific entities.

When philosophers and scientists have said time is not real, they have meant different things: (1) that being in time is a subjective quality like being green rather than a primary quality like the frequency of light waves; (2) that McTaggart's Atheory is incorrect in saying there is temporal becoming, and that the B-theory with its block universe is the proper way to understand what time is; (3) that only the present is real; (4) that the concept of time is essentially inconsistent or incoherent; (5) that time is not fundamental but rather emerges from something more fundamental. This 5th position can be meant in the sense that time emerges from spacetime, or that it emerges from something else even more fundamental. The 5th position is the super-realist sense of "real" in which water and ice are not real because they are composed of H20 molecules, which are more fundamental. The philosopher Craig Callender offers a different reason for believing time is not real. Time is more like money, a feature of reality that exists only because of conventions accepted by humans for their convenience. Although it would be inconvenient to do so, our society could eliminate money and return to barter transactions. Analogously, Callender asks us to consider the question, “Who needs time anyway”?

Most philosophers agree that time does exist, that it is objective rather than subjective, and that it is real regardless of whether it is fundamental or emergent. They just cannot agree on what time is.

One straightforward answer to our question, “What is time?” is that time is whatever the time variable t is denoting in the best-confirmed and most fundamental theories of current science (relativity, quantum mechanics, and the Standard Model of particle physics). Nearly all philosophers would agree that we do learn much about physical time by looking at the behavior of the time variable in these fundamental scientific theories; but they complain that the full nature of physical time can be revealed only with a philosophical theory of time that addresses the many philosophical issues that scientists do not concern themselves with.

Aristotle claimed that “time is the measure of change” (Physics, chapter 12). He never said space is a measure of anything. Aristotle emphasized “that time is not change [itself]” because a change “may be faster or slower, but not time…” (Physics, chapter 10). For example, a leaf can fall faster or slower, but time itself cannot be faster or slower. In developing his views about time, Aristotle advocated what is now referred to as the relational theory when he said, “there is no time apart from change….” (Physics, chapter 11). In addition, Aristotle said time is not discrete or atomistic but “is continuous…. In respect of size there is no minimum; for every line is divided ad infinitum. Hence it is so with time” (Physics, chapter 11).

René Descartes had a very different answer to “What is time?” He argued that a material body has the property of spatial extension but no inherent capacity for temporal endurance, and that God by his continual action sustains (or re-creates) the body at each successive instant. Time is a kind of sustenance or re-creation ("Third Meditation" in Meditations on First Philosophy).

In the 17th century, the English physicist Isaac Barrow rejected Aristotle’s linkage between time and change. Barrow said time is something that exists independently of motion or change and which existed even before God created the matter in the universe. Barrow's student, Isaac Newton, agreed with this substantival theory of time. Newton argued very specifically that time and space are like an infinitely large container for all events, and that the container exists with or without the events. He added that space and time are not material substances, but are like primary substances in not being dependent on anything except God.

Gottfried Leibniz objected. He argued that time is not an entity existing independently of actual events. He insisted that Newton had underemphasized the fact that time necessarily involves an ordering of events. This is why time "needs" events, so to speak. Leibniz added that this overall order is time. He accepted a relational theory of time and rejected a substantival theory.

In the 18th century, Immanuel Kant said time and space are forms that the mind projects upon the external things-in-themselves. He spoke of our mind structuring our perceptions so that space always has a Euclidean geometry, and time has the structure of the mathematical line. Kant's idea that time is a form of apprehending phenomena is probably best taken as suggesting that we have no direct perception of time but only the ability to experience individual things and events in time. Some historians distinguish perceptual space from physical space and say that Kant was right about perceptual space. It is difficult, though, to get a clear concept of perceptual space. If physical space and perceptual space are the same thing, then Kant is claiming we know a priori that physical space is Euclidean. With the discovery of non-Euclidean geometries in the 19th century, and with increased doubt about the reliability of Kant's method of transcendental proof, the view that truths about space and time are a priori truths began to lose favor.

In the early 20th century, Alfred North Whitehead said time is essentially the form of becoming—a cryptic, but interesting philosophical claim.

By contrast, a physics book will say time is locally a linear continuum of instants. Michael Dummett's model of time implies instead that time is a composition of nonzero periods rather than of instants.

His model also is constructive in the sense that it implies there do not exist any times which are not detectable in principle by a physical process.

Is Time "Real"?

Antiphon the Sophist (480-411 BCE) held that: *"Time is not a reality (ὑπόστασις, hypostasis), but a concept (νόημα, noêma) or a measure (μέτρον, metron)."* Parmenides went further, maintaining that time, motion, and change were illusions, leading to the paradoxes of his follower Zeno.

Time as an illusion is also a common theme in Buddhist thought.

These arguments often center on what it means for something to be unreal. Modern physicists generally believe that time is as real as space—though others, such as Julian Barbour in *The End of Time*, argue that quantum equations of the universe take their true form when expressed in the timeless realm containing every possible now or momentary configuration of the universe, called '*platonia*' by Barbour.

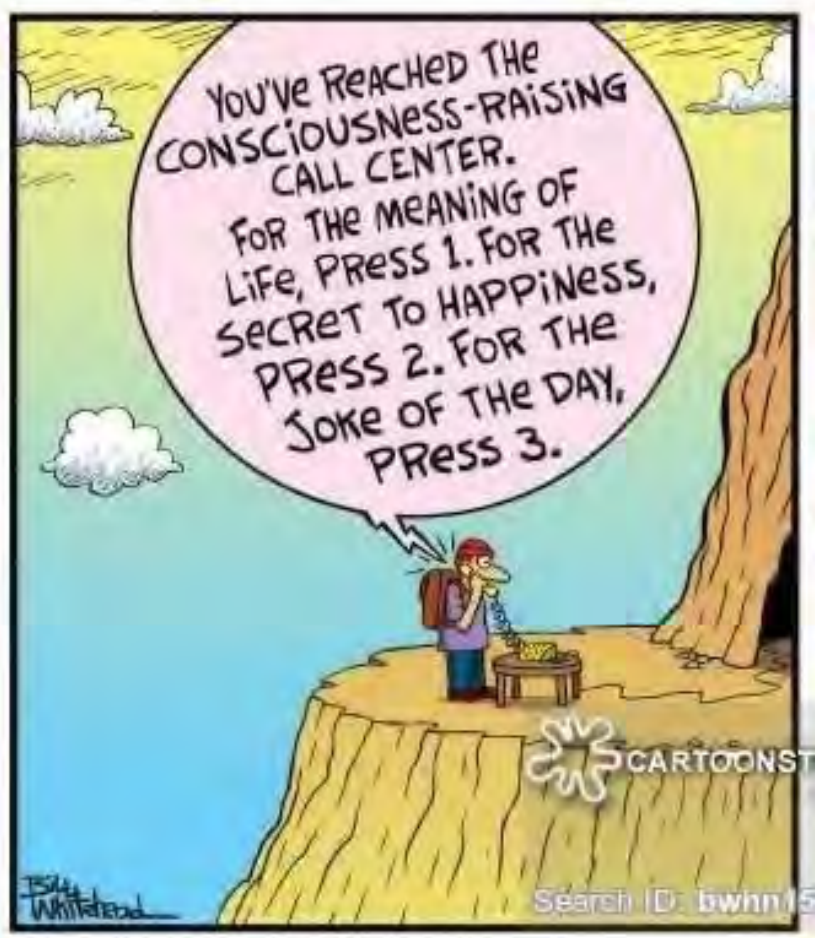
There is no agreed upon answer to why our universe exists instead of doesn't exist, and why it contains time instead of no time, and why it contains physical laws instead of no physical laws, although there has been interesting speculation on all these related issues. Assuming that the existence of time is not just a brute fact, the most popular reason from physicists for why time exists is that a timeless and spaceless nothing is unstable and will decay naturally and inevitably to a lower energy in which there is spacetime with events. Philosophers may ask the cosmologist at this point why there are laws that imply the world behaves this way, but there is a favored answer to this, too, which is that the laws just evolved at random without a supernatural Lawgiver. The Multiverse Theory describes this random evolutionary process.

Given that spacetime exists, why is it not empty—empty of all particles and fields? In other words, why isn't there pure nothingness? The leading answer from the physicists' cosmological theories is that the philosophers' pure nothingness is unstable and that the cosmologists' quantum vacuum is more stable because it is at a lower energy than pure nothingness. The quantum vacuum necessarily contains particles and fields. As to the natural follow-up question of why there are laws making the universe behave this way, there is an answer from the Multiverse Theory—the universe had to be this way because any specific 'way' is inevitable. This last point is that our universe might have the laws it has by a random process, by a process in which any possible universe inevitably arises as an actual universe according to the Multiverse Theory, in analogy to how continual reshuffling a deck of cards inevitably produces any possible ordering of the cards. And to improve the analogy, one should suppose that there is no Supernatural Shuffler involved.

A modern philosophical theory called presentism views the past and the future as human-mind interpretations of movement instead of real parts of time (or "dimensions") that coexist with the present. This theory rejects the existence of all direct interaction with the past or the future, holding only the present as tangible. This is one of the philosophical arguments against time travel. This contrasts with eternalism (all time: present, past and future, is real) and the growing block theory (the present and the past are real, but the future is not).

From a biocentric point of view, time is the inner process that animates consciousness and experience.

New experiments confirm this concept. In 2002, scientists carried out an amazing experiment, which showed that pairs of particles knew in advance what its twin would do in the future. Somehow, the particles knew what the researcher would do before it happened, as if there were no space or time between them. More recently (*Science,* 2007), scientists shot particles into an apparatus, and showed they could retroactively change something that had already happened. The particles had to decide what to do when they passed a fork in the apparatus. Later on the experimenter could flip a switch. It turns out what the observer decided at that point, determined what the particle did at the fork in the past. The knowledge in observer's mind is the only thing that determines how they behave.



Time Travel

Time travel is the concept of moving backwards or forwards to different points in *time*, in a manner analogous to moving through *space*, and different from the normal "flow" of time to an earthbound observer. In this view, all points in time (including future times) "persist" in some way. Time travel has been a plot device in fiction since the 19th century. Traveling backwards in time has never been verified, presents many theoretical problems, and may be impossible. Any technological device, whether fictional or hypothetical, that is used to achieve time travel is known as a time machine.

Most scientists and philosophers of time agree that there is good evidence that human time travel has occurred. To explain, let's first clarify the term "time travel."

We mean physical time travel, not psychological time travel, nor travel by dreaming of being at another time. Here is David Lewis' well-accepted definition:

"In any case of physical time travel, the traveler's journey as judged by a correct clock attached to the traveler takes a different amount of time than the journey does as judged by a correct clock of someone who does not take the journey."

David Lewis' definition of time travel has no implications about whether, if you travel forward to the year 2276 or backward to 1776, you can suddenly pop into existence then, or instead must have traveled continuously through all the intervening years. If Lewis' definition is acceptable, then any requirement that rules out sudden appearance and demands spatiotemporal continuity will have to be supported by an additional argument. The argument that relativity theory requires this continuity is such an argument.

One point to keep in mind is that even if a certain kind of time travel is logically possible, it does not follow that it is physically possible. Our understanding of what is physically possible about time travel comes primarily from the implications of Einstein's general theory of relativity. This theory has never failed any of its many experimental tests, so most experts trust its implications for time travel.

Einstein's general theory of relativity permits two kinds of future time travel—either by moving at high speed or by taking advantage of the presence of an intense gravitational field. Let's first consider the time travel due to high speed. Actually any motion produces time travel (relative to the clocks of those who do not travel). That makes every bicycle be a time machine. If you move at a higher speed, then the forward time travel is more noticeable. With extremely high speed, you can return to Earth to find that the year is 2276 (as measured by clocks fixed to the Earth) while your personal clock measures that merely ten years have elapsed. Both clocks can give correct readings of the time.

You can participate in that future, not just view it. But time travel that *changes* the future is impossible. And you cannot use high speed in order to visit the future of the world after your death. Nor can you reverse your velocity and go back to the time before you began your journey.

According to relativity theory, with time travel due to high speed, you do not suddenly jump discontinuously into the future. Instead, you have continually been traveling forward in both your personal time and the Earth's external time, and you could have been continuously observed from Earth's telescopes during your voyage, although these Earth observers would notice that you are very slow about turning the pages in your monthly calendar.

As measured by an Earth-based clock, it takes 100,000 years for light to travel across the Milky Way Galaxy, but if you took the same trip in a spaceship traveling at very near the speed of light, the trip might last only twenty-five years, as judged by your own clock. In principle, you have enough time to travel anywhere before you die.

A second kind of future time travel is due to a difference in the strength of the gravitational field between two places. If you left Earth in a spaceship that flew close to a black hole and then returned, you might return and find that you now look as youthful as your grandchildren although you would be much older than them, as judged by their clocks. You will not, however, be more youthful than the 'you' who stepped into the spaceship.

How about travel to the past, the more interesting kind of time travel? This is not allowed by either Newton's physics or Einstein's special theory of relativity, but appears to be allowed by the general theory of relativity, although this claim has been disputed. In 1949, Kurt Gödel convinced Albert Einstein that in some unusual worlds that obey the equations of general relativity—but not in the actual world—you can continually travel forward in your personal time but eventually arrive into your own past.

When we speak of our time traveling to the future, we normally mean travel to someone else's future but not to our *own* future. When we speak of our time traveling to the past, we normally mean travel to our own past. Unfortunately, say nearly all philosophers and scientists, even if you do travel to your own past, you will not do anything that has not already been done, or else there would be a contradiction. In fact, if you do go back, you would already have been back there. For this reason, if you go back in time and try to kill your grandfather before he conceived a child, you will fail no matter how hard you try. You will fail because you *have* failed.

The metaphysician David Lewis believes you can in one sense kill your grandfather but cannot in another sense. You can, relative to a set of facts that does not include the fact that your grandfather survived to have children. You cannot, relative to a set of facts that does include this fact. The metaphysician Donald C. Williams disagrees, and argues that we always need to make our “can” statement relative to all the available facts. Lewis is saying you can and can’t, and you can but won’t.

Williams is saying simply that you can’t, so you won’t.

A central problem with time travel to the past is the violation of causality; should an effect precede its cause, it would give rise to the possibility of a temporal paradox.

Some interpretations of time travel resolve this by accepting the possibility of travel between branch points, parallel realities, or universes.

Another solution to the problem of causality-based temporal paradoxes is that such paradoxes cannot arise simply because they have not arisen. As illustrated in numerous works of fiction, free will either ceases to exist in the past or the outcomes of such decisions are predetermined.

As such, it would not be possible to enact the grandfather paradox because it is a historical fact that your grandfather was not killed before his child (your parent) was conceived. This view doesn't simply hold that history is an unchangeable constant, but that any change made by a hypothetical future time traveler would already have happened in his or her past, resulting in the reality that the traveler moves from.

Here are a variety of philosophical arguments against past-directed time travel (into one's own past, not merely someone else's past):

1. You could go back in time and kill your grandfather, so then you wouldn’t be born and couldn’t go back in time and kill your grandfather. That’s a contradiction.
2. If past time travel were possible, then you could be in two different bodies at the same time, which is metaphysically impossible.
3. If you were to go back to the past, then you would have been fated to go back because you already did, and this rules out free will. Yet we do have free will, so travel to the past is impossible.
4. If past time travel were possible, then you could die before you were born, which is metaphysically impossible.
5. If you were presently to go back in time, then your present events would cause past events, which violates our concept of causality.
6. Time travel is impossible because, if it were possible, we should have seen

many time travelers by now, but nobody has encountered any time travelers.

7. If past time travel were possible, criminals could avoid their future arrest by traveling back in time, but that is absurd, so time travel is, too.

8. If there were time travel, then when time travelers go back and attempt to change history, they must always botch their attempts to change anything, and it will appear to anyone watching them at the time as if Nature is conspiring against them. Since observers have never witnessed this apparent conspiracy of Nature, there is no time travel.

9. Travel to the past is impossible because it allows the gaining of information for free. Here is a possible scenario. Buy a copy of Darwin's book The Origin of Species, which was published in 1859. In the 21st century, enter a time machine with it, go back to 1855 and give the book to Darwin himself. He could have used your copy in order to write his manuscript that he sent off to the publisher. If so, who first came up with the knowledge about evolution? Neither you nor Darwin. This is free information. Because this scenario contradicts what we know about where knowledge comes from, past-directed time travel isn't really possible.

10. The philosopher John Earman describes a rocket ship that carries a time machine capable of firing a probe (perhaps a smaller rocket) into its recent past. The ship is programmed to fire the probe at a certain time unless a safety switch is on at that time. Suppose the safety switch is programmed to be turned on if and only if a sensing device on the ship detects the “return” or “impending arrival” of the probe. Does the probe get launched? It seems to be launched if and only if it is not launched. However, the argument of Earman’s Paradox depends on the assumptions that the rocket ship does work as intended—that people are able to build the computer program, the probe, the safety switch, and an effective sensing device. Earman himself says all these premises are acceptable and so the only weak point in the reasoning to the paradoxical conclusion is the assumption that travel to the past is physically possible. There is an alternative solution to Earman’s Paradox. Nature conspires to prevent the design of the rocket ship just as it conspires to prevent anyone from building a gun that shoots if and only if it does not shoot. We cannot say what part of the gun is the obstacle, and we cannot say what part of Earman’s rocket ship is the obstacle.

These complaints about travel to the past are a mixture of arguments that pastdirected time travel is not logically possible, that it is not physically possible, that it is not technologically possible with current technology, and that it is unlikely, given today's empirical evidence.

If time were two-dimensional, we probably could travel back in time analogously to how we can get back to the starting point of our run around an oval racetrack. But time is not two-dimensional.

Time as Space

Although time is regarded as an abstract concept, there is increasing evidence that *time* is conceptualized in the mind in terms of *space*. That is, instead of thinking about time in a general, abstract way, humans think about time in a spatial way and mentally organize it as such. Using space to think about time allows humans to mentally organize temporal events in a specific way. This spatial representation of time is often represented in the mind as a Mental Time Line (MTL). Using space to think about time allows humans to mentally organize temporal order. Many environmental factors shape these origins –for example, literacy appears to play a large role in the different types of MTLs, as reading/writing direction provides an everyday temporal orientation that differs from culture to culture. In Western cultures, the MTL may unfold rightward (with the past on the left and the future on the right) since people read and write from left to right. Western calendars also continue this trend by placing the past on the left with the future progressing toward the right. Conversely, Israeli-Hebrew speakers read from right to left, and their MTLs unfold leftward (past on the right with future on the left), and evidence suggests these speakers organize time events in their minds like this as well.

This linguistic evidence that abstract concepts are based in spatial concepts also reveals that the way humans mentally organize time events varies across culture – that is, a certain specific mental organization system is not universal.

So, although Western cultures typically associate past events with the left and future events with the right per a certain MTL, this kind of horizontal, egocentric MTL is not the spatial organization of all cultures.

Although most developed nations use an egocentric spatial system, there is recent evidence that some cultures use an allocentric spatialization, often based on environmental features.

A recent study of the indigenous Yupno people of Papua New Guinea focused on the directional gestures used when individuals used time-related words. When speaking of the past (such as "last year" or "past times"), individuals gestured downhill, where the river of the valley flowed into the ocean. When speaking of the future, they gestured uphill, toward the source of the river. This was common regardless of which direction the person faced, revealing that the Yupno people may use an allocentric MTL, in which time flows uphill.

A similar study of the Pormpuraawans, an aboriginal group in Australia, revealed a similar distinction in which when asked to organize photos of a man aging "in order," individuals consistently placed the youngest photos to the east and the oldest photos to the west, regardless of which direction they faced. This directly clashed with an American group that consistently organized the photos from left to right. Therefore, this group also appears to have an allocentric MTL, but based on the cardinal directions instead of geographical features.

The wide array of distinctions in the way different groups think about time leads to the broader question that different groups may also think about other abstract concepts in different ways as well, such as causality and number.

Time in Physics

Until Einstein's reinterpretation of the physical concepts associated with time and space, time was considered to be the same everywhere in the universe, with all observers measuring the same time interval for any event. Non-relativistic classical mechanics is based on this Newtonian idea of time.

Einstein, in his special theory of relativity, postulated the constancy and finiteness of the speed of light for all observers. He showed that this postulate, together with a reasonable definition for what it means for two events to be simultaneous, requires that distances appear compressed and time intervals appear lengthened for events associated with objects in motion relative to an inertial observer.

The theory of special relativity finds a convenient formulation in Minkowski spacetime, a mathematical structure that combines three dimensions of space with a single dimension of time. In this formalism, distances in space can be measured by how long light takes to travel that distance, e.g., a light-year is a measure of distance, and a meter is now defined in terms of how far light travels in a certain amount of time. Two events in Minkowski spacetime are separated by an invariant interval that can be space-like, light-like, or time-like. Events that have a time-like separation cannot be simultaneous in any frame of reference, there must be a temporal component (and possibly a spatial one) to their separation.

Events that have a space-like separation will be simultaneous in some frame of reference, and there is no frame of reference in which they do not have a spatial separation.

Different observers may calculate different distances and different time intervals between two events, but the invariant interval between the events is independent of the observer (and his velocity).

Spacetime

Time has historically been closely related with space, the two together merging into spacetime in Einstein's special relativity and general relativity. According to these theories, the concept of time depends on the spatial reference frame of the observer, and the human perceptions as well as the measurement by instruments such as clocks are different for observers in relative motion. For example, if a spaceship carrying a clock flies through space at (very nearly) the speed of light, its crew does not notice a change in the speed of time on board their vessel because everything traveling at the same speed slows down at the same rate (including the clock, the crew's thought processes, and the functions of their bodies). However, to a stationary observer watching the spaceship fly by, the spaceship appears flattened in the direction it is traveling and the clock on board the spaceship appears to move very slowly.

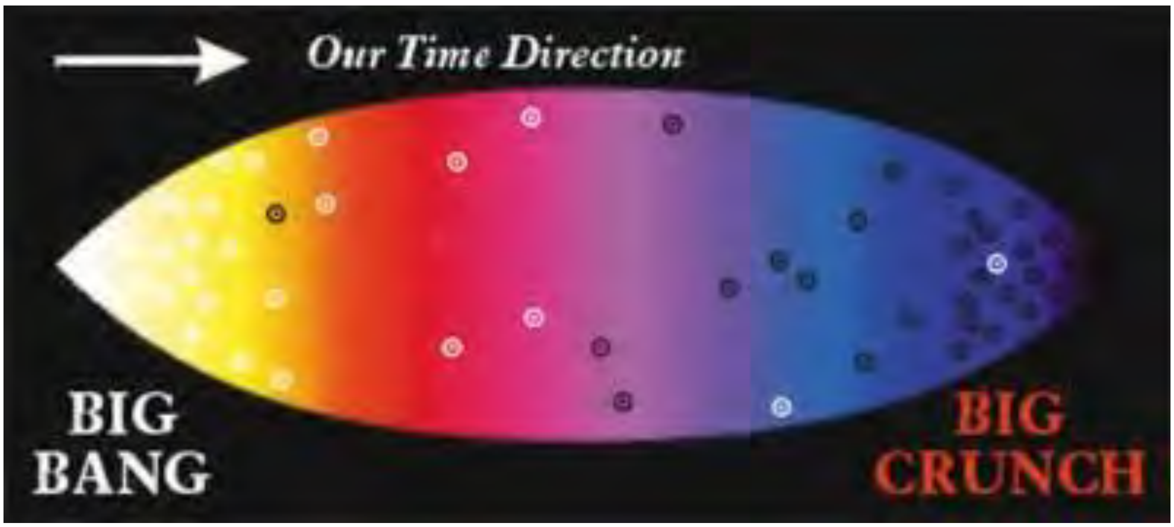
On the other hand, the crew on board the spaceship also perceives the observer as slowed down and flattened along the spaceship's direction of travel, because both are moving at very nearly the speed of light relative to each other. Because the outside universe appears flattened to the spaceship, the crew perceives themselves as quickly traveling between regions of space that (to the stationary observer) are many light years apart. This is reconciled by the fact that the crew's perception of time is different from the stationary observer's; what seems like seconds to the crew might be hundreds of years to the stationary observer. In either case, however, causality remains unchanged: the past is the set of events that can send light signals to an entity and the future is the set of events to which an entity can send light signals. Since 1985, more than half of the Nobel prizes in physics have been awarded for work done more than two decades previously. This year's prize, awarded on Tuesday 3 October 2017, was different. It went to Rainer Weiss, Barry Barish and Kip Thorne, all of whom were involved in the first-ever detection, just two years ago –an unusual feat! -, of gravitational waves. Such waves are one of the many predictions of Albert Einstein's century-old theory of relativity. As Einstein realized, gravity arises from the fact that mass distorts the space and time around itself. That distortion modifies the paths of objects moving nearby. Crunch the equations which describe the process, and they suggest that moving masses should create ripples which radiate out into the universe.

Several years ago, observations of the behavior of pairs of dead stars called pulsars provided indirect evidence that such waves are real. But detecting them directly has proved harder, for gravitational waves are ephemeral things. The ones spotted in 2015 came from the collision of a pair of black holes, one of the most violent events in the universe. By the time the ripples from that catastrophe had reached Earth, 1.3 billion years after the event, they had faded into the merest breath. Spotting such susurrations requires sensitive machines. All three laureates worked on an American gravitational-wave detector called LIGO, which was completed in 2002. LIGO works by splitting a laser beam in two and sending the daughter beams up and down a pair of tunnels, each four kilometers long, which are set at right angles to each other. Any passing gravitational wave should stretch and compress the two arms in different ways, causing infinitesimal changes in the time it takes the laser beams to traverse them. In order to confirm that it really is seeing gravitational waves the machine has two such pairs of tunnels—one in Washington state and one in Louisiana. A gravitational wave, as opposed to some transient local disturbance, will be seen almost (but not quite) simultaneously at both. Despite its sensitivity, LIGO's initial run came up empty-handed. It was only after a series of upgrades, starting in 2010, that it became sensitive enough to detect the waves finally and unambiguously. Spotting them meant ruling out interference created by things like lorries travelling on nearby roads, or ocean waves crashing against the shore hundreds of kilometers away.

Since 2015, more discoveries have been made. A few days before the Nobel award, LIGO announced the detection of its fourth gravitational wave. And more detectors are coming online. The most recent detection was aided by a European instrument, VIRGO, based in Italy. Other devices are under construction in India and Japan. A space-based system called LISA, with "arms" millions of kilometers long (and, thus, much higher sensitivity) is scheduled for launch in the 2030s. But the 2017 Physics Prize honors more than just another confirmation of Einstein's cleverness. Machines like LIGO and VIRGO are not merely detectors. They can be used as telescopes, too. Up until now, astronomers have had to rely on the electromagnetic spectrum—from radio waves, through visible light, to gamma radiation—to gaze at the universe. Gravitational waves offer a new window on the world, and could help astronomers see things, like black-hole collisions or the state of the universe, shortly after the Big Bang, that electromagnetism cannot.

Time appears to have a direction -the past lies behind, fixed and immutable, while the future lies ahead and is not necessarily fixed. Yet for the most part the laws of physics do not specify an *arrow of time*, and allow any process to proceed both forward and in reverse. This is generally a consequence of time being modeled by a parameter in the system being analyzed, where there is no "proper time": the direction of the arrow of time is sometimes arbitrary.

Examples of this include the Second law of thermodynamics, which states that entropy must increase over time; the cosmological arrow of time, which points away from the Big Bang, CPT (charge parity and time reversal) symmetry, and the radiative arrow of time, caused by light only traveling forwards in time. In particle physics, the violation of CP (charge conjugation parity) symmetry implies that there should be a small counterbalancing time asymmetry to preserve CPT symmetry. The standard description of measurement in quantum mechanics is also time asymmetric.



Is the existence of change all that is required for there to be time, as Aristotle believed? If so, it is physically possible for there to be a universe in which time exists but has no arrow. If that universe had changes, but those changes were all random in the sense that any process is no more likely to go one way rather than the reverse, then there would be time but no arrow of time. There would be no clocks either.

Some philosophers respond to this reasoning by saying it is distasteful to allow a universe to have time yet have no processes that could serve as clocks, so they recommend saying time's existence requires, by definition, some sort of arrow. They would say that time must be a certain asymmetric ordering of events rather than might be. The dispute between these two philosophical positions is still unresolved.

Now consider the difference between time's *arrow* and time's *arrows*. The direction of entropy change is the *thermodynamic arrow*. Here are some suggestions for additional arrows:

1. Causes precede their effects.
2. We remember last week, not next week.
3. It is easier to know the past than to know the future.
4. There is evidence of the past but not of the future.
5. Our present actions affect the future and not the past.
6. Possibilities decrease as time goes on.
7. Radio waves spread out from the antenna, but never converge into it.
8. Our universe expands in volume rather than shrinks.
9. We see black holes but never white holes; objects fall into but never out of black holes.
10. B meson decay, neutral kaon decay, and Higgs boson decay are each different in a time-reversed world.
11. Quantum mechanical measurement collapses the wave function.
12. We age and never get biologically younger.

Most physicists suspect most of these arrows are somehow linked so that we cannot have some arrows reversing while others do not. For example, the collapse of the wave function is generally considered to be due to an increase in the entropy of our universe. Regarding arrow 12, aging is a process of disorganization accumulating in our cells. It is well accepted that entropy increase can account for the fact that we remember the past but not the future (assuming memory is a form of organization), and that effects follow causes rather than precede them. However, the details of the linkage of the arrows are still an open question.

Could the cosmic arrow of time have gone the *other way*? Most physicists suspect that the answer is yes, and they say it would have gone the other way if the initial conditions of our universe at our Big Bang event had been different. There are initial conditions that make scrambled eggs turn easily into whole eggs but not vice versa, and make bells un-ring but never ring.

In 1902 in *Appearance and Reality*, the British idealist philosopher F. H. Bradley said that when time runs backwards compared to our current world, "*Death would come before birth, the blow would follow the wound, and all must seem irrational*." The

Australian philosopher J.J.C. Smart disagreed about the irrationality. He said all would seem as it is now because memory would become precognition, so an inhabitant of a time-reversed world would feel the blow and *then* the wound.

G. J. Whitrow in *The Natural Philosophy of Time*, defended Bradley and argued that memory would not become precognition; his justification was that memory, by definition, is of whatever happens first, so, "*all must seem irrational*".

Quantum Experiment and Time

(as we think we know it)

"We choose to examine a phenomenon which is impossible, absolutely impossible, to explain in any classical way, and which has in it the heart of quantum mechanics. In reality, it contains the only mystery." - Richard Feynman.

The concept of "*time*" is a weird one, and the world of quantum physics is even weirder. There is no shortage of observed phenomena that defy our understanding of logic, bringing into play thoughts, feelings, emotions –consciousness itself, and a post-materialist view of the universe. This fact is no better illustrated than by the classic double slit experiment, which has been used by physicists (repeatedly) to explore the role of consciousness and its role in shaping/affecting physical reality. The dominant role of a physical material (Newtonian) universe was dropped the second quantum mechanics entered into the equation and shook up the very foundation of science, as it continues to do today.

This quantum uncertainty is defined as the ability, *"according to the quantum mechanics laws that govern subatomic affairs, of a particle like an electron to exist in a murky state of possibility — to be anywhere, everywhere or nowhere at all — until clicked into substantiality by a laboratory detector or an eyeball."*

According to physicist Andrew Truscott, the experiment suggests that **"***reality does not exist unless we are looking at it."* It suggests that we are living in a holographictype of universe.

John Wheeler (1978) asks us to imagine a star emitting a photon billions of years ago, heading in the direction of planet Earth. In between, there is a galaxy. As a result of what's known as "gravitational lensing," the light will have to bend around the galaxy in order to reach Earth, so it has to take one of two paths, go left or go right. Billions of years later, if one decides to set up an apparatus to "catch" the photon, the resulting pattern would be an interference pattern. This demonstrates that the photon took one way, and it took the other way.

One could also choose to "peek" at the incoming photon, setting up a telescope on each side of the galaxy to determine which side the photon took to reach Earth. The very act of measuring or "watching" which way the photon comes in means it can only come in from one side. The pattern will no longer be an interference pattern representing multiple possibilities, but a single clump pattern showing "one" way.

What does this mean? It means how we choose to measure "now" affects what direction the photon took billions of years ago. Our choice in the present moment affected what had already happened in the past….

This makes absolutely no sense, which is a common phenomenon when it comes to quantum physics. Regardless of our ability make sense of it, it's real.

This experiment also suggests that quantum entanglement exists regardless of time. Meaning two bits of matter can actually be entangled, again, in time. Time as we measure it and know it, doesn't really exist.

Quantum Gravity's Time Problem

Theoretical physicists striving to unify quantum mechanics and general relativity into an all-encompassing theory of quantum gravity face what's called the "problem of time."

In quantum mechanics, time is universal and absolute; its steady ticks dictate the evolving entanglements between particles. But in general relativity (Albert Einstein's theory of gravity), time is relative and dynamical, a dimension that's inextricably interwoven with directions x, y and z into a four-dimensional "spacetime" fabric. The fabric warps under the weight of matter, causing nearby stuff to fall toward it (this is gravity), and slowing the passage of time relative to clocks far away. Or hop in a rocket and use fuel rather than gravity to accelerate through space, and time dilates; you age less than someone who stayed at home.

In a new paper (November 2016), Erik Verlinde of the University of Amsterdam argues that dark matter is an illusion caused by the holographic emergence of spacetime from quantum entanglement.

Unifying quantum mechanics and general relativity requires reconciling their absolute and relative notions of time. Recently, a promising burst of research on quantum gravity has provided an outline of what the reconciliation might look like — as well as insights on the true nature of time.

As Natalie Wolchover described in an article published on December 5th, 2016 in *The Atlantic* on a new theoretical attempt to explain away dark matter, many leading physicists now consider spacetime and gravity to be "emergent" phenomena: Bendy, curvy spacetime and the matter within it are a hologram that arises out of a network of entangled qubits (quantum bits of information), much as the three-dimensional environment of a computer game is encoded in the classical bits on a silicon chip. "*I think we now understand that spacetime really is just a geometrical representation of the entanglement structure of these underlying quantum systems*," said Mark Van Raamsdonk, a theoretical physicist at the University of British Columbia.

Researchers have worked out the math showing how the hologram arises in toy universes that possess a fisheye spacetime geometry known as “anti-de Sitter” (AdS) space. In these warped worlds, spatial increments get shorter and shorter as you move out from the center.

Eventually, the spatial dimension extending from the center shrinks to nothing, hitting a boundary. The existence of this boundary -which has one fewer spatial dimension than the interior spacetime, or “bulk” -aids calculations by providing a rigid stage on which to model the entangled qubits that project the hologram within. “*Inside the bulk, time starts bending and curving with the space in dramatic ways*,” said Brian Swingle of Harvard and Brandeis universities. “*We have an understanding of how to describe that in terms of the ‘sludge’ on the boundary*,” he added, referring to the entangled qubits.

The states of the qubits evolve according to universal time as if executing steps in a computer code, giving rise to warped, relativistic time in the bulk of the AdS space. The only thing is, that’s not quite how it works in our universe.

Here, the spacetime fabric has a “de Sitter” geometry, stretching as you look into the distance. The fabric stretches until the universe hits a very different sort of boundary from the one in AdS space: the end of time. At that point, in an event known as “heat death,” spacetime will have stretched so much that everything in it will become causally disconnected from everything else, such that no signals can ever again travel between them. The familiar notion of time breaks down. From then on, nothing happens.

On the timeless boundary of our spacetime bubble, the entanglements linking together qubits (and encoding the universe’s dynamical interior) would presumably remain intact, since these quantum correlations do not require that signals be sent back and forth. But the state of the qubits must be static and timeless. This line of reasoning suggests that somehow, just as the qubits on the boundary of AdS space give rise to an interior with one extra spatial dimension, qubits on the timeless boundary of de Sitter space must give rise to a universe with time — dynamical time, in particular. Researchers haven’t yet figured out how to do these calculations. “*In de Sitter space*,” Swingle said, “*we don’t have a good idea for how to understand the emergence of time*.”

One clue comes from theoretical insights arrived at by Don Page and William Wootters in the 1980s. Page, now at the University of Alberta, and Wootters, now at Williams, discovered that an entangled system that is globally static could contain a subsystem that appears to evolve from the point of view of an observer within it. Called a "history state," the system consists of a subsystem entangled with what you might call a clock. The state of the subsystem differs depending on whether the clock is in a state where its hour hand points to one, two, three and so on. "*But the whole state of system-plus-clock doesn't change in time*," Swingle explained. "*There is no time. It's just the state -it doesn't ever change*." In other words, time doesn't exist globally, but an effective notion of time emerges for the subsystem.

A team of Italian researchers experimentally demonstrated this phenomenon in 2013. In summarizing their work, the group wrote: "*We show how a static, entangled state of two photons can be seen as evolving by an observer that uses one of the two photons as a clock to gauge the time-evolution of the other photon. However, an external observer can show that the global entangled state does not evolv*e."

Other theoretical work has led to similar conclusions. Geometric patterns, such as the amplituhedron, that describe the outcomes of particle interactions also suggest that reality emerges from something timeless and purely mathematical.

It's still unclear, however, just how the amplituhedron and holography relate to each other.

The bottom line, in Swingle's words, is that "*somehow, you can emerge time from timeless degrees of freedom using entanglement*." Time will tell.

Next Step

Life, human *life*, and the *life* of the myriad of living organisms is absent from this review *cum* commentaries. It requires another essay, a complement or another vision. Breathe, rest, recover and you will be rewarded! Soon.

(Part 2)

Life Clocks Time, Time Clocks Life

Every child fears getting old, really old and crippled. This fear obsesses humans, whether they admit it or not. It is exclusively human and is nurtured by all organized religions that promise a paradisiac eternal afterlife –for fees or alms.

We know that life follows a course, never strictly predictable, with bumps and elations, laughter, sorrow –and ultimately death. The End of One's Time, of One's Life. Life was not the prevalent, dominant issue in the time of Newtonian physics, measurement, travel, arrow(s) or even philosophy.

It was only when the brain, hence the mind, was involved that living phenomena emerged. Biology studies life, and is confronted to time permanently. But *life* escapes

Newtonian physics; it requires another system that is based on *uncertainty*, *unpredictability*, or even *chance.*

My generation came to life with the lightning-speed development of quantum mechanics and physics. The subatomic particles did not fit into the Newtonian yoke; their behavior was *uncertain* (Werner Heisenberg) –just as *life* itself. Albert Einstein was –for a time- reluctant, and unexpectedly invoked "God", claiming that he/she *did not play dice*. Nor roulette; but Newtonian physics do NOT apply very well to *Nature* –i.e. *life*.

The prevalent, quite universal Western creed, since ancient Greece, tends to *rationality*. René Descartes was its champion. But then medicine was a mixture of crass ignorance, magic and religious blessings. Physicians (medical doctors) were killing patients, as the Diafoirus father-and-son of Molière.

The teaching of Quantum Mechanics and Physics was absent from the middle- and high-school curricula until the 1970s; Newtonian (and Euclidian!) physics reigned, undisputed, untouchable.

The *Enlightment* started it all, with its rejection of blind faith, its exploration of Nature –hence *Life* to bring doubt, questioning, and ultimately universal experimental approach that can be replicated (within certain *time* limits). But the victory was not won when *life* is involved. Even in 2017 –e.g. in vast areas of Europe, the United States and South America- religious interdictions rule when studying *life* is involved. It goes hand-in-glove with the worship of war and the death penalty…

Time and the Dao

“Time is a created thing. To say 'I don't have time,' is like saying, 'I don't want to.'” Laozi

Time is implicit in the *Daodejing*. The term *Dao* means a road, and is often translated as "the Way". This is because sometimes *dao* is used as a nominative (that is, "the dao") and other times as a verb (i.e. daoing).

Dao is the process of reality itself, the way things come together, while still transforming. All this reflects the deep--seated Chinese belief that **change** is the most basic character of things. In the *I Ching* 易經 (*Classic of Changes*, or *Book of Changes*) the patterns of this change are symbolized by figures (the “Ten Wings”) standing for 64 relations of correlative forces and known as the hexagrams.

Dao is the alteration of these forces, most often simply stated as yin and yang. The *Xici* is a commentary on the *I Ching* formed in about the same period as the *Daodejing*. It takes the *Taiji* 太極 (Great Ultimate) as the source of correlative change and associates it with the *dao*.

The contrast is not between what things are or that something is or is not but between Chaos (Hundun 混沌) and the way reality is ordering (de). Yet reality is not ordering into one unified whole. It is the 10,000 things (Wanwu 萬物). There is the dao but not "the World" or "the cosmos" in a Western sense.

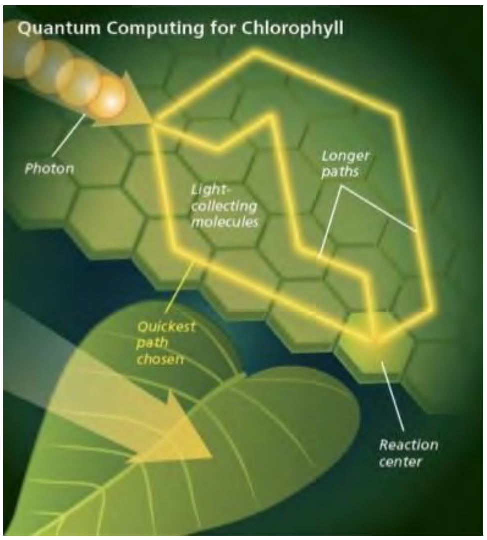
A central theme of the Daodejing is that correlatives are the expressions of the movement of dao. Correlatives in Chinese philosophy are not opposites, mutually excluding each other. They represent the ebb and flow of the forces of reality: yin/yang, male/female; excess/defect; leading/following; active/passive. As one approaches the fullness of yin, yang begins to horizon and emerges.

John Zerzan has extensively studied and commented the Daodejing; for him time can be seen as the master and measure of a social existence that has become increasingly empty and technicized. Time is expressed as history -which also limits humanity. History is eternal becoming and therefore eternal future. Nature is become and therefore eternal past. Hence the complexity of the YinYang symbol and its universal value.

Quantum Biology Takes Us Back to Laozi

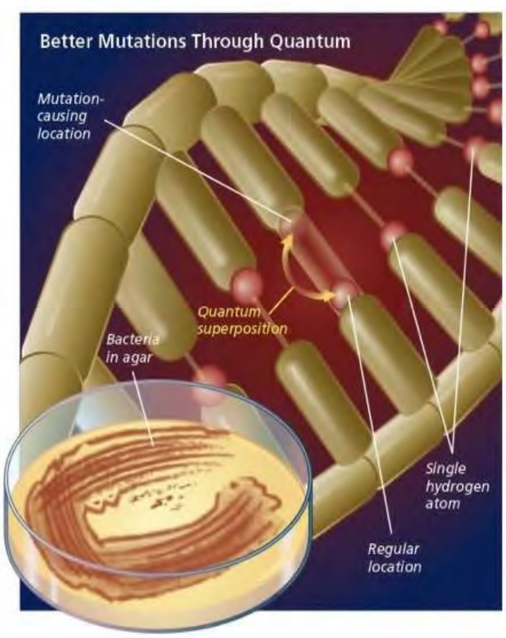
The field of quantum biology applies quantum mechanics to biological objects and problems. It can be defined as the study of quantum phenomena within biological systems.

Many biological processes involve the conversion of energy into forms that are usable for chemical transformations and are quantum mechanical in nature. Such processes involve chemical reactions, light absorption, formation of excited electronic states, transfer of excitation energy, and the transfer of electrons and protons (hydrogen ions) in chemical processes such as photosynthesis and cellular respiration.

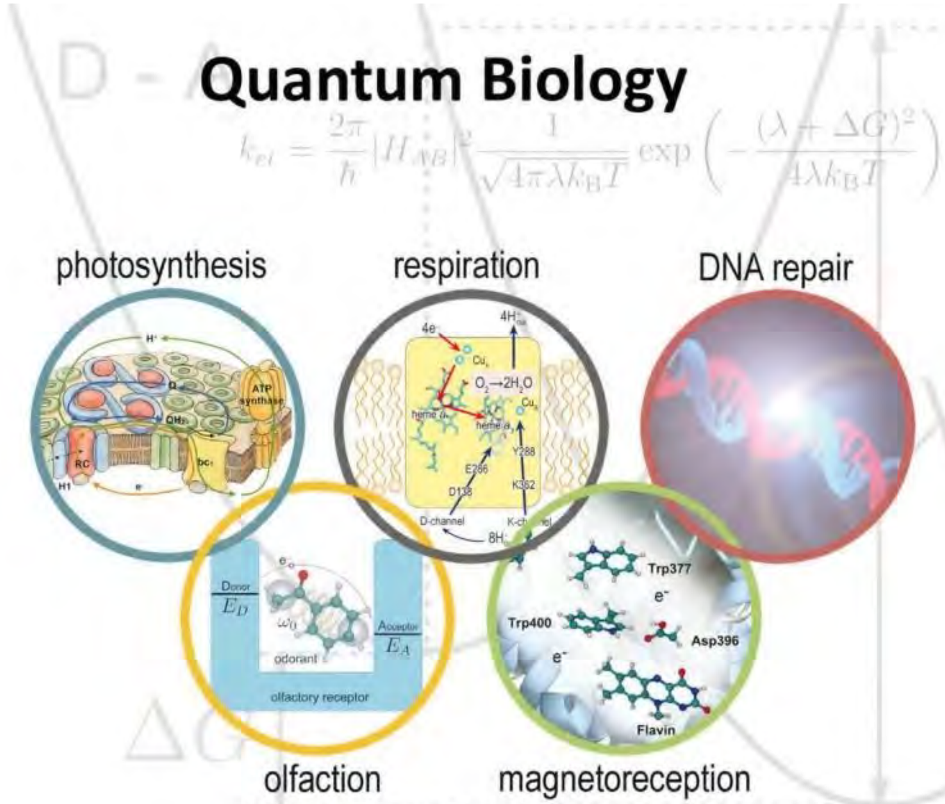


Quantum biology uses computation to model biological interactions in light of quantum mechanical effects.

Some examples of the biological phenomena that have been studied in terms of quantum processes are the absorbance of frequency-- specific radiation (i.e., photosynthesis and vision); the conversion of chemical energy into motion; magnetoreception in animals; DNA mutation and Brownian motors in many cellular processes.



Recent studies have identified quantum coherence and entanglement between the excited states of different pigments in the light-- harvesting stage of photosynthesis. The theory of orchestrated objective reduction argues that coherent quantum processes within microtubules are the *origin of consciousness*.



One of the most influential people to link quantum physics and biology was Erwin Schrödinger, whose book *What is Life?* inspired, among others, DNA pioneers James Watson and Francis Crick.

In fact, Schrödinger's view was based on biophysicist Max Delbrück's theory, put forward in the so--called *Three Man Paper*, written with geneticist Nikolay Timofeev-Ressovsky and biophysicist Karl Zimmer in 1935.

Schrödinger argued that if Delbrück's view of mutation was wrong, then "*we should have to give up further attempts*", meaning we would have to give up on using physics to explain genes.

Delbrück's approach was correct only at the most general level, and the discovery of the nature of mutations did not refer to his ideas at all.

Experimental studies at the interface between quantum physics and the life sciences have so far been focused on two different questions:

1. Can genuine quantum phenomena be realized with biomolecules?

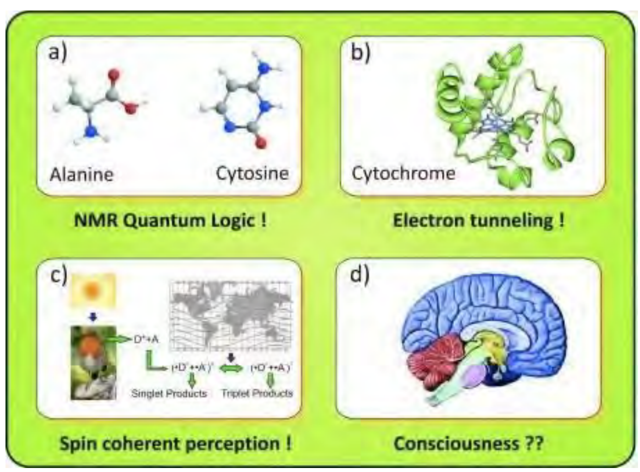
Photon antibunching in proteins, the quantum delocalization of biodyes in matter-wave interferometry and the implementation of elementary quantum algorithms in nucleotides are some recent examples.

These experiments are optimized for revealing fundamental physics, such as quantum statistics, delocalization, and entanglement. But they all also show that quantum phenomena are best observed in near--perfect isolation from the environment or at ultralow temperatures, in order to avoid the detrimental influence of decoherence and dephasing. They are thus not representative for life as such.

2. Are nontrivial quantum phenomena relevant for life?

Nontrivial quantum phenomena are here defined by the presence of long-ranged, long--lived, or multiparticle quantum coherences, the explicit use of quantum entanglement, the relevance of single photons, or single spins triggering macroscopic phenomena.

Photosynthesis, the process of vision, the sense of smell, or the magnetic orientation of migrant birds are currently hot topics in this context. In many of these cases the discussion still circles around the best interpretation of recent experimental and theoretical findings.



a. The nuclear spins of amino acids have been used as qubits in quantum computing demonstrations.

b. Electron tunneling on nanometer scales has been established as a common phenomenon in life, for instance, in reactions with cytochrome.

c. Electron spin entanglement and coherent spin transport are part of an explanation for the magnetic orientation of migratory birds.

d. Speculations about the influence of quantum physics on human consciousness are regarded as inspiring.

Fascinating combinations of physics and biology can be understood already now. We have identified a large number of interconnects between quantum physics and the life sciences and the status of present experimental skills is great. But the complexity of living systems and high--dimensional Hilbert spaces is even greater.

As Schrödinger and others have demonstrated, once we get inside the atoms of the nuclei of our cells, quantum physics apply; this means that we move into an imprecise, non-linear area where prevalence (not certainty) reigns. We rejoin the philosophy of Laozi. This affects us universally –as well as the universe.

Neurosciences and Time Perception

The field of neurosciences is exponentially growing since the 18th century CE. It is now using tools that are invented, created constantly, pushing back the limits of knowledge and opening areas that were unthinkable a few…weeks ago! One example –that attempts (soon succeeds) to mimic life- is Artificial Intelligence. The sky is not a limit anymore; it might still be the multiverse.

Among the many areas subjected to intense exploration is time perception, a field of study within psychology and neuroscience that refers to the subjective experience of life: time is measured by someone's own perception of the duration of the indefinite and unfolding of events. The perceived time interval between two successive events is referred to as perceived duration. Another person's perception of time cannot be directly experienced or understood, but it can be objectively studied and inferred through a number of scientific experiments.

Time perception is a construction of the brain that is manipulable and distortable under certain circumstances. These temporal illusions help to expose the underlying neural mechanisms of time perception.

Although the perception of time is not associated with a specific sensory system, psychologists and neuroscientists suggest that humans do have a system, or several complementary systems, governing the perception of time.

Time perception is handled by a highly distributed system involving the cerebral cortex, cerebellum and basal ganglia. One particular component, the suprachiasmatic nucleus, is responsible for the circadian (or daily) rhythm, while other cell clusters appear to be capable of shorter range (ultradian) timekeeping. There is some evidence that very short (millisecond) durations are processed by dedicated neurons in early sensory parts of the brain

Warren Meck found the representation of time to be generated by the oscillatory activity of cells in the upper cortex. The frequency of these cells' activity is detected by cells in the dorsal striatum at the base of the forebrain.

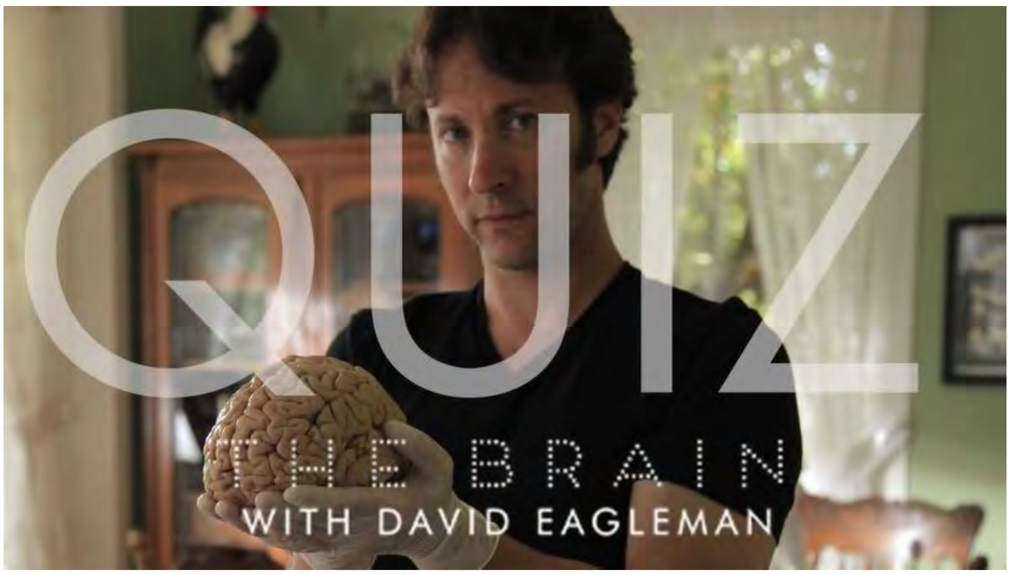
Explicit timing is used in estimating the duration of a stimulus. *Implicit timing* is used to gauge the amount of time separating one from an impending event that is expected to occur in the near future.

Implicit timing occurs to achieve a motor task, involving the cerebellum, left parietal cortex, and left premotor cortex.

Explicit timing involves the supplementary motor area and the right prefrontal cortex.

In "*The Brain*", David Eagleman explains that different types of sensory information (auditory, tactile, visual, etc.) are processed at different speeds by different neural architectures. The brain must learn how to overcome these speed disparities if it is to create a temporally unified representation of the external world: "*if the visual brain wants to get events correct timewise, it may have only one choice: wait for the slowest information to arrive. To accomplish this, it must wait about a tenth of a second. In the early days of television broadcasting, engineers worried about the problem of keeping audio and video signals synchronized. Then they accidentally discovered that they had around a hundred milliseconds of slop: As long as the signals arrived within this window, viewers' brains would automatically resynchronize the signals*". He goes on to say that *"This brief waiting period allows the visual system to discount the various delays imposed by the early stages; however, it has the disadvantage of pushing perception into the past.*

There is a distinct survival advantage to operating as close to the present as possible; an animal does not want to live too far in the past. Therefore, the tenth-of- a-second window may be the smallest delay that allows higher areas of the brain to account for the delays created in the first stages of the system while still operating near the border of the present. This window of delay means that awareness is postdictive, incorporating data from a window of time after an event and delivering a retrospective interpretation of what happened."



Experiments have shown that rats can successfully estimate a time interval of approximately 40 seconds, despite having their cortex entirely removed. This suggests that time estimation may be a low level (subcortical) process.

Changes with Age

Psychologists have found that the subjective perception of the passing of time tends to speed up with increasing age in humans. This often causes people to increasingly underestimate a given interval of time as they age. This fact can likely be attributed to a variety of age-related changes in the aging brain, such as the lowering in dopaminergic levels with older age.

B. Holmes, in *New Scientist* (Nov 1996) reports on an experiment involving a group of subjects aged between 19 and 24, and a group between 60 and 80, which compared the participants' abilities to estimate 3 minutes of time. The study found that an average of 3 minutes and 3 seconds passed when participants in the younger group estimated that 3 minutes had passed, whereas the older group's estimate for when 3 minutes had passed came after an average of 3 minutes and 40 seconds.

Very young children literally "live in time" before gaining an awareness of its passing. A child will first experience the passing of time when he or she can subjectively perceive and reflect on the unfolding of a collection of events.

A child's awareness of time develops during childhood when the child's attention and short-term memory capacities form—this developmental process is thought to be dependent on the slow maturation of the prefrontal cortex and hippocampus.

One day to an 11-year-old would be approximately 1/4,000 of their life, while one day to a 55-year-old would be approximately 1/20,000 of their life. This helps to explain why a random, ordinary day may therefore appear longer for a young child than an adult. The short-term time appears to go faster by square root of their age. So a year experienced by a 55-year-old would pass approximately 2¼ times more quickly than a year experienced by an 11-year-old. If long-term time perception is based solely on the proportionality of a person's age, then the following four periods in life would appear to be quantitatively equal: age 5 to 10 (1x), age 10 to 20 (2x), age 20 to 40 (4x), age 40 to 80 (8x).

The common explanation is that most external and internal experiences are new for young children, while most experiences are repetitive for adults. Children have to be extremely engaged (i.e. dedicate many neural resources or significant brain power) in the present moment because they must constantly reconfigure their mental models of the world to assimilate it, and properly behave from within. On the contrary, adults may rarely step outside of their mental habits and external routines. When an adult frequently experiences the same stimuli, their brain renders them "invisible" because the brain has already sufficiently and effectively mapped those stimuli.

This phenomenon is known as neural adaptation. Thus, the brain will record fewer densely rich memories during these frequent periods of disengagement from the present moment. Consequently, the subjective perception is often that time passes by at a faster rate with age.

Effects of Drugs

Stimulants produce overestimates of time duration, whereas depressants and anesthetics produce underestimates of time duration.

Psychoactive drugs can alter the judgment of time.

These include traditional psychedelics such as LSD, psilocybin, and mescaline as well as the dissociative class of psychedelics such as PCP, ketamine and dextromethorphan. At higher doses time may appear to slow down, speed up or seem out of sequence.

Psilocybin significantly impairs the ability to reproduce interval durations longer than 2.5 seconds, significantly impairs synchronizing motor actions (taps on a computer keyboard) to regularly occurring tones, and impairs the ability to keep tempo when asked to tap on a key at a self-paced but consistent interval.

With Mescaline "*time does not seem to end*".

Stimulants can lead both humans and rats to overestimate time intervals, while depressants can have the opposite effect.

The level of activity in the brain of neurotransmitters such as dopamine and norepinephrine may be the reason for this. Dopamine has a particularly strong connection with one's perception of time.

Drugs that activate dopamine receptors (e.g. nicotine) speed up one's perception of time, while dopamine antagonists cause one to feel that time is passing slowly (e.g. neuroleptics).

Effects of Clinical Conditions

Parkinson's disease, schizophrenia, and attention deficit hyperactivity disorder (ADHD) have been linked to abnormalities in dopamine levels in the brain as well as to noticeable impairments in time perception.

Neuropharmacological research indicates that the internal clock, used to time durations in the seconds-to-minutes range, is linked to dopamine function in the basal ganglia. Studies in which children with ADHD are given time estimation tasks shows that time passes very slowly for them. Children with Tourette's syndrome, for example, who need to use the pre-frontal cortex just behind the forehead to help them control their tics, are better at estimating intervals of time just over a second than other children.

In his book "*Awakenings*", Oliver Sacks discussed how patients with Parkinson's disease experience deficits in their awareness of time and tempo. For example, Mr. E, when asked to clap his hands steadily and regularly did so for the first few claps before clapping faster and irregularly; culminating in an apparent freezing of motion. When he finished, Mr. E asked if his observers were glad he did it correctly to which they replied "*no*". This offended Mr. E because to him, his claps were regular and steady. When given L-DOPA, these deficits are lessened or subside entirely depending on the dose. This case not only shows that Parkinson's disease is related to time perception deficits but it also demonstrates how dopamine is involved.

Dopamine is also theorized to play a role in the attention deficits present with attention deficit hyperactivity disorder.

Specifically, dopaminergic systems are involved in working memory and inhibitory processes, both of which are believed central to ADHD pathology. Children with ADHD have also been found to be significantly impaired on time discrimination tasks (telling the difference between two stimuli of different temporal lengths) and respond earlier on time reproduction tasks (duplicating the duration of a presented stimulus) than controls.

Biological Rhythms and Chronobiology

Disclosure: *Since I have been personally involved in research on pharmaceuticals (mostly of natural origin) and their complex metabolic effects (before they manifest any potential usefulness in therapeutics, chronopharmacology was an intrinsic –albeit widely ignored or neglected- part of that research.*

It started very early, since I cared for asthmatic and allergic patients. I noticed that timing was everything, but not by just multiplying doses over the 24 hours. Each medication, and each patient has its own schedule to optimize the effect –or increase dramatically the "side-effects".

Alain Reinberg was my inspiration. Already when we met in 1944, as refugees in Switzerland, he appeared as a solid, muscular, VERY smart, witty, omniscient leader (he had fought brilliantly in the Resistance during WWII). He has acumen, flawless judgment, a cornucopia of ideas and a knack to identify worthwhile trails to follow. With Franz Halberg and Michael Smolensky, he is one of the undisputed leaders in Chronobiology, and possibly the inventor of chronopharmacology. At age 95 –and counting- he still triumphs in sports, teaching, inspiring and tutoring, traveling, writing (including successful novels), and an unmatched generosity and sense of social justice too rare these days. His groundbreaking work opened the gates for my own rigorous evaluation of many medications, supplements and food components.

From left to right: Michael Young, Jeffrey Hall, and Michael Rosbash

Jeffrey Hall and Michael Rosbash of Brandeis University in Waltham, Massachusetts, and Michael Young of The Rockefeller University in New York City shared the 2017 Nobel Prize in Physiology and Medicine equally for their work on how several genes work together to control the *basic circadian clock*, encoding proteins that build up during the night and are broken down during the day. These clocks are ticking inside plants, fungi, protozoa, and animals. In recent years, researchers have found that the clock is related not only to our sleep cycle, but also to metabolism and brain function.

Circadian, or daily, rhythms are "*just as fundamental as respiration*," says Charalambos Kyriacou, a molecular geneticist at the University of Leicester in the United Kingdom. "*There isn't any aspect of biology that circadian rhythms aren't important for. They are totally fundamental in a way that we didn't anticipate*" before the discoveries honored by this Nobel Prize.

The presence of a biological clock was already surmised in the 18th century. In 1729, French astronomer Jean Jacques d'Ortous de Mairan showed that mimosa leaves, which open at dawn and close at dusk, continued this cycle even when kept in darkness. But it wasn't until the 20th century that the idea of an internal clock—as opposed one that responds to external cues like light—was settled.

The genetic basis for a daily physiological cycle was first discovered in fruit flies in the 1970s. Seymour Benzer and Ronald Konopka at the California Institute of Technology in Pasadena created mutant flies that had abnormal biological clocks. One type had a broken clock—its patterns of activity became arhythmic— whereas the others now had either a 19-hour or a 28-hour cycle. Benzer and Konopka showed the mutations all had hit the same gene, presumably in different ways. They and other researchers homed in on a gene called *period*.

Hall and Rosbash finally sequenced the gene in 1984, as did Young. Hall and Rosbash showed that its protein, called PER, rose and fell over 24 hours, peaking at night. They suspected the clock was driven by a feedback loop, with the protein PER interfering with the *period* gene. ("*It makes you scratch your head and wonder if it's even possible*," Young said in 1985.

For the clock to work, PER had to get into the nucleus. Young figured out how that happened. In 1994, he and colleagues discovered a second clock gene, *timeless*, that allowed PER to enter the nucleus and stop *period* from making more.

Researchers have since found half a dozen more genes that influence the cycle. For example, *period* and *timeless* are turned on by *clock*, discovered in 1997 by Joseph Takahashi, now at UT Southwestern in Dallas, Texas, and his colleagues. Within a year, this group discovered another key part of the feedback loop: When PER and TIM get into the nucleus, they also curtail the activity of the *clock.*

Clock genes are extremely influential, affecting the activity of most other genes in the body in one way or another. Circadian mechanisms influence metabolism—how our body uses and stores energy—blood pressure, body temperature, inflammation, and brain function. Time of day can influence the effectiveness of drugs and their side effects. And mismatches between the clock and the environment, for instance because of jet lag or shift work, have been shown to play a role in mood disorders and even cancer risk.

"Since the seminal discoveries by the three laureates," the Nobel Assembly wrote, "circadian biology has developed into a vast and highly dynamic research field, with implications for our health and wellbeing."

Every living organism depends on rhythms, cycles, regular changes that often vary over *time*.

We all know some: birth-infancy-childhood-adulthood-seniority and death; the cardiac beats; our breathing; wake and sleep; eating, digestion, excretion; etc.

The term Chronobiology comes from the ancient Greek χρόνος, already presented, and *biology*, that pertains to the study, or science, of life. The related terms chronomics and chronome have been used in some cases to describe either the molecular mechanisms involved in chronobiological phenomena, or the more quantitative aspects of chronobiology, particularly where comparison of cycles between organisms is required.

Chronobiological studies include but are not limited to comparative anatomy, physiology, genetics, molecular biology and behavior of organisms within biological rhythms mechanics. Other aspects include development, reproduction, ecology and evolution.

The variations of the timing and duration of biological activity in living organisms occur for many essential biological processes. These occur (a) in animals (eating, sleeping, mating, hibernating, migration, cellular regeneration, etc.), (b) in plants (leaf movements, photosynthetic reactions, etc.), and in microbial organisms such as fungi and protozoa. They have even been found in bacteria, especially among the cyanobacteria (aka blue-green algae).

Physiological processes in all these organisms the circadian rhythm -a roughly 24-hour cycle show the most important rhythm in chronobiology. The term circadian comes from the Latin *circa*, meaning "around" and *dies*, "day", meaning

"approximately a day." Circadian clocks regulate it.

The circadian rhythm can further be broken down into routine cycles during the 24hour day:

- Diurnal, which describes organisms active during daytime
- Nocturnal, which describes organisms active in the night
- Crepuscular, which describes animals primarily active during the dawn and dusk hours (ex: white-tailed deer, some bats)

While circadian rhythms are defined as endogenously regulated, other biological cycles may be regulated by exogenous signals. In some cases, multi-trophic systems may exhibit rhythms driven by the circadian clock of one of the members (which may also be influenced or reset by external factors).

Many other important cycles are also studied, including:

- Infradian rhythms, which are cycles longer than a day, such as the annual migration or reproduction cycles found in certain animals or the human female menstrual cycle.
- Ultradian rhythms, which are cycles shorter than 24 hours, such as the 90minute REM cycle, the 4-hour nasal cycle, or the 3-hour cycle of growth hormone production.
- Tidal rhythms, commonly observed in marine life, that follow the roughly 12.4hour transition from high to low tide and back.
- Lunar rhythms follow the lunar month (29.5 days). They are relevant e.g. for marine life, as the level of the tides is modulated across the lunar cycle.
- Gene oscillations –some genes are expressed more during certain hours of the day than during other hours.

More recently, light therapy and melatonin administration have been actively studied to reset animal and human circadian rhythms. Additionally, the presence of low-level light at night accelerates circadian re-entrainment of hamsters of all ages by 50%; this is thought to be related to simulation of moonlight. Humans can be morning people (*disclosure: I am one of these due to the FSAPS gene*) or evening people; these variations are called chronotypes for which there are various assessment tools and biological markers.

As reported by Veronique Greenwood (*New York Times,* 8

November 2017 (https://nyti.ms/2hSZd3x) our sense of smell may fluctuate in sensitivity over the course of 24 hours, in tune with our circadian clocks, with our nose best able to do its job during the hours before we go to sleep, according to a study published 17 October 2017 in the journal

Chemical Senses (https://doi.org/10.1093/chemse/bjx067), and is part of a larger push to explore whether adolescents' senses of taste and smell influence obesity.

Rachel S. Herz, a sensory researcher at Brown University, and her colleagues designed this study to see if there might be times of day when the sense of smell was more powerful — perhaps making food smell particularly inviting.

For the experiment, 37 adolescents ranging in age from 12 to 15 came into a lab for a very long sleepover party. For nine days, they followed a strict schedule to allow researchers to focus on the circadian clock, which helps control wake and sleep, but also influences other processes in the body, including metabolism. Dr. Herz says that as you grow up, the makeup of the smell receptors inside your nose doesn't seem to change, although there is evidence your body clock may.

The team kept track of where the teenagers were in their circadian cycle by measuring their saliva's levels of melatonin, a hormone that rises and falls regularly over the course of 24 hours. Every few hours, the subjects took a scent test, sniffing different concentrations of a chemical that smells like roses. The researchers recorded the lowest concentration they could detect at each time point.

When the results were tallied up, the researchers saw a range of responses. *"Nobody has the same nose*," Dr. Herz said. Some adolescents had only very mild changes in sensitivity, while sensitivity altered dramatically in others.

Averaged together, however, the results showed that overall the circadian clock does affect smell, and that the times when the subjects' noses were most sensitive tended to correspond to the evening, with an average peak of 21:00.

"*The results make sense — the circadian clock affects virtually every organ system in the body*," writes Dr. Leslie Vosshall, a researcher at Rockefeller University who studies smell and was not involved in the study.

Smell was at its lowest ebb, intriguingly, from about 02:00 to 10:00. It is already known that when we are asleep, a strong smell won't disturb us the way a loud noise or a bright light will. Perhaps the biological machinery behind smell shuts itself down for the night, at least in some people. But Dr. Herz speculates that having stronger olfactory abilities as dusk fell might have helped our ancestors survive. "*It really underscores the importance of auditory fire alarms*," she said. Still, the experiment was designed to test the effect of the circadian clock, and that is not the only factor involved in smell sensitivity. Researchers have already found that another big player is how long someone has been awake and what variety of smells they have been exposed to. It's likely that all these have a role in determining when, in real life outside the lab, our sense of smell works best.

There is also a food-entrainable biological clock that seems to be located in the dorsomedial hypothalamus. During restricted feeding, it takes over control of such functions as activity timing, increasing the chances for successfully locating food resources –at least in rodents.

A new study suggests that timing also matters in skin healing: skin cells that help patch up wounds work more quickly in the daytime than they do at night, thanks to the workings of our circadian clock. Patients might recover from injury more quickly if they have surgery during the right time of day.

Biologists and neuroscientists long thought the body's time keeper, our circadian clock, resided only in the brain. In mammals, that place is a region of the hypothalamus called the suprachiasmatic nucleus, which receives signals from the eyes. However, recent research demonstrated that cells in other parts of the body—including the lungs and liver—keep their own time. Researchers aren't quite sure how they maintain their own 24-hour schedule, whereas other cells need external reminders.

John O'Neill, a biologist at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, U.K., and his team studied a type of skin cell known as fibroblasts that are essential for wound healing. Fibroblasts invade the void left by a scratch and lay the foundation for new skin to grow.

The cells are also known to keep their own time. For example, cultured cells exhibit rhythmic oscillations in gene expression where there is no input from the master clock. Given the fibroblasts' time-keeping abilities, O'Neill and colleagues searched for proteins within the cells that ebb and flow with daily rhythms. They came back with an unexpected result: proteins that direct the construction of the cell's actin based skeleton worked daytime shifts. These cellular contractors tell fibroblasts to move into an injury to begin the healing process; the finding suggested that the time of day a wound occurs may affect how quickly it heals.

The researchers then tested that hypothesis with cells grown in a flat layer in a Petri dish. The fibroblasts filled in scratches more quickly during the day than at night. "*You can see by eye, when the cell is wounded only 8 hours apart from each other, in a different circadian phase, the [daytime] wounded ones take off, and the [nighttime] one drags,"* O'Neill said.

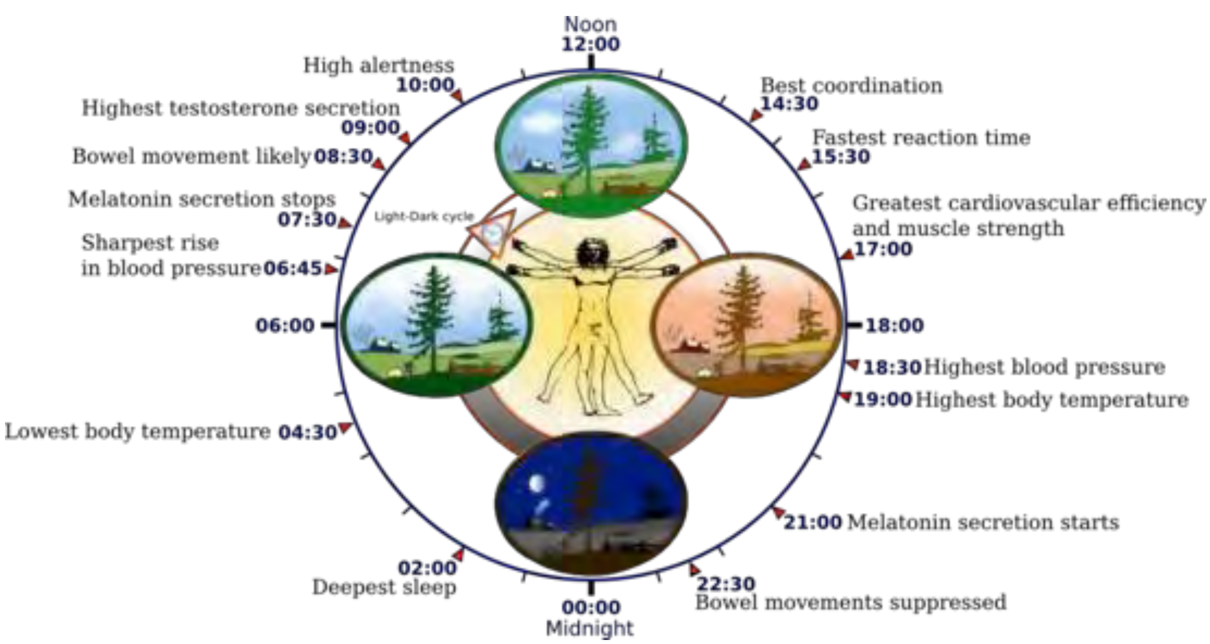
The researchers then showed in mice that skin wounds suffered during their waking hours healed better than ones incurred during their resting hours. What's more, those increases lined up with the cell culture data. About twice as many fibroblasts migrated into the daytime wounds as nighttime ones.

"*We were really astonished*," O'Neill said. Finally, O'Neill and colleagues looked for evidence of such an effect in humans. The team examined data from the International Burn Injury Database, which records, among other things, the time of day an injury occurred. The analysis revealed that nighttime burns took an average of 11 days longer to heal than burns incurred during the day, the researchers reported in *Science Translational Medicine* on November 8, 2017.

O'Neill emphasized the need for further controlled clinical studies to confirm the effect. He speculates that if real, the effect could help people recover more quickly by scheduling surgeries in time with their personal circadian rhythms, earlier for morning larks and later for night owls.

The researchers say that fibroblasts' time-varying response may be an evolutionary adaptation. As people are more likely to sustain injuries when primed to respond more quickly in the daytime.

Chronobiology is an interdisciplinary field of investigation. It interacts with medical and other research fields such as sleep medicine, endocrinology, geriatrics, sports medicine, space medicine and photoperiodism.



Chronopharmacology

Most facets of mammalian physiology and behavior vary according to time-of-day thanks to an endogenous “circadian” clock. Therefore, it is not surprising that many aspects of pharmacology and toxicology also oscillate according to the same 24-hour clocks. Daily oscillations in abundance of proteins necessary for either drug absorption or metabolism result in circadian pharmacokinetics; and oscillations in the physiological systems targeted by these drugs result in circadian pharmacodynamics. These clocks are present in most cells of the body, but organized in hierarchical fashion. Interestingly, some aspects of physiology and behavior are controlled directly via a “master clock” in the suprachiasmatic nuclei of the hypothalamus, while “slave” oscillators in separate brain regions or body tissues control others. Recent research shows that these clocks can respond to different cues, and thereby show different phase relationships.

Therefore, full prediction of chronopharmacology in pathological contexts will likely require a systems biology approach considering “chrono-interactions” among different clock-regulated systems.

As a result of living on a planet whose principal source of light and heat is only periodically present, organisms on Earth rapidly adapted physiological systems to exploit these variations for maximum fitness. Collectively, these clocks are named “circadian” (Latin: *circa diem* –about a day). In mammals, circadian clocks influence all major organ systems, and this influence translates directly into disease pathology that also varies with time of day.

Historically, it was early recognized that rhythmic physiology resulted in rhythmic disease symptoms. Hippocrates already noticed ca. 400 BCE that daytime sleepiness is indicative of disease, and nighttime sleeplessness can indicate pain and suffering. By medieval times, reports existed of daily variations in diseases such as bronchial asthma. For over thirty years, it has been known that drug absorption and distribution is subjected to diurnal variation in rodents and humans. A twenty-fourhour change in drug bioavailability has therefore been established for hundreds of drugs in rodents and humans. For example, acetaminophen/paracetamol or theophylline (see Fig.) show different pharmacokinetics in the morning compared to evening. These changes are the results of several time-dependent modifications of physiological and molecular aspects that influence drug absorption and distribution.

Considering the wide scope of circadian (patho-) physiology, it is logical that the pharmacodynamics and pharmacokinetics (PK/PD) of many drugs would be circadian, and therefore that drug efficacy and safety profiles would also vary with time of day.

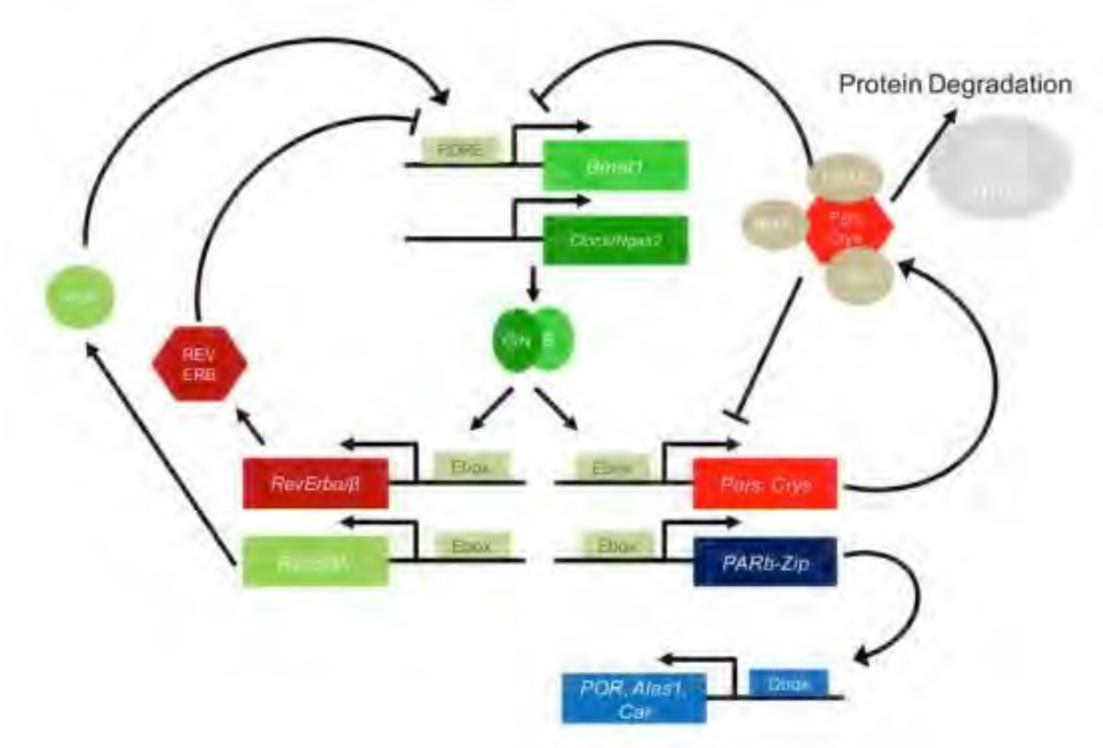
Nevertheless, clinicians, drug developers, or regulators only seldom consider this variation. In part, this apathy may stem from a lack of insight into the molecular mechanisms governing this control. However, two decades of intensive research have uncovered a wealth of information not only about basic mechanisms of circadian clocks, but also about how they interact with physiology and disease.

The basic unit of circadian timekeeping is the cell: even in very complex organisms, most cells contain autonomous circuitry for circadian oscillations. Generally speaking, this mechanism is comprised of negative feedback loops of transcription and translation: activation of a repressor gene results in its later repression by its own protein product, and the instability of this repressor insures this repression is short-lived, so that a new cycle can begin.

In mammals, the principal activators within this system are the CLOCK and BMAL1 proteins and their homologs, which dimerize and bind to cis-acting E-box elements (with the simple consensus DNA sequence CAANTG) to activate transcription of a large number of circadian genes.

There are many steps, and at each of these steps, additional precision and regulatory finesse is achieved through interaction with a wide range of auxiliary proteins: kinases that phosphorylate clock proteins to modify their stability or activity; chromatin modifying proteins that phosphorylate, acetylate, or deacetylate histones and in some cases clock proteins to regulate chromatin structure and transcriptional activation potential; and RNA-binding proteins that serve as scaffolds for coactivating and corepressing activities (see Fig.).

A parallel and independent circadian mechanism independent of transcription also exists in parallel to the “canonical” transcription-translation-based clock in mammalian cells. Evidence of this oscillator exists in the form of diurnal variation in oxidation states of hemoglobin and antioxidant molecules. Both the mechanism and the physiological relevance of these posttranslational clocks remain unknown in mammals, though posttranslational clocks based on phosphorylation are well studied in bacteria.



The canonical mammalian circadian oscillator and output relevant for xenobiotic metabolism

Two interlocked feedback loops composed of activators (green) and repressors (red) that drive gene expression of output genes such as those important for xenobiotic metabolism.

Components of these loops make extensive use of auxiliary factors including histone methyltransferases (HMTs), histone deacetylases (HDACs), DHBS family RNA-binding proteins (beige), and kinases and proteasome machinery (grey). Important output genes, involved in transcriptional control of the detoxification metabolism (blue).

The basic timekeeping mechanism of circadian oscillators is cell-autonomous, and self-sustained clocks exist in most cells of the body. However, under most circumstances these clocks are organized into a hierarchy: a “master clock” tissue within the suprachiasmatic nuclei (SCN) of the hypothalamus receives light input via the retina, and communicates timing signals to “slave” oscillators of similar molecular mechanism in cells from other tissues. Multiple redundant signals have been described. These include direct signals like innervation by the autonomous nervous system and hormones like glucocorticoids, and indirect signals emanating from SCN-controlled rhythmic behavior, such as timing of food intake and small rhythmic changes in body temperature from activity.

Under most circumstances, entrainment signals from the SCN to clocks in peripheral tissues act in concerted fashion, resulting in somewhat coherent phase among different organs. The exact phase of circadian clocks varies somewhat from organ to organ, perhaps because of tissue-specific differences in clock gene expression, or perhaps due to local differences in accessibility to entrainment signals. These differences become particularly acute under certain perturbation. For example, during an altered lighting cycle caused by time zone travel or shiftwork, the SCN will shift its phase much more quickly (within a day or two) than peripheral clocks (which can take a week or more), creating a situation in which clocks in different organs exhibit gross differences in "internal clock time". Similarly, systematic manipulation of external cues such as feeding time to different phases of the light-dark cycle result in a phase change for peripheral clocks, but not for the SCN.

This hierarchical clock structure has two important implications for chronopharmacology.

First, if clocks in different tissues govern different aspects of drug activity and metabolism then these different phases must be considered in calculating the timing for optimal drug efficacy. The situation is further complicated because recent research suggests that these phase relationships are altered by age: older rodents show later SCN phases but earlier peripheral clock phases.

Secondly, increasing evidence suggests that chronic circadian dysphasing by itself has significant negative consequences for health; either for rodents subjected to laboratory conditions of chronic jetlag or shiftwork, or in humans subjected to similar stresses. Documented changes include *cancer susceptibility, inflammation, and altered metabolism*. Thus, increasing evidence suggests that basal physiology may differ in individuals with clock disruption.

Such an observation is particularly relevant to pharmacology because many diseases ranging from *psychiatric and neurodegenerative disorders to cancer* are themselves associated with mild to severe clock disruption. The question of how disease specific to a peripheral organ might affect clockwork within this tissue has not been studied yet, but could also be highly pertinent to pharmacology.

Whereas SCN clocks are entrained by light, and peripheral clocks are entrained by indirect and hormonal cues, individual aspects of cellular physiology are in turn directed by both local and central clocks through a variety of mechanisms. One fundamental mechanism is via transcription: in total, about ten percent of all transcripts in each tissue are regulated in circadian fashion. In large part, this regulation occurs through the same cis–acting promoter elements that direct the rhythmic transcription of clock genes themselves.

Nevertheless, this mechanism represents only a portion of circadian transcription in living animals. Experiments in mice lacking functional clocks in specific tissues show that only a portion of circadian gene expression is abolished by such manipulations, while another portion persists because it is systemically driven. A portion of this transcription likely arises through rhythmic activity of the hypothalamic-pituitaryadrenal axis, and another portion through circadian stimulation of action/SRF signaling by unknown ligands.

Additional contributions likely arise from heat shock signaling and immune signaling, also regulated by time of day. In all four cases, specific externally-activated transcription factors bind to cis -acting elements to drive transcription of certain genes. For example, rhythmic glucocorticoid production results in rhythmic activation of glucocorticoid receptor. Likewise, circadian body temperature variation results in rhythmic occupancy of heat shock elements (HSEs). The result is circadian transcription of specific genes due to cell-extrinsic influences, and independent of the circadian clockwork present in that cell or tissue.

In addition to circadian transcription recent research has unearthed extensive evidence of circadian posttranscriptional regulation in mammals – including translational control, control of transcription termination and/or elongation, and to a lesser extent circadian control of splicing. Thus, the actual number of transcripts showing circadian abundance is significantly greater than the number of genes transcribed in circadian fashion, and the number of proteins that are expressed in circadian fashion is greater than the number of transcripts where this question has been addressed. Major signaling molecules like cAMP show circadian variations that both control clock output and play a role within the clock, and recent links between clocks and sirtuins suggest a similar influence of redox potential. Altogether, through a myriad of different mechanisms, the circadian clock regulates a significant amount of cellular physiology.

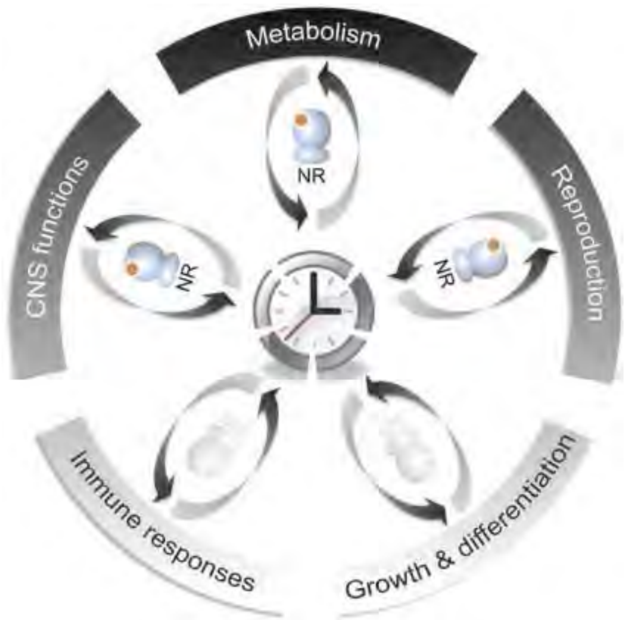
One case of such regulation meriting special attention is the circadian regulation of the cell cycle and DNA repair. Given the central importance of cell cycle deregulation to cancer, it is easy to understand why circadian control of cell division in adult animals could be of central importance to clinical pharmacology. In fact, multiple studies have documented circadian or diurnal regulation of cell division, both *in vivo* during rodent liver regeneration, and *in vitro* in cultured cells. Even in humans, skin blister transcriptional profiling suggests a similar link.

This circadian interaction has been demonstrated to be directly important for tissue regeneration. Related to circadian cell cycle control, extensive regulation of DNA damage repair by the circadian clock has also been documented, and this control would directly influence susceptibility to cancer.

To date, the prevailing view of the circadian system is a hierarchical structure in which the light--sensing master pacemaker and other environmental cues synchronize numerous peripheral oscillators via the "input" pathways and, subsequently, drive rhythmic physiologic "outputs." Much effort is focused on the identification of molecular components of the input and output pathways. However, as exemplified by the interactions between the circadian clock and nuclear receptors, feedback loops are pervasively present at the molecular, cellular, tissue, and systems levels. The boundary between the input and output pathways is dissolving. Thus, it is probably time to revisit the role of the circadian system in whole--body physiology.

In addition to keeping internal physiology synchronized with the environment—predominantly the light/dark cycle—circadian clocks may serve at least two other ancient purposes: (1) to temporally separate chemically incompatible metabolic processes, such as anabolism and catabolism; and (2) to coordinate distinct physiological processes to maintain dynamic homeostasis. Evidence for these scenarios is emerging.

As illustrated in figure below, it seems that connections between the circadian clock and most (if not all) physiological processes are bidirectional. Therefore, the circadian system might provide a potential means of communications between different physiological domains. In view of the dissolving boundary between different physiological processes, the circadian clock is probably not merely a timekeeper, but also a guardian of physiological homeostasis.



From Physiology to Chronopharmacology

As demonstrated above, at cellular level large portions of cellular physiology – from transcription and translation to intracellular signaling cascades – can show daily variations in activity. This cellular diurnal variation translates directly into diurnal physiological variation in most organ systems, which in turn provides the mechanistic rationale for circadian variation in PK/PD.

Neurotransmitters and Circadian Behavior

Nearly all behaviors show diurnal patterns of activity. In most cases, these oscillations have been shown to manifest themselves independently of external environment or the sleep-wake cycle. For example, long-term memory shows a direct dependence upon the circadian oscillator: not only do rodents and humans learn better at certain times of day than another, but mice with a functional circadian system learn better than those without. Similarly, anxiety show a clear diurnal pattern that is modulated both by sleep-wake and by the circadian oscillator, and anxiety behaviors are elevated in mice lacking the *Period* clock genes. Even perception of multiple different types of pain varies in circadian fashion in both humans and animal models.

The likely basis for these circadian variations is that virtually all major neurotransmitter systems show either marked circadian variations or clock interactions. For example, circadian variations in opioid receptor abundance, as well as in the abundance of natural opioids themselves, have been reported numerously over the past two decades.

The serotonergic system shows clear ultradian variations corresponding to sleep state, but these faster oscillations interact markedly with the circadian clock, and serotonergic signals appear necessary for integration of circadian information by the basal forebrain in controlling sleep timing.

In the cholinergic system, numerous circadian variations have also been documented. For example, after a sustained attention task with daily repetition, daily increase in prefrontal cholinergic neurotransmission is observed even in the absence of the task. In general, the cholinergic system has been documented to play a critical role in this type of circadian "time–stamping" of behavior. It is sustained by circadian release of acetylcholine during the active phase of many mammals, accompanied by increase in choline acetyltransferase and decrease in acetylcholinesterase activity. Globally, availability of muscarinic acetylcholine receptors shows an inverse pattern to acetylcholine availability, with increased abundance during the quiescent phase of the 24-hour day, irrespective of activity *per se*.

Examination of the dopaminergic system also shows a diurnal pattern of dopamine abundance within the rodent forebrain. Interestingly, this circadian expression appears necessary for oscillation of the circadian clock gene Per2 in forebrain neurons, suggesting a role for dopamine in mediating circadian information to this brain region.

Multiple other neurotransmitters show circadian abundance that strongly interacts with the sleep-wake cycle. For example, adenosine shows circadian variations within the brain that are believed to be sleep-wake-dependent. More broadly, purinergic signaling shows a strong circadian component, and interacts directly with the circadian machinery through ATP, cAMP, and AMP.

The hypocretin/orexin system also has circadian variation that regulates in particular REM sleep. Circadian release of GABA and glutamate – the principal inhibitory and excitatory neurotransmitters of the brain, respectively – in turn not only control behavior, but also hypothalamic hormone release to regulate many aspects of physiology.

Circadian clocks, hormones, and control of metabolism, digestion and cardiac function

Beyond the neurotransmitters whose circadian output is directly or indirectly regulated by the SCN, numerous other hormones show diurnal regulation that significantly regulates physiology and pharmacology.

Melatonin, a circadian hormone of the pineal gland, influences various aspects of retinal and cardiovascular function, as well as affecting local clocks in diverse brain regions.

Circadian regulation of the adrenal gland results in diurnal secretion of glucocorticoid hormone, which in turn strongly influences metabolism, and in fact directly regulates 60% of the liver transcriptome.

Circadian regulation of gastrin, ghrelin, and somatostatin, as well as direct regulation by autonomous clocks within the gastrointestinal tract, mediate circadian influences upon digestive function.

More generally, autonomous circadian clocks not only within the GI tract, but also in numerous other tissues, have considerable influences upon physiology and metabolism. For example, ablation of clocks in pancreatic islets results in diabetes because of defects in coupling of β-cell stimulus to insulin secretion, and local clockwork controls expression of multiple ion channels and kinases in heart that influence cardiac function and triglyceride metabolism. Recent transcriptome studies have identified widespread local circadian regulation not only in heart, but also in skeletal muscle and fat, showing that clocks in these tissues directly regulate physiology.

Circadian Immune Regulation

A second prominent pharmacological target with strong circadian regulation is the immune system.

Diurnal variations in white blood cell count and susceptibility to endotoxic shock have long been documented. However, recent research shows that cell-autonomous clocks within immune cells themselves direct variation in a large number of circadian immune parameters. For example, the response of T-cells to stimulation varies in circadian fashion, and macrophages in turn stimulate immune responses in equally diurnal fashion with their own clocks. By contrast, far fewer reports exist of circadian B-cell activity, and indeed the oscillations documented in circadian gene expression in peripheral blood mononuclear cells is much lower in amplitude than that observed in other tissues such as the liver.

The consequences of pervasive circadian regulation of immune function are numerous, and range far beyond the aforementioned diurnal variation in infective susceptibility. For example, a pronounced circadian oscillation of blood clotting has long been known, and is supported by circadian variation in factors ranging from platelet aggregation (*take your 80/81mg Aspirin at night; it works better & longer*) and adhesion to actual expression of clotting factors like PAI-1.

Circadian clocks also regulate circulation of many immune cells such as hematopoetic stem cells.

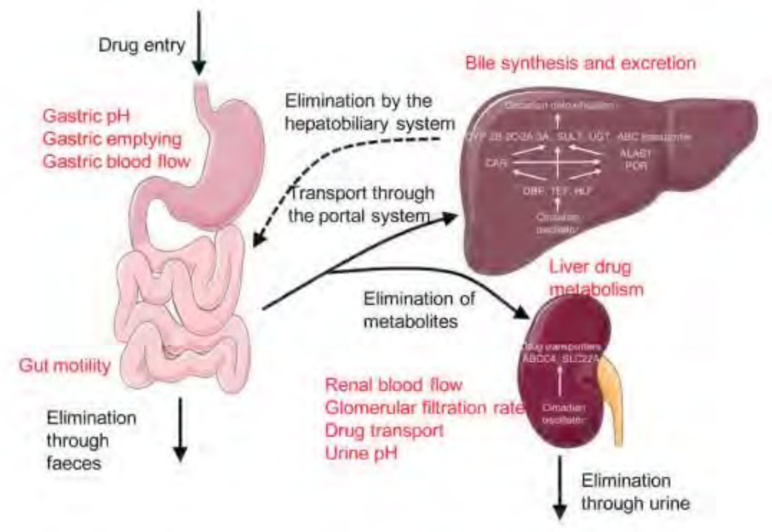
Finally, circadian immune regulation results in diurnal variations in related immune parameters like inflammation, which plays a strong role in circadian variation in many diseases.

Circadian Pharmacokinetics in Different Body Systems

Gastric & Intestinal Absorption

Drug transport and diffusion is highly dependent on gastric pH that regulates drug ionization and hydrophobicity. In most animal species including man, gastric pH presents a strong circadian pattern influencing drug solubility. At the same time, gastric emptying after a meal and gastrointestinal mobility present a higher speed during the day than at night, increasing in this way absorption during the day. Interestingly, at least for the colon, this rhythmic motility seems to be regulated by the circadian clock, as it is severely perturbed in mice without a clock.

Finally, the increased blood flow to the gastrointestinal tract in the beginning of the day also contributed to increased drug distribution in daytime in humans.



Modulation of drug pharmacokinetic by the circadian clock

All rhythmic parameters influencing drug transport and metabolism are highlighted in red. Characteristic functions of the circadian clock on these processes are indicated in the respective organs.

Rhythmic Liver Drug Metabolism

Xenobiotic detoxification is organized as a multistep system consisting of three groups of proteins assuming distinct and successive functions.

The phase I proteins functionalize drugs (possibly for inhibition or activation) by the oxidase, reductase, and hydroxylase activities of the microsomal P450 cytochrome (CYP P450) family of enzymes.

The phase II proteins conjugate drugs to a hydrophilic molecule in order to increase solubility. They help to make lipophilic compounds hydrophilic enough to facilitate their excretion into urine, bile, and feces. Mainly sulfotransferases, UDPglucuronotransferases, glutathione S-transferases, and N-acetyltransferases achieve these reactions.

Finally, phase III transporters – mainly ABC transporters – transport xenobiotics outside the cell.

Inversely, transporters of the solute carrier family (Slc) are involved in cellular import.

In addition to these three classes of enzymes, other proteins globally regulate the activity of most of the phase I enzymes of the P450 oxydoreductase family.

Importantly for pharmacokinetics, expression of all of these proteins is carefully coordinated to favor efficient liver detoxification. This control is achieved through the complex transcriptional regulation of these genes in a manner that is cell-type specific, daytime dependent, and inducible by xenobiotics themselves. Transcriptional induction involves a heterogeneous class of transcription factors collectively named "xenobiotic receptors". The three main xenobiotic receptors are the nuclear receptors constitutive androstane receptor (CAR) and pregnane X receptor (PXR), and the PAS-domain helix-loop-helix transcription factor aryl hydrocarbon receptor (AhR). Mainly expressed in the liver and the small intestine, these xenobiotic receptors are associated with chaperone proteins in the cytoplasm. In response to xenobiotics – either through direct binding or by way of signal transduction – these proteins accumulate in the nucleus where they activate transcription of phase I, II and III genes.

Historical transcriptome analysis of mouse liver revealed that genes coding for enzymes involved in the three phases of xenobiotic detoxification represent an important part of the rhythmically expressed genes. Recent evidence suggests that these genes are not direct targets of BMAL1, but rather suggest regulation by circadian clock-controlled transcription factors.

Acetaminophen/paracetamol time-dependent toxicity seems to be a result of rhythmic expression of the CYP2E1, due itself to the rhythmic inhibition of the HNF1 nuclear receptor by CRY1 on the Cyp2e1 promoter.

Whereas the relative importance of all these systems on global rhythmic drug detoxification in mouse liver is not yet clearly demonstrated, there is no doubt that the circadian clock is a major actor in this arena.

Elimination by the Hepatobiliary System

Although most metabolized drugs are finally excreted into plasma and subsequently urine, several of them are first excreted through the hepatobiliary system into the gut and are subject to a second round of hepatic metabolism or fecal excretion. The hepatobiliary transport system is required not only for bile formation, but also elimination of various endo- and xenobiotics including cholesterol, phospholipids, and drugs.

Depending on the nature of the molecule, a broad range of liver-specific export systems are involved. Bile is formed by excretion of bile salts (BS) and non-bile salt organic anions via ABC transporters. Monovalent BS are excreted via the bile salt export pump (BSEP or ABCB11), while divalent BS and anionic conjugates of endo- or xenobiotics are excreted via the conjugate export pump (MRP2 or ABCC2). The phospholipid export channel (MDR2 or ABCB4) allows the excretion of phosphatidylcholine (PC), which forms micelles in bile together with BS and cholesterol. Cationic metabolized drugs are excreted by the multidrug export channel (MDR1 or ABCB1). Other export pumps include the two-half transporter ABCG5/8 for cholesterol and the breast cancer resistance protein (BCRP or ABCG2) for anionic conjugates.

Excretion of bile acids, lipids, and xenobiotics into the bile follows a stringent circadian rhythm, at least in rodents, and clock involvement has been documented at multiple different steps.

First, bile acid synthesis follows a stringent diurnal rhythm in both rodents and humans. Conversion of cholesterol into bile acids involved the rate-limiting cholesterol-7α-hydroxylase (CYP7A1), whose rhythmic expression is directly regulated mainly through REV-ERBα.

In addition, most of the genes encoding transporters involved in bile secretion are expressed according to a circadian pattern in the liver. As a consequence, it has been observed that the biliary excretion of drugs, for example ampicillin or flomoxef, presents a diurnal pattern in rats and patients under percutaneous transhepatic biliary drainage.

Elimination by the Kidney

Most water-soluble drugs or drug metabolites are eliminated by urine through the kidney.

The rate of drug elimination in the urine depends on several intrinsic variables related to the kidney function including the renal blood flow (RBF), the glomerular filtration rate (GFR), the capacity of the kidney to reabsorb or to secrete drugs across the epithelium, the urine flow, and the urine pH, which influences the degree of urine acidification.

Interestingly, all these variables present a circadian behavior in different mammalian models. Around 20% of the RBF is converted into the urine through glomerular filtration. In the proximal tubule, many ionized drugs can be secreted in the urine from the remaining unfiltered blood via various active transports. Finally, filtered and secreted drugs can be passively or actively reabsorbed out of the urine into the blood. Because, the RBF is a key determinant of glomerular filtration and secretion, it is intimately associated with the elimination of most ionized drugs through urine. The RBF has been demonstrated to follow a circadian oscillation with a peak during the active phase. Although this rhythm is probably partially entrained by circadian arterial blood pressure and the cardiac output, the rhythmic RBF could also be generated by an intrinsic renal mechanism. For example, Cry1/Cry2 knockout exhibit disrupted activity of the renin-angiotensin-aldosterone system, one of the major mechanisms regulating RBF.

Rhythmic oscillations of the GFR are synchronized with those of RBF, but they are not fully determined by it, as GFR rhythm persists during continuous bed rest and in condition of inverted blood pressure. Rhythmic GFR is also maintained in transplanted human kidneys, indicating that sympathetic innervation is not required for this rhythm. These data indicate that GFR is generated by an intrinsic renal mechanism but the mechanism responsible for this functional rhythmicity remains unknown.

Renal reabsorption and secretion of water-soluble drugs depends on the expression of membrane transporters of the ABC and Slc families that facilitate diffusion of polar molecules through the apical and/or basolateral membranes of tubular cells. Most of drug reabsorption/secretion takes place in the proximal tubule of the kidney that is enriched in various transporters with a preferential affinity for small organic anions. It has been shown that several of these transporters present a robust diurnal expression in the more distal nephron segments, namely in the distal nephron and the collecting duct.

Drug ionization, which is mainly determined by urine pH, determines drug solubility and the rate of drug reabsorption in the nephron. Human urine pH may range from 4.5 to 8 and is controlled by a complex system of reabsorption/secretion/production of bicarbonate and secretion of protons. It usually exhibits lower values in the morning. The most important transporter involved in renal proton secretion is the sodium-proton exchanger 3 (NHE3 or Slc9A3) expressed in the proximal tubule. Expression of Nhe3 mRNA and protein in the kidney exhibit a robust circadian rhythm in rodents, with the maximal expression in the middle of the active phase (109). Interestingly, this circadian expression is significantly blunted in Cry1/Cry2 knockout mice, indicating that the circadian clock can influence the renal drug disposal via the control of urine acidification.

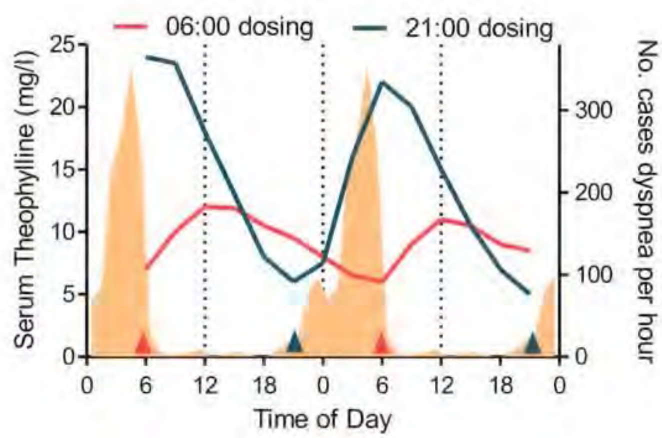
Chronobiology & Drug Treatment

To what extent has the knowledge presented above translated to effective pharmaceutical interventions? The most obvious examples for successful chronotherapy are ones with obvious time-of-day-dependent symptoms. Treatment of bronchial asthma has been tuned to exhibit maximum plasma levels at the time of highest occurrence of dyspnea, and therefore alleviate symptoms most effectively.

Cetirizine, a non-sedative, very active anti-histamine is effective ~8 hours when absorbed in the morning, while its effects are recoded up to 20hours after a nighttime intake.

Similarly, blood pressure shows a sharp peak in the early morning, importantly coinciding with the peak for cardiovascular events, and an extended trough during the night. Both healthy normotensive and patients suffering from essential hypertension exhibit this variation (take your long-acting antihypertensive medication at night). The L-type calcium channel blocker Verapamil, for example, uses extended-release formulation to have therapeutically effective plasma levels in the early morning after bedtime oral administration. In addition, such delayed release drugs have been beneficial for hypertensive patients that do not show a nocturnal dip in blood pressure, so called “non-dippers”. Non-dipping is a risk factor for congestive heart failure even in clinically normotensive subjects.

As mentioned above, not only PK/PD parameters are modulated by time-of–day, but also drug metabolism. For example, the over-the-counter acetaminophen/ paracetamol (APAP) is a leading cause of drug-induced liver failure. APAP is exclusively metabolized by the CYP P450 system of the liver, and toxicity is dependent on generation of N-acetyl-p-benzoquinone imine (NAPQI) by CYP2E1. APAP toxicity is time-of-day dependent, but liver specific ablation of the clock in mice blunts this rhythm.



Time of day dependent variation in pharmacokinetics.

Average 3-hourly steady state serum concentrations of theophylline from eight asthmatic children dosed with Theo24© before breakfast (06:00, red) or at bedtime (21:00, blue) as indicated by arrows. Shaded area represents the occurrence of dyspnea.

Cancer

While the chronotherapeutic approach of the examples above is based on relatively few well-established variables, in the case of chemotherapy and associated cancer treatments the predictions for optimal treatment schedules become highly complex.

On the one hand, chemotherapeutics should be dosed high enough to be toxic to the cancer, but on the other hand the dose should be low enough to prevent serious damage to healthy tissue or organs.

That means pharmacokinetics and dynamics operate in a tight therapeutic range. Under these pre-conditions, the variations introduced by the circadian system on multiple levels can be crucial. This is further complicated by the possibility that not only the healthy tissue has a clock but also the tumor. In vivo, this has been shown measuring the incorporation of P32 in tumors of terminally ill breast cancer. These results are in line with newer in vitro data from various human and mouse cancer cell lines like the human U2 osteosarcoma.

This is an important factor because most cancer drugs are toxic only to dividing cells or have a mechanism of action that is particularly effective in one phase of the cell cycle, that is -at least in healthy tissues – gated by the clock. The topoisomerase I inhibitor irinotecan, for example, is most effective in S-phase, while alkylating agents cross-link DNA at any phase of the cell cycle. In case of an arrhythmic tumor, as is the case in the mouse xenograft Glasgow osteosarcoma model, a further interesting complication emerged: seliciclib, a cyclin dependent kinase inhibitor, seemed to induce rhythmic gene expression in tumors and might slow down tumor progression additionally by this mode of action.

Given the known disturbance of circadian behavior in multiple human cancers, additional efficacy might be achieved harmlessly by this type of clock resynchronization.

Overall, in several different experimental rodent models it has been shown that efficacy and side effects of anticancer therapies vary up to 10-fold depending on time-of-day. However, these parameters are model-and-drug-specific. Common to most, efficacy is based on the mechanism of action, metabolism, and toxicity, and the best treatment schedule has to take into account all those parameters. The therapeutic index of the alkylating agent cyclophosphamide, for example, is significantly better if the compound is administered during the first part of the active dark phase.

This rhythm has been suggested to be dependent on CLOCK:BMAL1 binding in Bcells, changes in CYP P450 enzyme activity and even more importantly higher reduced glutathione levels at night might contribute, as has been described for other alkylating agents such as cisplatin. In contrast, 5- fluorouracil's first and rate limited step in metabolism is dependent on the availability of dihydropyrimidine dehydrogenase (DPD), and certain 5-FU metabolites then block the activity and de novo synthesis of thymidilate synthase (TS), which is important for DNA synthesis. DPD and TS expression are high and low, respectively, during the first part of the light phase. Therefore, 5-FU exhibits best tolerability and efficacy 180° out of phase with cyclophosphamide and most other alkylating agents. Leucovorin (LV) is an inhibitor of TS and often co-administered with 5-FU. This adds to the effectiveness of 5-FU and changes the DPD to TS ratio in the same direction as observed at the optimal time of day established in animal experiments.

Interestingly, there are further common traits between irinotecan and 5-FU. For both, added value of chronotherapeutic treatment regimens is gender-specific in experimental animal models. In the case of 5-FU this has even been observed in clinical populations. While chronomodulated delivery of 5-FU improves survival for male patients compared to conventional treatment, the opposite was true for female study participants. The authors speculate that since disruption of the rest/activity rhythm during chemotherapy has been shown to predict overall survival for metastatic colorectal cancer, the men could exhibit more robust circadian rhythms.

Implications for Drug R&D

Classically, the drug discovery process is preceded by the validation of a given target. The mechanism of action is established and molecular targets defined. Taking diurnal changes of relevant parameters into account might mean significantly higher costs because the same experiments might have to be conducted at multiple different times of day in order to assess if, for example, a certain type of receptor or protein is only expressed at a specific time of day. However, there are online resources that can be mined for information about the circadian expression of a given transcript or metabolite. A special case presents in the quest for drugs against age-related diseases. Similarly to human beings, rodent species typically used in these assays exhibit attenuated circadian rhythms. Thus, the PK/PD profile and target availability itself could change during the course of aging.

Once the target is confirmed, and the lead optimization process started, the properties of the novel chemical entities are evaluated and selected. Typically, CYP P450 induction and inhibition in human and rodent primary hepatocytes is tested. This might introduce bias towards only one phase of the circadian cycle, since the cells that are used to evaluate the compounds contain a functional cell autonomous clock that can influence drug metabolism. The CACO-2 monolayer assay is an industry standard not only used to predict absorption after oral application through the intestinal barrier but also to assess interactions with important transporters such as P-gp. Interestingly, like the intestinal barrier itself, the human tumor derived CACO-2 cells have a functioning clock that has been shown to directly control expression levels of Mdr1.

Two of the most common reasons for novel chemical entities to fail in drug development or even marketed drugs to be withdrawn are liver toxicity and cardiac safety. In fact, QT prolongation often associated with blockade of the K+ -channel encoded by human ether-à-go-go related gene (hERG) and a surrogate marker for torsade de pointes was the single most common cause for withdrawal of marketed drugs in recent years.

Therefore, an extensive battery of tests from *in vitro* channel function to *in vivo* electrophysiology in the freely moving dog or monkey has been established and is performed before a so-called "thorough QT/QTc" study in Phase I of development. Although new models have been developed that adjust for circadian variability due to changes in heart rate over the day, the possibility that drug dependent QT-interval prolongation is directly influenced by time of day in patients has not yet been fully explored, but is not unsupported. Moreover, there is a clear rationale for how the circadian clock would influence cardiac repolarization, namely krüppel-like factor 15.

Together these findings suggest that a time-of-day bias in testing drug induced QT–prolongation might lead to a misjudgment of risk to patients. If, based on these considerations, drug developers would adopt a circadian testing policy, there is a further complication. In contrast to most pre-clinical animal models, there is a great deal of inter-individual variability in the circadian phenotype of people: period or phase and amplitude of clock-controlled rhythms described above varies greatly in human populations. These are no small differences, and the lay terms "larks" and "owls" for people with an early and late activity phase, respectively, illustrate their magnitude.

Moreover, diseases can even more severely alter rhythmic rest/activity and endocrine patterns. Some schizophrenic patients, for example, exhibit a nearly arrhythmic behavioral pattern, and not only are the cortisol levels in depressed patients elevated but their diurnal variation is blunted. Twin studies suggest that genetic traits are partially determining the chronotype. In fact, there are multiple loci that have been determined to contribute to differences in chronotype and sleep. Moreover, there are quite consistent age-dependent changes of chronotype, and recent results suggest relatively stable changes dependent on previous light history. Inter-individual differences in clock phase are sizable and therefore probably clinically relevant. Albeit significant methodological advances have been made to determine the properties of an individual's circadian clock in a simple test, this goal has not been possible so far. The ability to use human skin biopsies that are lentivirally transduced with circadian reporters to determine period is one cellular method in this direction, and hair follicles samples have also been used. Alternatively, clock-controlled neuroendocrine signals such as the dim-light melatonin onset (DLMO) have been used to estimate clock phase.

Due to large inter-individual variation in the levels of these hormones between individuals multiple sampling is necessary to establish meaningful results, which is also dependent on ambient light levels. To overcome these limitations, transcriptome and metabolome datasets have been used to establish timetable methods for internal time in mice and men. All of these methods, however, rely on at least two sampling times that are optimally 12 hours apart to compensate for interindividual difference in the absolute levels of gene or metabolite expression, and "internal time" can be approximated with 2 hours' precision. Thus, a feasible and accurate circadian test remains to be established.

Given aforementioned examples of arrythmicity in disease and inter-individual differences in clock phase, the circadian clock itself might be an interesting target for drug development.

In fact, multiple pharmacological agents have been reported to phase-shift behavioral and biochemical rhythms in experimental animal models and people, and for example melatonin, melatonin agonists, or a combined melatonin agonist/5HT2c antagonist have already received market approval, although not necessarily as phase shifting drugs. In addition to the melatonin receptors, several independent molecular targets have been identified to alter clock function. Amongst the first that was identified was casein kinase 1, and even subform- specific tool compounds have been described. As a target, however, kinase inhibitors are not without problem. Casein kinase 1 is, for example, involved in Wnt signaling and linked to cell proliferation and survival.

Furthermore, a number of compounds that target core molecular clock components or are believed to be important links between the clock and HPA axis have been identified and tested, including a Neuropeptide Y Y5-receptor, a tachykinin antagonist, an inverse agonist of RORα, and a corticotrophin releasing factor (CRF) antagonist. Most recently, several unbiased small molecule screens have been undertaken in an *in vitro* model of the circadian oscillator, and they have identified new molecular entities that target known clock components such as CRY, CK1, and REV-ERBα. Whether these *in vitro* data from U2OS cells will be able to translate in the *in vivo* situation will be very interesting.

More generally, it remains to be proven if the clock does indeed present a "druggable" target, or if there are unsuspected mechanistic problems in altering circadian rhythms. Should such compounds exhibit safety profiles as favorable as melatonin, for example, they could prove useful in a wide spectrum of possible indications, ranging from sleep/wake problems in shift workers to amplitude related problems in aging-related diseases. On the one hand such drugs could help to "boost" circadian rhythmicity beyond what can be achieved through behavioral measures, and on the other hand re-adjust specific rhythmic components to a favorable phase. This would be especially useful given the tendency of modern society towards a 24/7 lifestyle.

In this respect, more and more evidence has accumulated showing the some times disastrous effects of such clock disruption on health. Unfortunately, there seems to be a vicious cycle between cause and effect. Clock disruption over time can lead to various major pathologies and these in turn can feedback onto the clock and further abrogate rhythms. Interestingly, however, strengthening the clock by imposing strong timing cues can alleviate symptoms. In a mouse model of Huntington's disease, for example, either the use of hypnotics and scheduled meals can normalize circadian gene expression rhythms and improve disease symptoms. Similarly, melatonin and bright light treatment have been shown to have a positive effect on institutionalized Alzheimer patients.

Tentative Directions

The recent findings that we have highlighted all yield insight into the growing field of chronopharmacology, and into the mechanistic basis for the variations in PK/PD that have been observed in a vast number of instances. However, many important questions remain unanswered. Most if not all of the circadian expression data at the genomic level on which these conclusions are based are available only for rodents. Considering the fact that expression and functional properties of drug metabolizing enzymes and drug transporters are highly species-specific, extrapolation of these results to humans is not a foregone conclusion. In order to translate research data into clinical application, significant progress in the characterization of circadian variations in protein expression and activity in human is absolutely necessary.

Although there has been much more awareness of the impact of the circadian clock on health, disease, and treatment in recent years, these findings seem to not have translated into clinics or regulatory agencies on a broad scale. Publicly available clinical trials databases such as clinicaltrials.gov list a historic total of 205 hits for the search term "circadian".

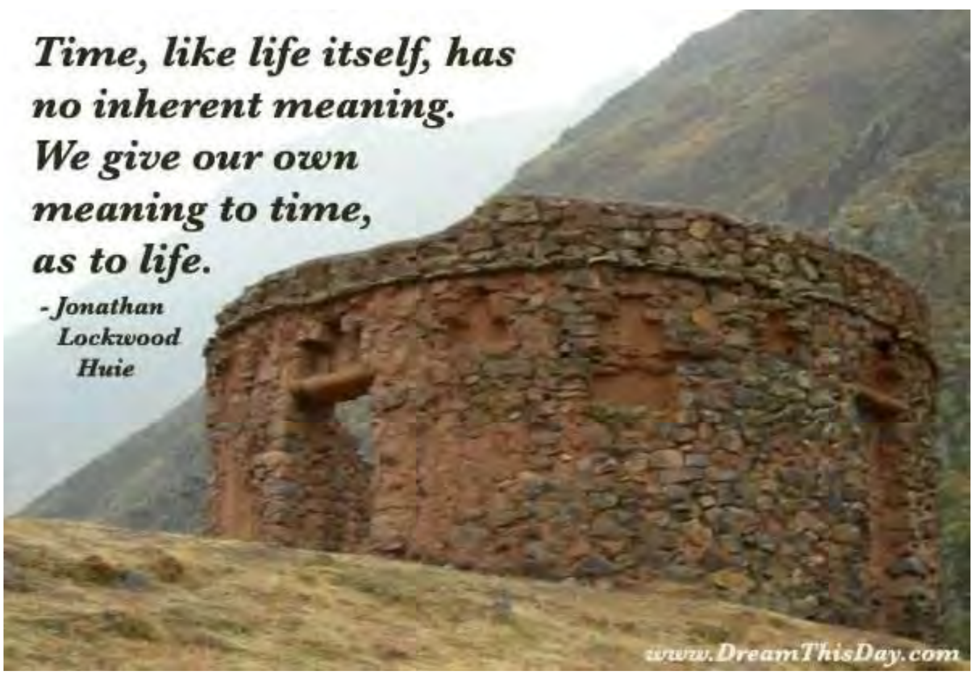
Twelve of these are cancer-related but none try to establish chronotherapeutic treatment regimens. The search term "chronotherapy" results in 14 hits. In contrast, the search term "cancer" produces 38331 results. Similar results were obtained from the EU clinical trials register. Given the fact that about 20% of the transcriptome, proteome and metabolome are under clock control, this seems disproportionate. In the case of regulatory authorities, none of the chronobiological effects upon PK/PD outlined here are mentioned in guidelines published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This is surprising, especially considering that unexpected hepatoxicity and cardiac side effects are the most common reasons for withdrawal of marketed drugs.

Finally, the large proportion of physiology regulated by the circadian clock suggests that the clock itself might present a possible pharmaceutical target to increase efficacy and reduce side effects. In order for such treatments to be effective, a more detailed knowledge will be required not only of how clocks control physiology, but also of how clocks in different organ systems contribute to different processes relevant to PK/PD.

Epilogue

Time, these days, is an obsession. It is also, possibly, one of the rare notions that has always driven me into a form of obsessive (but not compulsive) neurosis. Being on *time* at school; delivering homework on *time*; getting to the examination room on *time* and not staying over*time*; irritation when a flight (or a patient, or guests, or a date) was late; cooking meals well-*time*d, and serving them on *time*; *tim*ing properly my 200km daily drive to and from UC Davis, while taking a guess on traffic (before the GPS era); and you can add your own loooong list of *time* obsessions, real or fancy. Then there is chronobiology, and chronopharmacology. Practicing medicine and developing novel modes of treatment while ignoring these is unacceptable; you must consider *time* and *timing* all the time.

I am now waiting to learn and understand much more from the future conference on *Time* tentatively scheduled in 2018 at the *Para Limes* Institute (NTU) in Singapore, and from avidly reading and discussing *time*, since –for me- *time* is running out.



https://www.youtube.com/watch?v=ZH7dG0qyzyg

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Without Yves P. Huin mastering the complexity of the website, this essay would be just lost time –and why not?

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