Time in living systems

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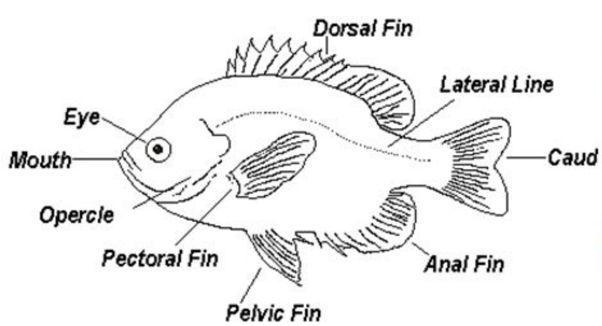
1. Time and change

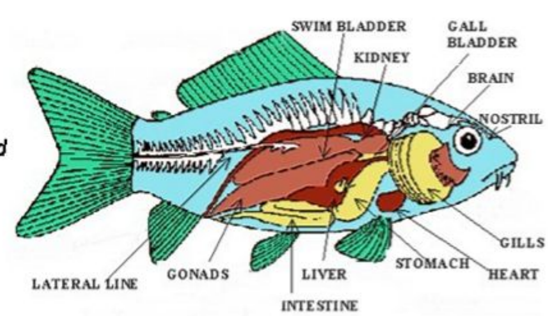
There is no consensus among scientists on what time is. Most physicists view time and space as fundamental properties of the world, where change is described as a trajectory in space and time. They optimistically assume that all changes can be explained in terms of effective cause. However, Aristotle pointed out that effective cause is only one of four possible kinds of causation, and not every change can be fully explained by following trajectories in time and space. According to Aristotle, change is a more fundamental category than time; in fact, time is made of changes. Also time is not universal, it can be specific for some systems. This view of time is assumed by several biologists who think that living systems have their own time scales and time sequences. For example, organisms show different pace in their development or aging.

In order to study time we first need to learn how to study change. This question was investigated in detail by a Russian paleobotanist, Sergei Meyen. His main ideas can be summarized as follows:

1. Change is first qualitative and only then quantitative; time represents quality (archetype). Thus, Meyen called his conception of time as "typological time".
2. To detect change we need a model of a system (i.e., a list of parts and relations between parts).
3. Change follows certain rules (logic) and we need to reconstruct these rules
4. Change leaves footprints which can be used for temporal reconstructions

Let us first address the problem of modeling. A living organism can be modeled as a system of interconnected parts. For example, fish has head, eyes, fins, tail. More parts can be found inside. There is liver, guts, gills, heart, and other organs.

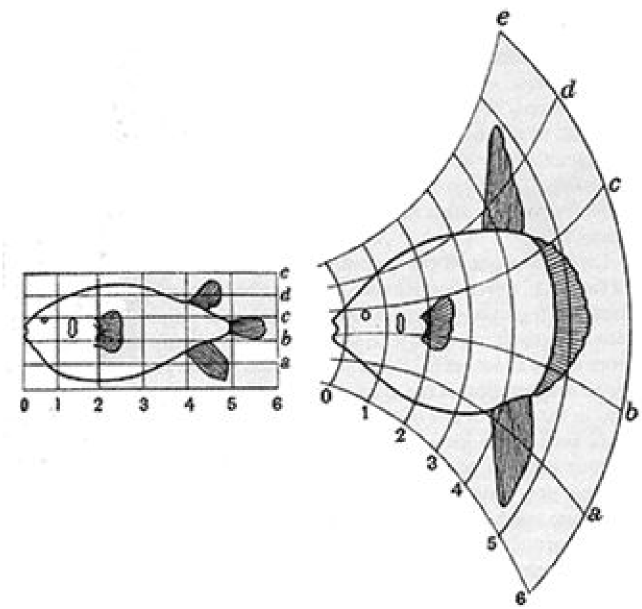


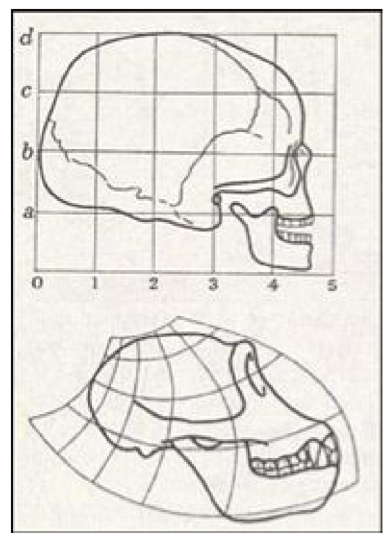


Meyen suggested a term "meronomy" for a science about parts of systems and principles of partitioning. Paleontologists often find isolated parts of organisms (e.g., leaves or fruits of plants), which are difficult to classify unless somebody is lucky to find an attachment of a part to the whole organism. Each part can be further partitioned into smaller parts up to the cellular or even molecular level, and each level of organization brings additional details about the structure and function of each part.

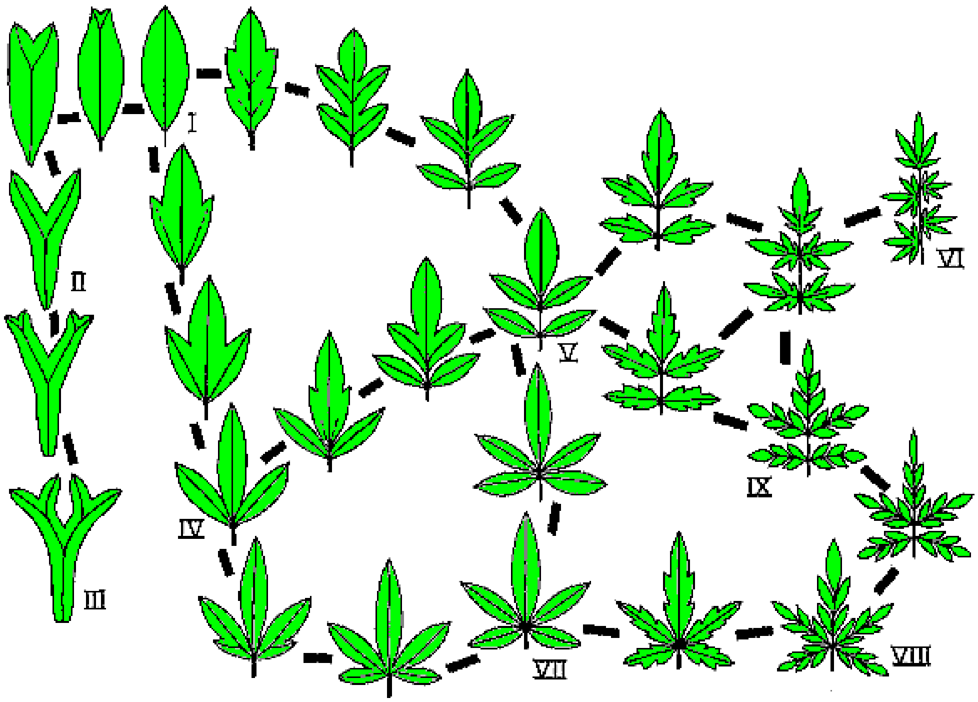
Change of organisms in the individual life or in evolution can be described in terms of alteration of the composition of parts or relations between parts. For example, a tadpole has a tail, but the frog which develops from it has no tail. The evolution of fish can be described by the change of part size (e.g., paddlefish has a long nose), or by the loss of parts (e.g., eels lost most of the fins that other fish have).

Using a model of an animal we can start understanding the rules (i.e., logic) of animal evolution. We can learn which new parts can emerge, and how relations can be modified. Below is an example from the famous book of D'Arcy Thompson "On Growth and Form". The picture shows that the change of metric (i.e., distance between parts) can transform one kind of fish into another, or transform the skull of a monkey into the skull of a human. These transformations take time, so we can measure evolutionary time by the degree of geometric change.



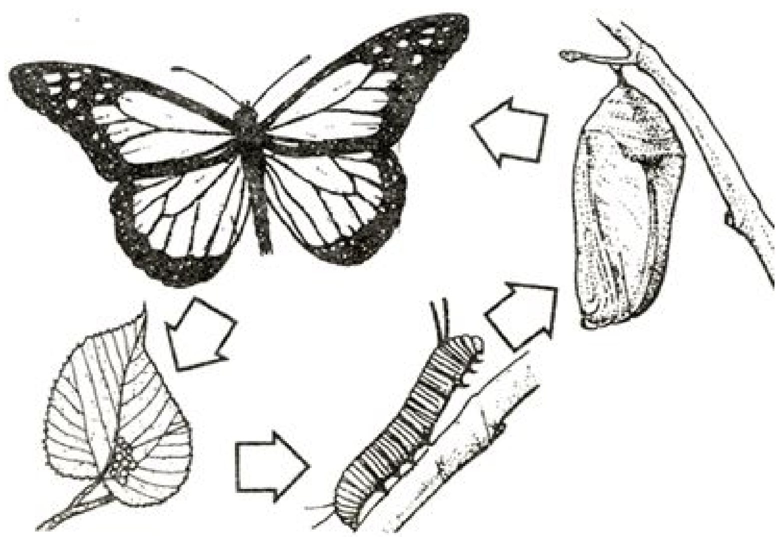


Dr. Meyen was specifically interested in following the logic of leaf evolution. It appears that the evolution of leaves follows its own internal logic, shown below. A leaf can be modified in 3 basic ways: (a) splitting the end into two branches, (b) producing feather-like nodes, or (c) palm-like nodes. Also, there may be combinations of different patterns, as shown in the picture which is taken from the book "Fundamentals of Paleontology" by Sergei Meyen.



2. Life cycle, individual time

Now let us switch from evolutionary time to a shorter time scale, which is individual time or a life cycle. Change becomes time only when it is *reproducible*. The main reproducible element of any living organism if its life cycle. The butterfly lays the eggs, small caterpillars emerge from eggs, they start feeding and growing, and then a caterpillar becomes a motionless pupae, attached to a branch. Finally, a new butterfly emerges from the pupae.



Platonic philosophers view change as a destruction of form, which may be true in the case of death. However, the change can also make a new level of form as in the life cycle. We tend to consider an organism in its current form, which is a wrong approach because the organism is a circular process of its life cycle. Some parts of the organism may be not functional currently, but they are needed for the next phase of the cycle. You cannot understand a caterpillar unless you know that it will eventually become a butterfly.

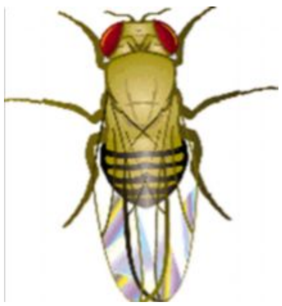
We, humans, also have a reproducible life cycle, which is a form of our existence. We can understand our life at a new level if we think that any stage of our physical and psychological development is transient is a part of a life cycle. Several organs change their function as a human grows up and then ages. Many philosophers and artists attempted to comprehend human life from the perspective of the life cycle, and here examples of paintings on this topic.

Three ages of women (fragment)
Gustav Klimt

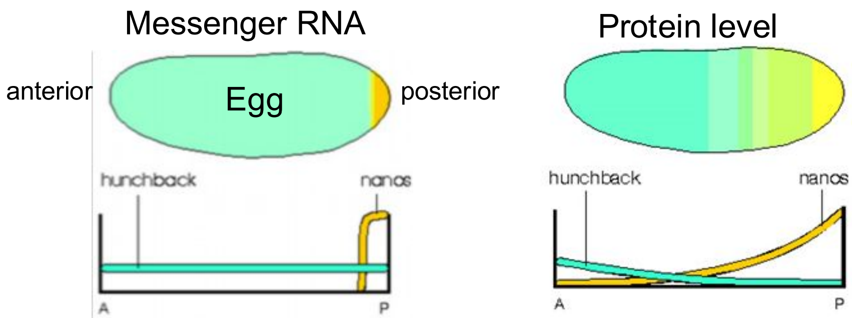
Old and young
Huang Shan Shou

Aging should be viewed as a part of our nature, as our biological time scale. Also, aging is not just a fate, it can be modified if we learn its logic. Below is the logo of the National Insitute on Aging (where I work) showing that the aging clock can be adjusted, and we can throw an extra handful of sand into our sand clock.

The life cycle has internal logic, which is extremely complex and we understand only a small fraction of it. Here is an example of a logical switch in the early development of Drosophila embryo. Two major genes control the formation of the anterior-posterior polarity of the embryo: *hunchback* is transcribed in the entire egg, but *nanos* is transcribed only in the posterior pole. Nanos protein binds to hunchback mRNA and blocks its translation. Thus, at the protein level, the embryo has two opposite gradients of both genes, which affect the activation and suppression of other genes that control the formation of body parts along the anterior-posterior axis.

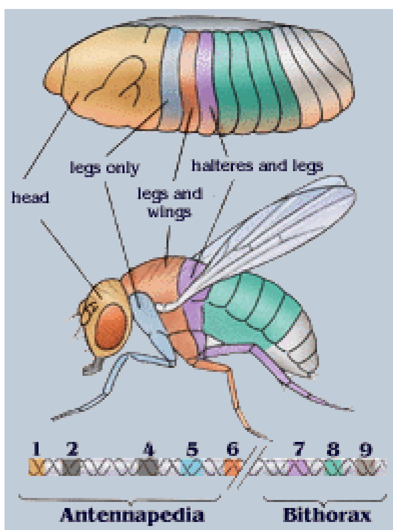


Drosophila fly



Nanos blocks translation of hunchback

At a later stage, body segmentation is formed and maintained via segment-specific expression of several homeobox genes shown by different colors below:

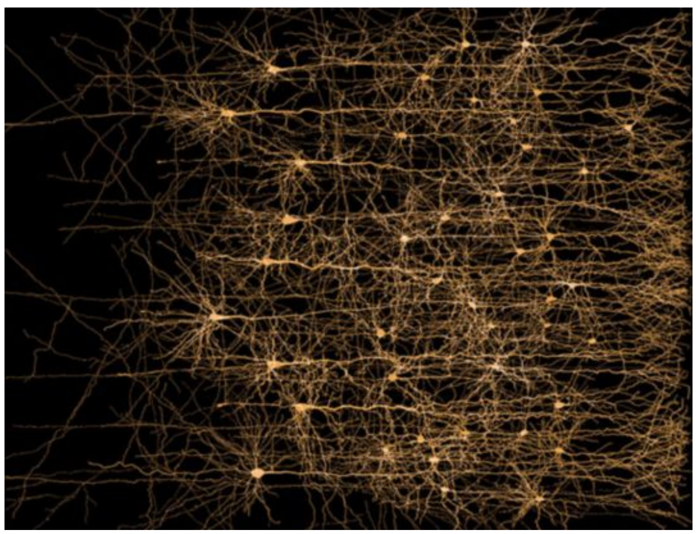


3. Tempofixation

Past change leave their footprints which allow us to reconstruct historical events. Sergei Meyen was a paleontologist; thus it was his direct professional interest to make historical reconstruction of such footprints of time which he called “tempofixators”. The most common tempofixation is tree rings which indicate the rate of growth, climate changes, pest insect outbreaks, and forest fires. Smaller chambers of the shell of the Nautilus mollusk represent its size at earlier stages of development.

Tree rings Shell of Nautilus

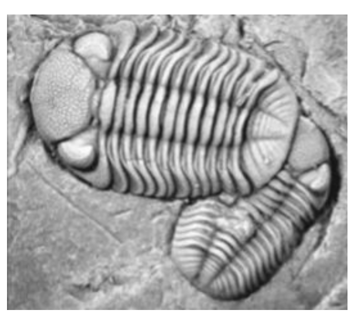
Tempofixation is not designed for scientists who do historical reconstructions, it is useful for the organisms themselves. For example, tree rings have important structural and water-conducting functions. Neurons layers in the cortex of the brain (see below) represent multiple waves of neuron migration, and this layered structure is very important for brain functionality.



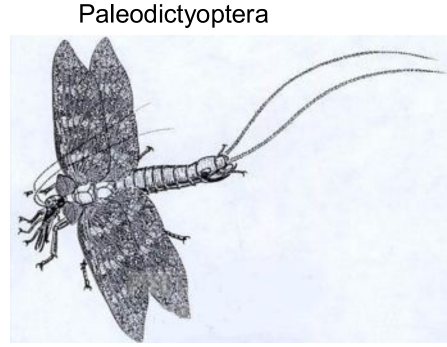
Paleontologists used fossilized organisms for reconstruction of past evolution. This is the ancient bird Archaeopteryx, trilobites (giant sea cockroaches), giant dragonflies which has nothing in common with contemporary dragonflies.

Archeopterix

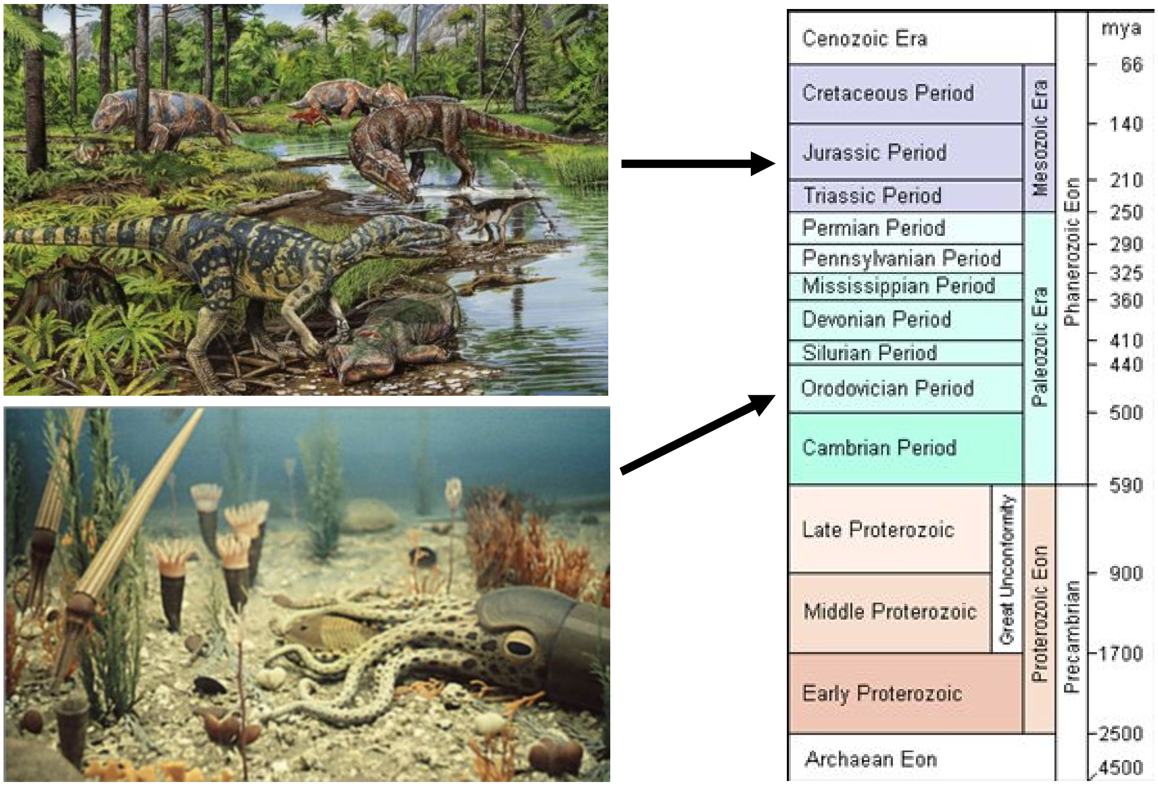
Trilobites



Paleodictyoptera



Paleontologists are interested not in just individual organisms but also at reconstruction of ecosystems of the past. It is important to know which organisms lived together at specific time and place. Fossils can be dated by evolutionary periods. For example, the Ordovician period was the era of gigantic cephalopods and trilobites, and the Jurassic period was the era of dinosaurs. Evolutionary periods is a perfect example of a qualitative time scale. Each period has its own key features, and the absolute time is not that important.



4. Living systems make their own time

So far we were using the Aristotle's conception of time as change in living systems. But what is the source of change?Here I want to focus on the idea that change is controlled/encoded by living systems, in other words, living systems make their own time. Living organisms are self-referential systems. Thus, external observer is not needed to detect or make change. Estonian biologist Jacob von Uexkull developed a theory of meaning (Bedeutungslehre, 1940).

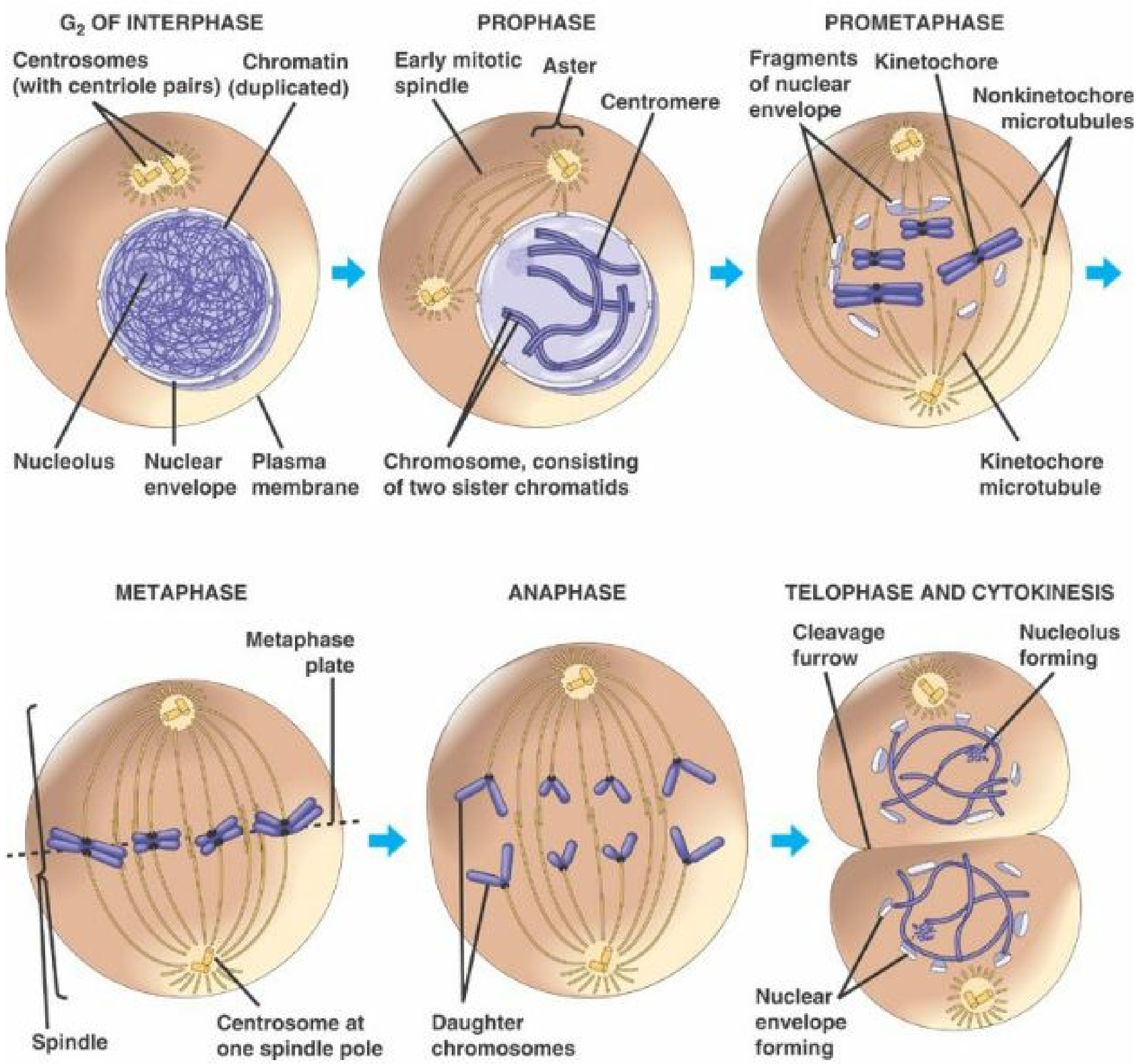
Jakob von Uexküll (1864-1944)

He suggested that all organisms develop a model of their environment, which he called Umwelt. Organisms make meanings out of objects, interpreting them as food, shelters, or enemies. Living systems are different from non-living objects because they can create new meanings. Organisms perceive the world through their functions and their tools. According to the law of instrument attributed to Mark Twain, "To a man with a hammer, everything looks like a nail". By making a new tool or organ, organisms can modify their perception of the world. This concept has developed into a novel area of science called Biosemiotics (see http://www.biosemiotics.org). The main thesis of biosemiotics is that Life and Meaning are coextensive. Every living organism makes and communicates a model of its environment, and all meanings are produced in this way. This idea is opposite to the Platonic philosophy, which considers all forms and meanings as given a-priori.

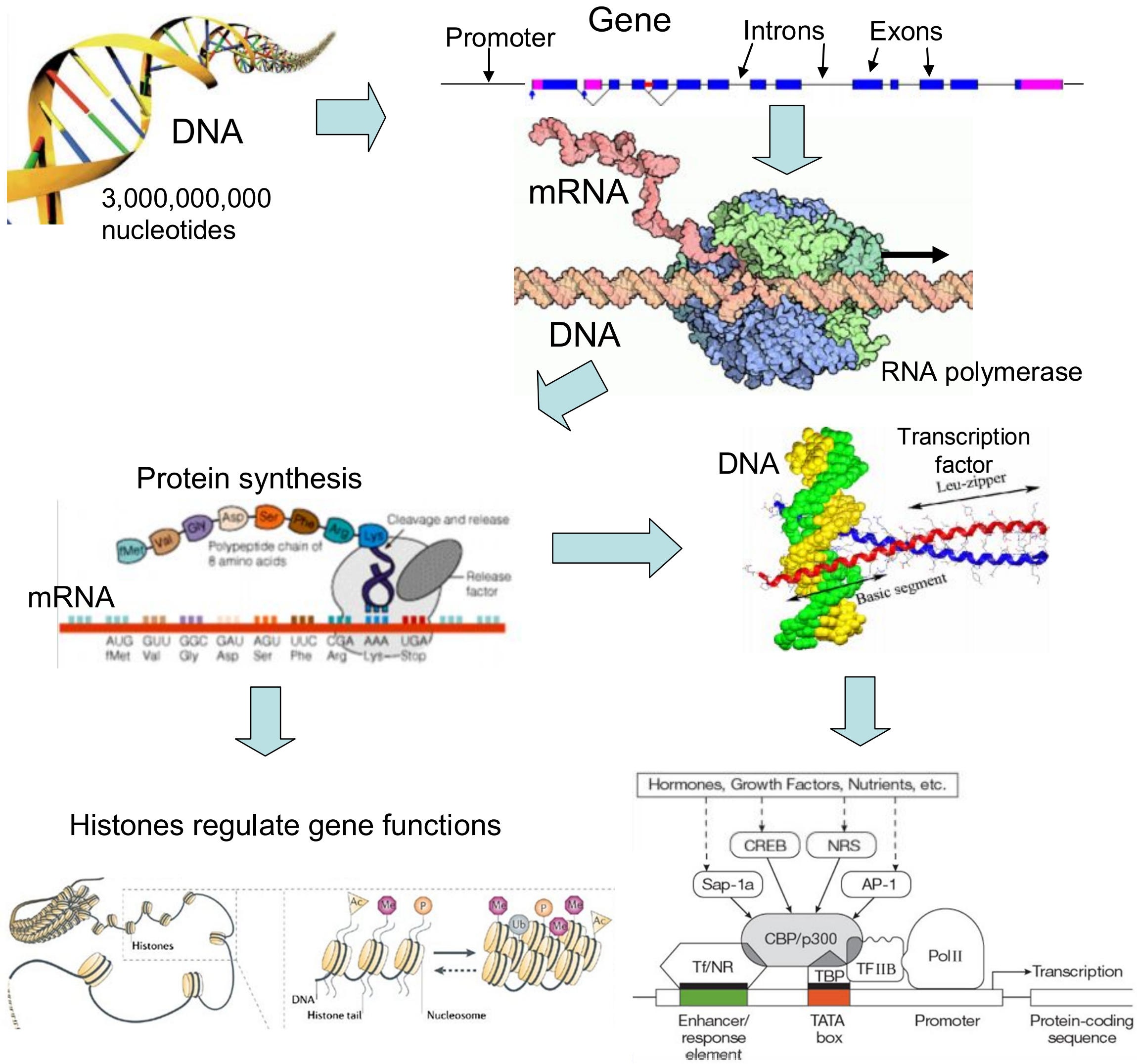
Time can be viewed as a part of the Umwelt of an organism, which is needed to organize individual processes into functional behavior. Some processes need to be synchronized, whereas others should be invoked sequentially in a specific order. Even single-cell organisms can make their Umwelt and their time; thus, the brain is not necessary for making models. Nucleus is the brain of eukaryotic cell. It carries long-term memory which is communicated across generations and is represented by the genome. In addition it carries short-term memory represented by epigenetic marks, which are various modifications of DNA-binding proteins called histones. Histones can be methylated, acetylated, phosphorylated, or ubiquetinated, and these modifications control the activity of genes in the genome. There is a hypothesis that brain memory is based on the epigenetic memory of individual neurons.

Let us consider the most fundamental temporal phenomenon in biology which self-reproduction. Because the majority of living organisms are represented by cells, self-reproduction is implemented as a cell cycle. For example, bacterial cells grow and then divide to produce offspring cells. The division of a bacterial cell starts with the duplication of its circular DNA. DNA rings are distributed between daughter cells, and they become separated by a cell wall. This process is repeated indefinitely until resources are available in the environment.

Most organisms are much bigger and more complex than bacteria. They are called eukaryotic organisms. Their cells have a nucleus, and DNA is organized into multiple chromosomes as shown below. The reproduction cycle of the eukaryotic cell is much more complex, it can be viewed as a dance of chromosomes with macromolecular partners like microtubules, centrosomes, and others. Chromosomes duplicate, condense, and make pairs along the center of the cell. Nuclear envelope disintegrates into small vesicles. Then chromosomes are pulled to the poles and de-condense there.

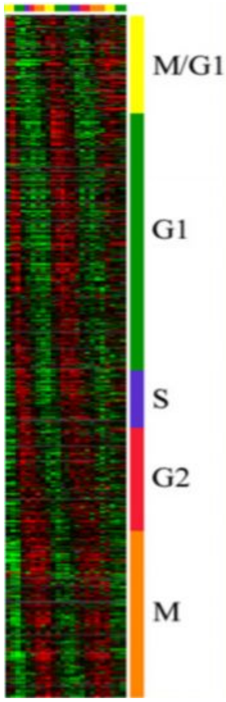


The question is how this dance of chromosomes is designed and orchestrated. Cell division is a living clock with periodic divisions. A clock has a barrel with a spring, and various wheels. In the cell there are no wheels, however there is a perfectly tuned wet mechanism which controls the cycle. I brief, each chromosome in a cell is a huge DNA molecule which is a sequence of nucleotides. All chromosomes in a human genome carry about 3 billion nucleotides which we can read as A, T, G, and C characters. Some parts of this sequence are used to encode proteins, they are called genes. Genes are first transcribed, which means making an RNA copy of the gene. Then the protein is manufactured using RNA sequence as a template. Some proteins can regulate the activity of other genes; they are called transcription factors. These transcription factors can bind to a specific short sequence of nucleotides near the beginning of the gene, and then they can either activate or suppress the transcription of the gene. Regulation of gene activity is a very complex process, which involves hundreds of regulatory proteins with sophisticated rules of assembly and disassembly. They make logical switches resembling human logic. Some regulators can start working only in the presence of specific partners, but they become inactivated by specific repressors. Biologists still understand only a small portion of these interactions. To add the complexity, there is so called "histone code" which is the basis for epigenetic short-term memory in the nucleus. It is also controlled by hundreds of proteins with logical switches.



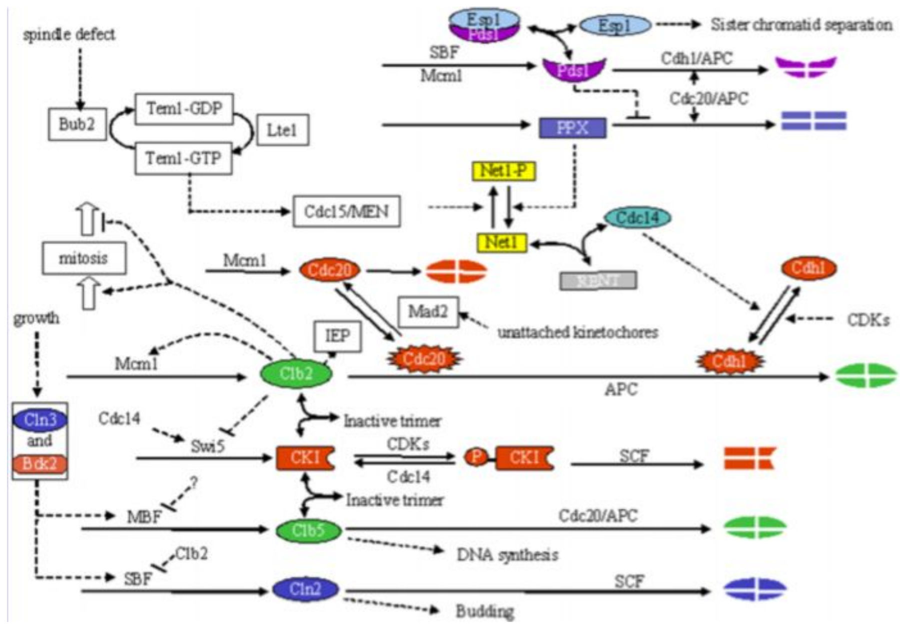
Mechanisms of cell cycle were studied in more details in the yeast. There is a technology called "microarray" which makes it possible to measure the activity of all genes in the genome at each time point. The left panel of the figure below shows the results of analysis of multiple microarrays taken at different time points through the cell cycle (cells are synchronized). Data are shown as a matrix where genes are rows, time points are columns, and gene expression is color-coded. It appears that a large number of genes have a cyclic activity synchronized with the cell cycle. Analysis of regulatory genes in this data set has led to a model of yeast cell cycle, shown at the right panel of the figure below. This is a simplified version of the model which, however, covers the most important regulatory switches.

Data



Time

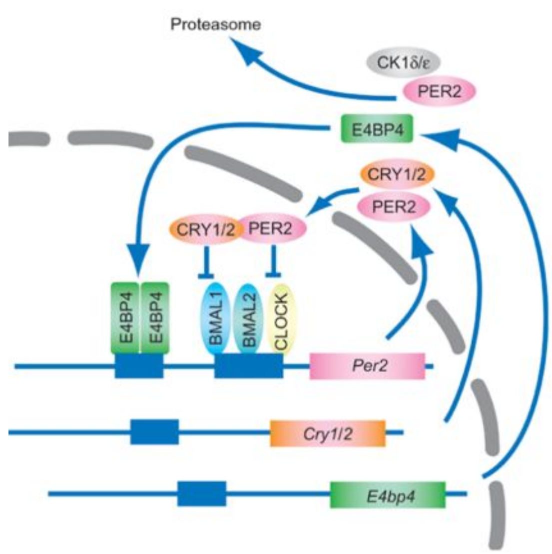
Wiring diagram



Circadian clock is another cyclic process in organisms. In contrast to the cell cycle of yeast, this clock is adjustable by external light periodicity. As a result, the organism can anticipate environmental changes by addressing its circadian clock. Molecular mechanisms of this clock include several key proteins like transcription factors Per2, Cry1, and others. Circadian clock includes cell cycle-related genes and it is often synchronized with cell division.

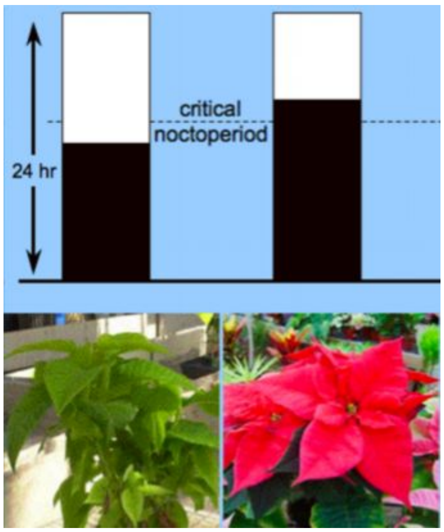
Circadian clock

Part of the mechanism

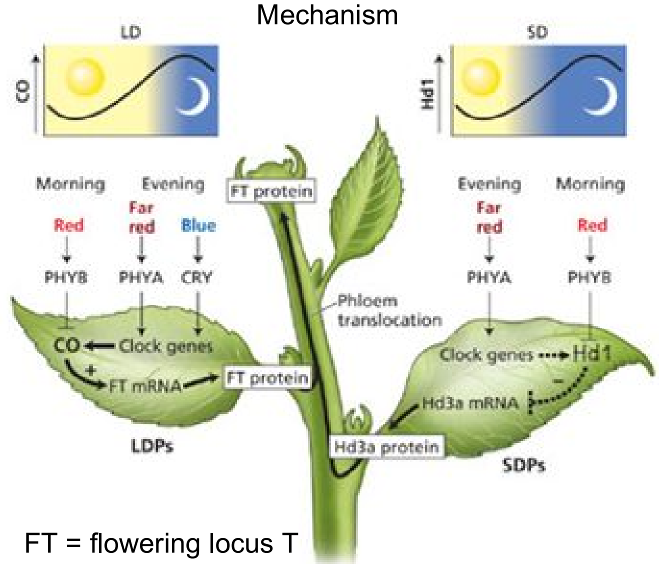


Photoperiodism adds more complexity on the top of the circadian clock. Organisms can detect changes in the length of light and dark periods of the day and adjust their activity to the seasonal changes. Here is an example of the well-known Christmas plant Poinsettia. If grown in long day conditions, poinsettia produces only green leaves and no flowers. However, after transition to a short day and long night, it produces red-color leaves which we like to see on Christmas. The actual flowers are very small and are hardly seen on this picture. Thus, plants and animals developed their own calendar based on photoperiodism.

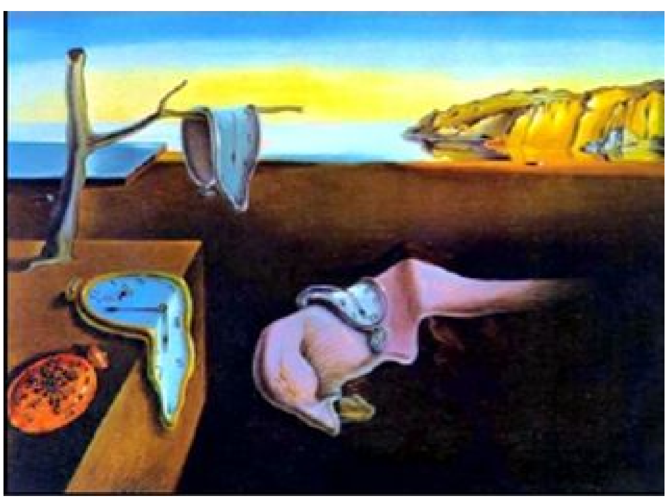
Poinsettia



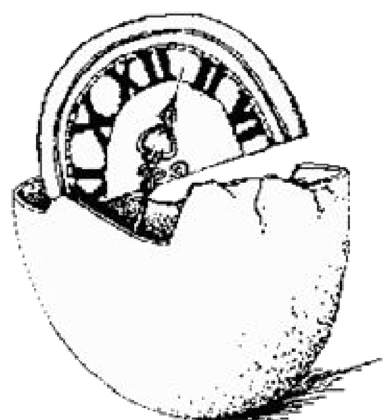
Mechanism



Molecular functions of organisms are often described as “mechanisms”. Unfortunately, the word “mechanism” has unjustified connotation of something foreign to life, something that often destroys life. However, some artists like Dali and Astrin realized that mechanisms are alive in some sense.



S. Dali



A. Astrin

The obvious difference is that mechanisms are human products; thus, they are not autonomous, whereas organisms are autonomous and autopoietic, which means self-producing. Famous biologists Maturana and Varella developed a theory of autopoiesis and applied it to the function of the brain. Mechanisms can be viewed as components of the human autopoietic system. They are external and replaceable organs, which support human production system that includes agriculture, industry, and science. Cellular structures and molecules are also manufactured (not by humans but by the cell), so they also can be called mechanisms and artifacts. These mechanisms include various kinds of clocks which determine the structure of internal time. In other words, we build our own time.

In conclusion I would like to point out the unity of time and life. This unity was foreseen by Heidegger who called his famous book "Being and time". Life cannot exist without making clocks because: (1) life is based on self-reproduction, and (2) self-reproduction is a periodic clock-like process. Does time exist without life? We can reconstruct past events, including the origin of life; but we (who do the reconstruction) are alive. Time structure is needed for preservation and communication of useful functions (e.g., well tuned sequence of processes in cell division, life cycle); and useful functions and communication exist only in living organisms. Thus, time is a product of life. However, we can extrapolate processes beyond human life and biological evolution. But we should not forget that time without life is an abstraction.

5. Conclusions

1. Time represents reproducible change (Aristotle's time)
2. Reproducible change requires modeling and logic
3. Time is a product of life and it is organism-specific
4. Various cyclic processes in organisms emerged in the course of evolution: cell cycle, circadian clock, photoperiodism
5. Living organisms are autonomous and autopoietic clocks; the boundary between organisms and mechanisms is blurred
6. Time and life are inseparable; time without life is an abstraction