MULTIPLICITY OF TIME SCALES IN THE BIOLOGICAL EVOLUTION

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Abstract. Life on Earth is about 4 billion years old. The evolution of the biological systems (phylogenesis) is conventionally described as Darwinian. However, the life and the evolution of individual biological systems (ontogeny) ranges from a few weeks for a fruit fly to thousands of years for pine trees and sponges. The time scales for biological systems are given by the reaction coefficients in the metabolism and the systems genetics. Here it is argued that the two evolutions (phylogenesis and ontogeny) are connected by the fact, that the evolution of cell polarity, leading to the Cambrian explosion, is related with the metabolism. This suggests that evolution may be controlled by mechanisms other than the Darwinian, namely by Turing structures for reactions in the confined systems of cells and multicellular embryos.

Keywords: Time scales in the biological evolution; Turing patterns; Origin of Animals; Ontogenesis and phylogenesis

1. Introduction

Biological evolution operates under a multiplicity of time scales, ranging from the reactions in a prebiotic environment, over bacteria, multicellular primitive organisms, animals and plants to today's life. Evolutionary time scales must be given in large time units. The oldest signs of life are at least 3.5 billion years old [Djokic(2017), Schopf(2018)] pp.1, 6, and 9, resp., p.53, and they appear as fossilized microorganisms (bacteria) found in hydrothermal vent precipitates [Cavalazzi(2021), Dodd(2017)] p.1, resp., p.60. A bacterium is already a very complex biological organism, and the prebiotic self-assembly is believed to have developed under a multiplicity of time scales [Nghe(2015)]. After the emergence of life, an important step in biological evolution was the evolution of multicellularity [Grosberg(20007), Parfrey(2013)] p.622, resp., p.345, with cellular differentiation [Márquez-Zacarias(2021)] p.49, which took place in the time period before the Cambrian explosion. The first and simple multicellular organism with bilateral symmetry, a metazoa or animal appeared at the end of the Ediacaran period 635-541 million

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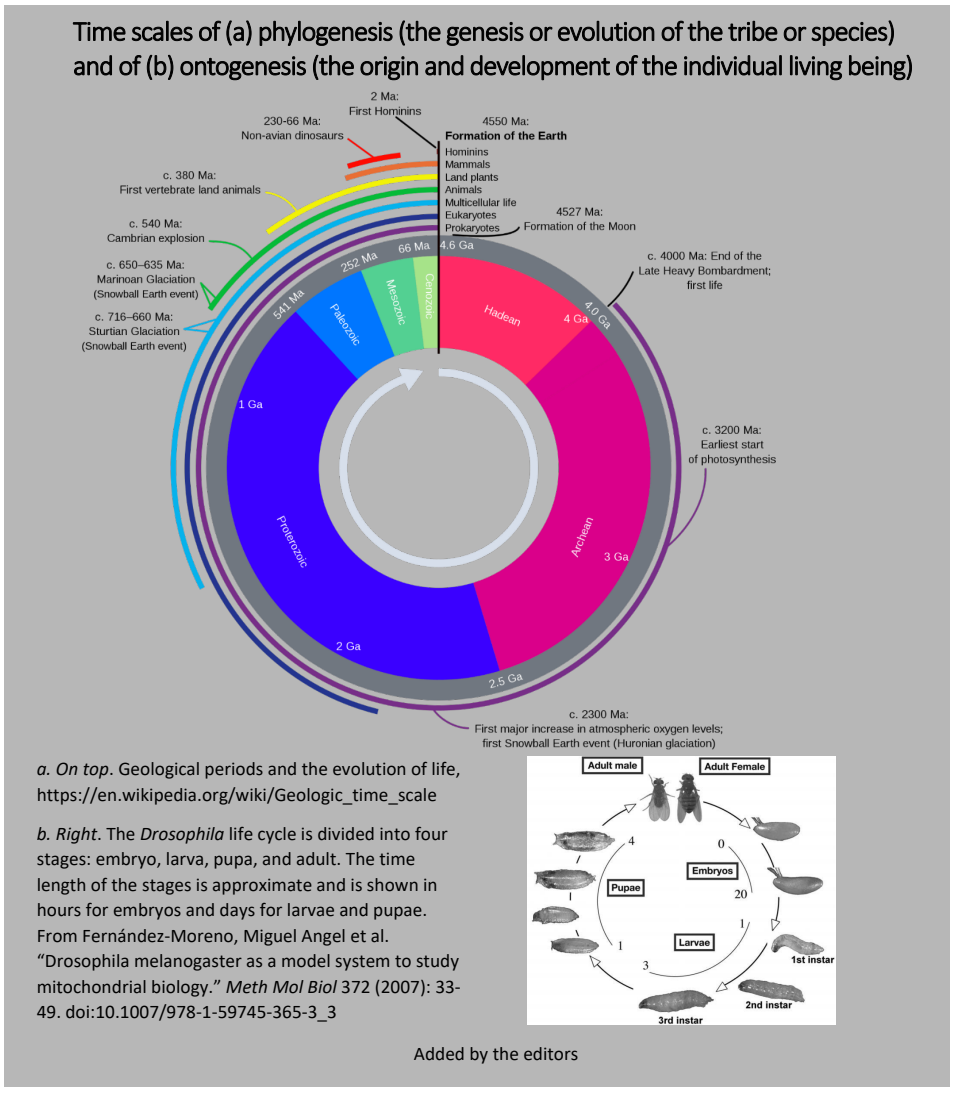
years ago (Mya) [Dunn(2018] p.915, and was part of the diversity of biological organisms that arose in the Cambrian explosion [Bottjer(2000)] p.3.



Box 1. Time scales in the evolution of biological systems and individual life spans

Although biologists have located the Cambrian explosion as occurring $\approx$ 541 Mya, it took in fact millions of years, with new findings indicating that the appearance of the animals occurred before 541 Mya and spread over a longer period of time [Budd(2008), Evans(2020)] Section 4, resp., p.7845. Bilateral symmetry in animals probably developed from a sea anemone (Cnidaria) with rotational symmetry [Leclère(2019),

Finnety(2004), Putnam(2007)] p.801, resp., p.1335, resp., p.86. In addition, many plants exhibit different kinds of symmetry, e.g., rotational symmetry, but also bilateral symmetry. Today, most plants are flowering plants which, however, evolved much later than the animals at $\approx$ 140-250 Mya ago [Foster(2017), Sauquet(2017)] Figure 1, p.339, resp., p.1.

From a physicochemical point of view, all biological systems are open–driven non–equilibrium systems with a network of chemical reactions, each of which with a characteristic time scale given by its kinetic reaction constant. The network of reactions can be sort into the genetics and the metabolism. The *genetics* describes the evolution and maintenance of each biological system's structure and the *metabolism* is a set of life–sustaining chemical reactions in the organism. However, the evolution of the biological systems from prebiotic materials to animals including humans, taking place in a time period of $\approx$ 4 billion years or more, is sustained by many other complex reactions and other time scales than the time scales of individual biological systems. A typical time scale for the reactions in a biological system spans from the fastest enzymatic reactions, with a reaction constant of $\approx 10^{-5} sec^{-1}$ to reaction processes that take *sec, min, hours*, and even *years*. All individual biological systems are unstable in the long run, with a mortality of weeks for a fruit fly, over hundreds of years for a Greenland shark to thousands of years for pine trees and sponges. In sum, there is a vast difference between the time scales of the reactions in the biological evolution and the time scales for the reactions in the individual biological species, see also Box 1.

An important question is whether there is a connection between the reactions in a living organism and the overall evolution of a biological system with regard to their characteristic time scales. The general opinion about the evolution of biological systems is it proceeds along Darwinian lines as described, for example, by Monod [Monod(1971)]: according to Monod, evolution is governed partly by necessity, understood as the survival of the fittest, and partly by chance, understood as the survival of the survivor, given by successful mutations. Under this view, there should be no link between the time scales of the biochemical reactions in individual organisms and their 3–4 billion-year-long evolution, given by successful mutations in new species. The Darwinist description is of course correct, but the development may also depend on other factors. That leads us here to argue that the two sets of time scales are connected.

2. Correlations between reactions in biological systems and the biological evolution

A correlation between the chemical reactions in biological systems and the biological evolution is possible, if the chemical reactions involved in the metabolism of living organisms can influence the evolution of their genetic code. Although metabolism and genetics are already connected in a trivial sense, since almost all the reactions in the metabolism are controlled by enzymes, here I suggest,

(1) by describing the evolution, which led to the first metazoa or animals at the Cambrian explosion, that the spatial arrangement of genes within a cell and an embryo is directly influenced by metabolic reactions, and
(2) that this spatial gene structure and its spatial change at a cell division built up during evolution, led to the appearance of animals during the Cambrian explosion.

2.1. **The evolution of gene structures and the appearance of the first animals.** An extensive review literature exists about the developmental spatial gene structures in a biological system, focusing on changes in cell polarity [Li(2009), Dworkin(2009), Buskila(2014), Laloux(2014), Brown(2011), Orlando(2009), Kim(2018), Manuel(2009), Hollo(2017)] pp.1; 10–11; 1057; 12, Figure 1; Section 3.2; pp.11; 542, Figure 1; —; 7. Cell polarity refers to spatial differences in shape, structure, and functions within a cell, and on a cellular level there is already cell polarity with asymmetries in simple bacteria and prokaryotes.

A prokaryote exhibits a complex cell polarity with asymmetries, cf. [Spitzer(2011)] p.500, Figure 5. In [Dworkin(2009)] loc. cit., the authors conclude that such a small–scale asymmetry in the polarity of cytoskeletal filaments in two bacteria (*Caulobacter crescentus* and *Bacillus subtilis*) plays a central role in the symmetry break at the cellular level through a protrusive force generation and directional transport of molecular assemblies and organelles. In [Buskila(2014)] loc. cit., the cellular polarity of RNA in bacterial cells is reviewed. Their cell division is caused by three polarity protein determinants, *MinC*, *MinD*, and *MinE*, which oscillate between the cell poles during cell division. The mechanism for the self–organization of proteins is reviewed in [Laloux(2014)] loc. cit., focusing on a possible recruiting of specific proteins to the cell poles by self–assembling. Another review of articles concerning polarity and growth mechanism in bacteria is given in [Brown(2011)] loc. cit., with emphasis on polar growth in bacteria

with *cell elongation* and *septum formation*, the two distinct phases of bacterial cell growth prior to cell division.

The kinetics in cell membranes with emergence of cell polarization is reviewed in [Orlando(2009)] loc. cit., where the authors conclude that membrane kinetics is responsible for cell polarity. The self–organization of structures in a cell with cell polarity and mechanical forces is reviewed in [Kim(2018)] loc. cit., with the hypothesis that it is formed by a "feedback interaction between polarity, mechanics and fate" through self–organizing interactions in this tripartite relationship. In sum, these reviews conclude that polarity in bacteria and prokaryotes is not at all a reductionistic chemistry in a bag. Instead, bacteria and prokaryotes are highly ordered systems with a complex polarity at the stage of cell division. The polarity covers already for bacteria over a highly ordered gene structure with oscillations (change of local positions) of genes during the cell division [Buskila(2014)] loc. cit.. The question is what kind of evolutionary kinetics could have established this spatial organization and its dynamics.

The first metazoa or animals appeared at the end of the Ediacaran period at $\approx$ 541 Mya ago. These simple organisms can best be described as a multicellular organism formed as an open bag, where the opening served as a common mouth and gat, and with a biological membrane that covered both the outside as well as the inner part of the multicellular organism.

This was the first animal in biological evolution with bilateral symmetry, a form that turned out to be particularly suited as it resulted in the Cambrian explosion of new species such as insects. Such bilateral symmetry is preserved in almost all animals, including fish, insects and primates. It is already observed in the embryo of one of the earliest animals, the fruit fly *Drosophila melanogaster*, shown in Figure 1. The symmetry is of course ensured by genes.

Although the bilateral gene structure is unique for the embryo of Drosophila, all biological systems show a complex cell polarity and cell division. The symmetry evolution from Cnidaria to Animals is reviewed in [Leclère(2019), Finnety(2004), Putnam(2007)] loc. cit., and the evolution in polarity is reviewed in [Manuel(2009), Hollo(2017)] loc. cit.. The common observation in all reviews of the multicellular organisms is that there is a polarity in the cells, the cell–membranes and the location of the cell proteins and genes. These reviews explain the evolutionary emergence of the bilateral symmetry as caused by the structural order in the cell and the location of the genes, altogether with an environmental impact on the cells. Although the literature does not provide a description/observation of what kind of impact on the cell

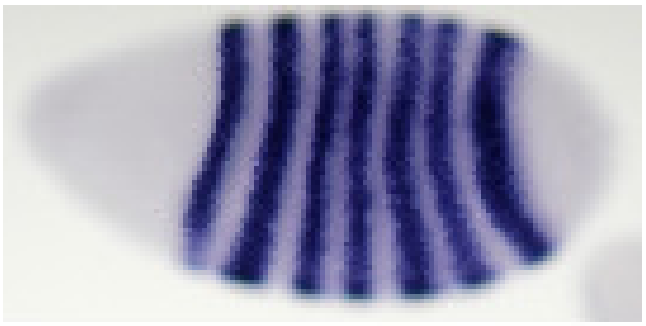


FIGURE 1. Striped expression pattern (violet) of the of *eve-skipped* gene in an early *Drosophila* embryo [Fujioka(2013)] Figure 1.

polarity may have influenced its evolution, common for all reviews is that the genetics alone is not sufficient to ensure the evolution of cell polarity and bilateral symmetry.

2.2. **Precursor for the cell polarity and the bilateral symmetry in animals.** A gap of the order of 3 billion years separates the emergence of the first simple bacteria and the Cnidarians in the Ediacaran and Cambrian period. The evolution of polarity in a simple bacterium to a (eukaryote) multicellular Cnidaria with its cell polarity probably evolved rather continuously in the biological systems in the oceans over this enormous time span. The most obvious candidate for the cause of the polarity in the cell and the changes in polarity at the embryonic development is the metabolic kinetics in cells, present throughout this long period of time.

Cell kinetics are very complex, but the central part in cell metabolism, glycolysis, is common for all living organisms and genetically controlled by enzymes, see also Box 2. The consecutive biochemical reactions in the process of glycolysis is what ensures the homochirality of carbohydrates. Glycolysis is probably also responsible for the emergence of the homochirality in the carbohydrates [Toxvaerd(2018)].

Metabolism and Glycolysis

In music and architecture, *metabolism* is a generic term for *modulations* of harmony and *metamorphoses* of building materials. In biochemistry and cell physiology, since the 19th century, **metabolism** is the generic term for the ensemble of all chemical reactions occurring inside cells between organelles that extract energy from nutrients (catabolism) and build cell materials (anabolism). Biologists conveniently organize these reactions into metabolic processes (called *pathways*) consisting of sequences of enzyme catalysed reactions of chemicals (called *metabolites*) and organized in networks.

The three main purposes of metabolism are: the conversion of the energy in food to energy available to run cellular processes; the conversion of food to building blocks for proteins, lipids, nucleic acids, and some carbohydrates; and the elimination of metabolic wastes. These enzyme-catalysed reactions allow organisms to grow, take shape and reproduce, maintain their structures, and respond to their environments.

The metabolic pathway utilized by most microorganisms (yeast and bacteria) and by all "higher" animals (including humans) for the degradation of sugar (glucose) is called **glycolysis**. The process is a series of consecutive chemical conversions that require the participation of eleven different enzymes, most of which have been crystallized and thoroughly studied. Glycolysis begins with a single six-carbon molecule of glucose ($C_6H_{12}O_6$) and concludes with the production of two three-carbon molecules of pyruvic acid (CH_3COCO_2H). Much of the energy that is liberated upon degradation of glucose is conserved by the simultaneous formation of the so-called high-energy molecule adenosine triphosphate (ATP).

Glycolysis is a metabolic pathway that does not require oxygen. The wide occurrence of glycolysis in other species indicates that it is an ancient metabolic pathway. Indeed, the reactions that make up glycolysis and its parallel pathway, the pentose phosphate pathway, occur in the oxygen-free conditions of the Archean oceans, also in the absence of enzymes.

Further Reading:

Great Soviet Encyclopedia, Third Edition, Vol. 18, entry metabolism, Moscow 1974, English Translation 1978.

The Columbia Electronic Encyclopedia™, entry glycolysis, © 2022, Columbia University Press.

I. Klapper, D.B. Szyld, K. Zhao, Metabolic Networks, Elementary Flux Modes, and Polyhedral Cones, SIAM, Philadelphia 2021.

Added by the editors

Box 2. Metabolism and glycolysis

Furthermore, it has a remarkable property: the concentrations of the chemical components in the process of glycolysis oscillate over time. Oscillations in the concentration of nicotinamide adenine dinucleotide, reduced (NADH) in a cell have been known for a long time [Ghosh(1964)]. Figure 2 shows the oscillation in the in vivo concentration of NADH in a yeast cell *Saccharomyces cerevisiae* [Danø(1999)]. A comprehensive model for the consecutive metabolic reactions in the glycolysis of the yeast cell exhibits oscillations of the concentrations in agreement with experimental observation [Hynne(2001)]. However, the experimentally–determined time–oscillating concentration in the NADH of yeast cells and the concentrations in the kinetic model for glycolysis are mean concentrations in the cells. The question is whether

there could be a connection between the oscillations in the concentrations of the chemical components of the metabolism and the polarity in the cell during the process of cell division.

2.3. **Early embryonic pattern formation in** *Drosophila*. The metamorphosis of the fruit fly *Drosophila melanogaster*, one of the animals that appeared at the Cambrian explosion, has been heavily investigated [Leclère(2019)]. A remarkable feature in the evolution of *Drosophila* is the early embryonic pattern formation with seven stripes with genes for regulation of the development in multicellular organisms with cell differentiation and morphogenesis (Figure 1). The stripes reflect the expression of pair-rule genes in the embryo preceding gastrulation (i.e., where the blastula in the embryo goes from a single layer to a multilayer blastula) [Mc Ginnis(1984), Carrasco(1994)] Figures 1 and 4, resp., Discussion. The stripes in the multicellular embryo contain genes for the early endosome organization for sorting of the cells in the embryo [Sakuma(2014)] and for the homobox genes for the bilateral evolution [Pearson(2005), Solnica-Krezel(2012)] Figure 1, resp., p.693. The figure of the embryo has an apparent bilateral symmetry, although the genes for the bilateral evolution may have asymmetrical positions in the stripes. The formation of the three–dimensional bilateral structures from patterned epithelial cell sheets in *Drosophila* is modelled in [Misra(2017)] Figures.

2.4. **Models for polarity at the emergence of the bilateral evolution.** The stripe patterns in *Drosophila* can be modelled as a reaction–diffusion process with cross inhibition or activation of the kinetics for a morphogen in a cell [Hunding(1990)] Figure 3, and the embryonic development during gastrulation is correspondingly obtained by another reaction–diffusion model [Borzorgui(2017)]. The patterns obtained by the reaction–diffusion models for the embryogenesis are well–known examples of *Turing structures*, which depend on the structure of the confinement [Turing(1952)], see also Box 3. In the case of oscillations of a morphogen, the spatial stripes depend on cross inhibition or cross activation, as well the ratio D/R^2 between the diffusion coefficient D for the morphogen and the size R for the biological system [Hunding(1988)].

For a bacterium, R is the size of the cell. For *Drosophila*, R is the size of the embryo. As the embryo grows, the process of diffusion may be regulated enzymatically in order to maintain the ratio D/R^2 and the pattern in the embryo [Hunding(1988)].

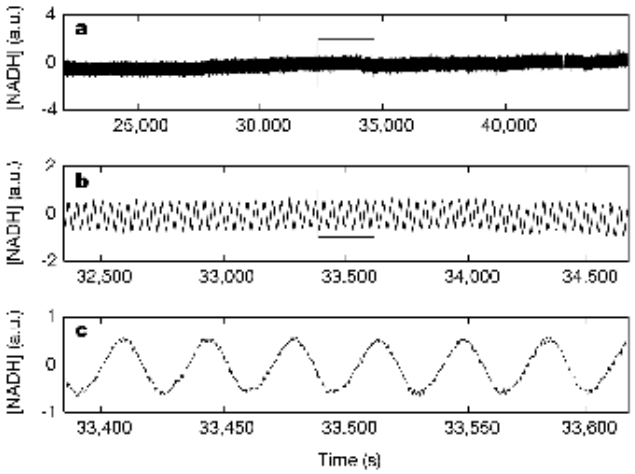


FIGURE 2. *In vivo* oscillations of NADH concentration in *Saccharomyces cerevisiae* (yeast) [Danø(1999)]. The concentration with different time resolutions (a,b,c) of NADH in arbitrary unit (a.u.) in the yeast bacteria as a function of time after the start of the measurement.

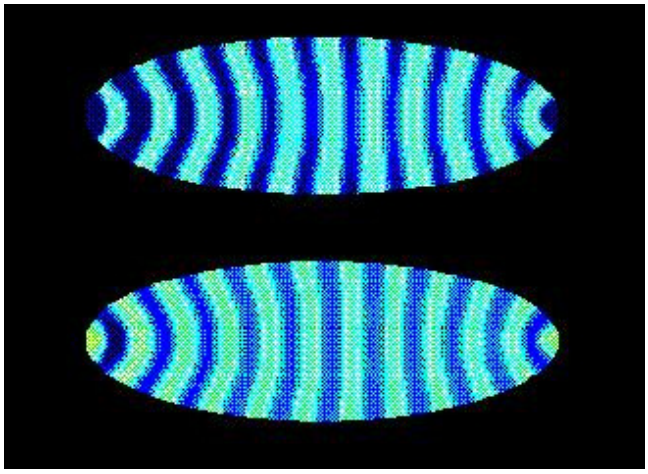
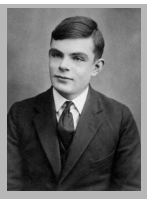


FIGURE 3. Turing concentration patterns of a morphogen in an elliptically shaped cell with reaction-diffusion dynamics [Hunding(1990)] Figure 2. The blue color corresponds to a relative high stationary concentration of the morphogen, while yellow is for a relative small concentration.

Figure 1 and Figure 3 show a striking resemblance, although there is no direct evidence of such a connection between glycolytical oscillations and the formation of stripe patterns in the embryo. The polarity and gene patterns in *Drosophila* obtained in [Hunding(1990)] are for a reaction–diffusion model of a morphogen with autocatalysis, but it is in fact also a simple model for the oscillation in the glycolysis [Selkov(1968)] (see Appendix in [Hunding(1990)]). Note that a time–oscillating system can induce stationary patterns in another system. The stationary wavy sand patterns in a beach bottom are an example of such induced patterns caused by the surface waves. Consequently, the chemical reaction with oscillations in the glycolysis may have induced the cell polarity in bacteria and the multicellular organisms before the emergence of animals, as well as the stripe patterns of genes in *Drosophila*.

Alan Turing - Who He Was and What He Thought



Alan Turing (1912-1954) was an English mathematician who wrote his name in the history of science for at least three times.

1. **Computability**. In 1936, Turing discerned in [2] mathematically the power and the limits of machine computation.
2. **Cryptanalysis and early computers**. During the Second World War, Turing was a leading participant in the breaking of German ciphers at Bletchley Park.
3. **Pattern formation and mathematical biology**. In 1952, Turing proved in [3] that a metabolic system of chemicals reacting with each other and diffusing across space, termed a reaction–diffusion system, initiated by genetics, would provide semi-stable patterns and could account for "the main phenomena of morphogenesis".

Later in [1], the Oxford mathematician and science historian A. Hodges showed that each of these three scientific century events demonstrates Turing's search for deep underlying holistic structures to explain the disparity of phenomena, or as Hodges put it: "The business of getting to the heart of something, abstracting its meaning, and connecting it with something that worked in the physical world", i.e., mind and machine; form and algorithm; life and pattern.

Turing must have been lonely at some time. But he was not alone. In the golden half century 1917-1967 of mathematical biology, a couple of outstanding mathematicians and physicists shared Turing's search, though with quite different approaches and as quite different characters: D'Arcy Thompson´s *On Growth and Form* (1917), Alfred Lotka's *Elements of Physical Biology* (1925), Vito Volterra's "Variazioni e fluttuazioni del numero d'individui in specie animali conviventi" (1926), Erwin Schrödinger's *What Is Life*? (1944), Norbert Wiener's *Cybernetics: Or Control and Communication in the Animal and the Machine* (1948), and René Thom's *Structural Stability and Morphogenesis* (written in the 1960s, published in 1972).

Further Reading:

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[3] ----- (1952). "The Chemical Basis of Morphogenesis", *Phil. Trans. R. Soc. B* **237**, 37-72. doi: 10.1098/rstb.1952.0012.
[4] Wikipedia contributors, "Alan Turing," *Wikipedia, The Free Encyclopedia,* https://en.wikipedia.org/w/index.php?title=Alan_Turing&oldid=1088656918 (accessed May 23, 2022).

Added by the editors

Box 3. Who was Alan Turing?

3. Conclusions. Biological evolution under multiple time scales

A living organism consists of one cell, or ensembles of cells, with chemical reactions. The time scales of the reactions, given by their reaction coefficients including the individual organism's biological evolution, are in the range from $10^{-5}sec$ for enzyme reactions to hundred of years for Greenland sharks and even many thousand of years for some glass sponges [Jochum(2012)] Section 5. The complex network of chemical reactions in a biological organism is consecutive, and the time scales for the slow reactions are ensured by the time scales for fast reactions, e.g., the glycolysis.

The evolution of life is ensured by cell division and evolution of new biological copies of the biological organism. Biological organisms have evolved from a bacterium for more than 3 billion years before the first bilateria appeared; a simple bacterium is already a very complex system with cell polarity. Although biological evolution is governed by Darwinian selection, the evolutionary mechanisms that have caused the development of cell polarity may also have been affected by other conditions. All living organisms have some characteristic features, but a given feature is normally distributed with small deviations from the mean value. Traditionally, Darwinian evolution is described as enhancements of a deviation from the mean by *chance* and/or a *survival of the fittest* evolution. Under this view, the time scales of biological evolution are decoupled from the reactions in individual organisms, except for when a successful mutation appears. But if the evolution of cell polarity with the imposed gene–stripes is built op during billion of years by the oscillating metabolism in the biological organism, this is of course a successful gene structure by chance, but it is another kind of chance than Monod's and it connects the chemical reactions in the individual organisms with the biological evolution with its time scales.

Summary : Life on Earth is at least 3.5 billion years old, and already the metabolism (glycolysis) in simple eukaryotic yeast cells exhibits oscillations (Figure 2). Reaction–diffusion models for the consecutive reactions in glycolysis show not only oscillations of the concentrations of the reactants, but that these concentrations also appear as stationary patterns with bilateral symmetry (Figure 3). These stripe patterns have also a remarkably similarity with the cell polarity of genes in the embryo of one of the early animals (*Drosophila*) (Figure 1).

Hypothesis: Cell polarity evolved during the whole time span of the biological evolution from a yeast cell to an animal. Here it is suggested that the very fast oscillations in glycolysis imposed cell polarity with

bilateral structural order during the biological evolution of the Cambrian explosion 541 Mya ago. Further experimental evidence of gene polarity during this process may verify this hypothesis, namely that all the time scales in biological systems are combined, with a time span from $10^{-5} sec$ to at least ≈ 3.5 billion years.

4. Acknowledgment

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