

## Life

LIFE IS A WONDER of its own. It conceivably struck this planet at least some 3.8 billion years ago,<sup>1</sup> arguably the consequence of a phospholipidic layer-bound *quantum leap* in a soup of organic precursors.<sup>2</sup> From that singular moment on, little has been spared in guise of amazement.

The first factual evidence of life on Earth appears inscribed in the fossil record some 3.5 billion years ago. It consists mainly of microfossils and ancient rock structures in Greenland and Australia called stromatolites,<sup>3</sup> the product of the metabolism of photosynthesizing cyanobacteria.

While the fine details of the abiogenic<sup>4</sup> model for the origin of life<sup>5</sup> remain to be chalked, its primed instances are often depicted as self-replicating units able to regulate their own chemical processes within the confinement of a cellular membrane. Such primeval unicellular organisms were most likely composed of some form of nucleic acid secluded from its external environment by a bilayer of phospholipids.

Nucleic acids, RNA and DNA, are the sole organic molecules fit to direct their own replication and to act as genetic material. RNA was proposed as the original genetic system since it was shown to be able to catalyze a variety of chemical reactions, notably the polymerization of nucleotides.<sup>6</sup> However, as the genetic load stored within cells increased, the lesser stability and reliability of RNA molecules rendered them unsuitable for the furtherance of genetic systems, a stage at which DNA eventually took over as universal hereditary material.

These very simple and self-organized systems emerged in seas densely enriched in organic molecules and therefore didn't require sophisticated toolkits for intake of food or generation of energy. Only when systematic interactions between RNA and specific amino acids became enshrined in the genetic code<sup>7</sup> did evolution start to shape concerted molecular reactions between proteins that animated cells with metabolic activity.

Among the first elaborations of metabolic pathways are likely to have been some simpler form of modern-day glycolysis, the anaerobic breakdown of glucose to lactic acid. Glycolysis is a fixture of all present-day cells and drives the generation of ATP molecules, their universal source of energy. This in turn enabled cellular life to fuel ever more complex metabolic reactions—notably photosynthesis.

Photosynthesis is a metabolic reaction that gathers energy from sunlight to synthesize organic molecules, at the expense of carbon dioxide and water, and generating free oxygen as a by-product. The emergence of oxygen-forming photosynthesis in cellular life, some 2.5 billion years ago, had two major impacts in the course of evolution. Firstly, it liberated cells from the need to directly access preformed organic molecules to sustain their metabolism; and, secondly, it biologically enriched the content of Earth's atmosphere in

<sup>1</sup> Mojzsis et al., 1996

<sup>2</sup> Miller and Urey, 1959

<sup>3</sup> Ohtomo et al., 2014; and Noffke et al., 2013

<sup>4</sup> From the Greek “spontaneous generation”, this model posits that autocatalytic polymers able to function as simple molecular replicators are at the origin of life. Alternative models exist, most notably panspermia—the extraterrestrial origin of life.

<sup>5</sup> Much debate has been stirred around the definition of life itself, see for instance Benner, 2010.

<sup>6</sup> Bass and Cech, 1984

<sup>7</sup> The central dogma of molecular biology, postulated by Francis Crick in 1958 and reasserted in 1970 (Crick, 1958, 1970), pertains to the rules that govern the sequential flow of genetic information between DNA, RNA and proteins. It can be summarized as “DNA makes RNA makes protein”, which provides the template for the enactment of hereditary information for all living organisms and frames the scope of evolutionary forces on genetic systems.

oxygen,<sup>8</sup> which is thought to have been a pre-condition for the thriving of eukaryotic life.

Up to that stage, all forms of life on Earth could still be modeled from the blueprint of modern Prokaria: a single-celled organism devoid of any membrane-bound organelles, capable of lateral DNA transfer and that mainly reproduces itself through binary fission. The Prokaria taxon comprises both Archae (e.g., *Thermoplasma*-like organisms) and Eubacteria (e.g., *Spirochaeta*-like organisms), which fundamentally differ at the level of the chemical composition of their cell walls; the lipidic composition of their plasma membranes; and the number of subunits in their RNA polymerases.

An hypothetical permanent whole-cell fusion between members of Archaea and Eubacteria has been proposed to be at the origin of the earliest anaerobic Eukarya,<sup>9</sup> of which the first fossil record evidence could date from a 2.1 billion year black shale formation found in Gabon.<sup>10</sup> Eukarya<sup>11</sup> are thus defined by the presence of specialized organelles enclosed within membranes, namely the presence of a discrete nucleus wherein all genetic material is confined.

The evolution of aerobic respiration, now a possibility in an oxygen rich environment, is thought to have occurred about 2.2 billion years ago in prokaryotic cells. The endosymbiotic theory proposes that eukaryotic organelles, such like chloroplasts and mitochondria, evolved from certain types of bacteria that early eukaryotic cells engulfed through endophagocytosis and retained in a mutualistically beneficial relationship.

The appearance of the integrated eukaryotic cell set the stage for a vast collection of evolutionary experiments that propelled a remarkable diversification of life forms. Two critical features were behind this radiation: the advent of sexual reproduction and that of multicellular life.

Sexual reproduction first evolved in a single-celled eukaryotic entity some 1.2 billion years ago.<sup>12</sup> The exchange of genetic information through recombination during meiosis provided cells with a new powerful source of genetic variation, both capable to accelerate adaptation rates to new environmental challenges as well as to supply evolution with novel genetic backgrounds to operate on.<sup>13</sup>

On the other hand, multicellularity is known to have recurred multiple times as an evolutionary experiment throughout different prokaryotic and eukaryotic taxa, including animals, fungi, plants and slime moulds.<sup>14</sup> The first evidence of transition between unicellular to multicellular organization is epitomized by fossils of prokaryotic filamentous and mat-forming cyanobacteria-like, dating back to 3 to 3.5 billion years.<sup>15</sup> However, cell differentiation within these colonies of aggregated cyanobacteria only appears more than 2 billion years ago.<sup>16</sup> The first multicellular eukaryotes might have emerged some 1 billion years ago<sup>17</sup>, while the most significant burst of metazoan diversification happened some 600–700 million years ago, at a time when levels of oxygen in the oceans and in the atmosphere were already rising

<sup>8</sup> This so called “Great Oxygenation Event”, dated to 2.3 billion years ago, was arguably caused by photosynthesizing organisms whose presence was tracked long before it occurred (Flannery and Walter, 2012). The GOE likely had a catalytic effect in the evolution of life also through the oxidation of exposed rocks, liberating phosphorus and iron that flew into the oceans, there acting as fertilizer (Zimmer, 2013).

<sup>9</sup> Margulis, 1996

<sup>10</sup> Albani et al., 2010

<sup>11</sup> From the Greek, “*eu*”—true—and “*karyon*”—kernel.

<sup>12</sup> Bernstein et al., 2012

<sup>13</sup> Burt, 2000

<sup>14</sup> Kaiser, 2001

<sup>15</sup> Knoll, 2003; and Schopf, 1993

<sup>16</sup> Tomitani et al., 2006

<sup>17</sup> Knoll et al., 2006

sharply.<sup>18</sup>

The main implication of multicellularity is the integration of the cell physiology, first at the tissue, then at the organism level—with the concomitant progressive loss of individualization and, ultimately, independence of the cellular unit. This integrative process required the emergence of a number of essential features, such as cell adhesion, cell-cell communication and coordination, and programmed cell death, which are likely to have evolved in an unicellular context.<sup>19</sup>

From the evolutionary point of view, the appearance of the molecular apparatuses underpinning these innovations and the corresponding genomic structures scaffolding them is thus relatively recent. Consequently, one could argue that the genetic networks supporting the necessary acquisitions for multicellular life are less likely to be as incorporated and resilient as those representing older, more fundamental metabolic pathways for the bearing of unicellular life.

Furthermore, the degrees of cooperation between distinct genetic lineages during the transition to multicellularity must also be taken into consideration. Conflicts may arise between lineages devoted to promote the cooperative establishment of an efficient multicellular organism and lineages focused on selfish proliferation regardless of the integrity and performance of the organism.<sup>20</sup>

The transition to multicellularity is likely to have been driven by the advantages associated to increase in size (evasion from predation) and perhaps more importantly to the functional specialization and division of labour (metabolic cooperation).

A vivid example of the latter is given by the *volvox*, a genus of chlorophytes. These green algae can form colonies of up to 50 000 cells that can display a degree of differentiation between internal, unflagellated germ cells that can divide and give rise to new colonies; and flagellated, external somatic cells that keep the colony suspended<sup>21</sup> and promote nutrient exchange.<sup>22</sup>

One important distinction between the germinal and somatic lineage in the *volvox* is that the somatic cells appear to be terminally differentiated and have a limited capacity to proliferate once they form. This attribute illustrates the concept of cell potency, or the cell's ability to differentiate into distinct cell types.

Once this discretization between germinal and somatic lineages has been achieved, the evolution of complexity in multicellular organisms then became a function of the orderly incorporation on genomes of the rules that guide the precise orchestration of cell growth, differentiation and morphogenesis from a totipotent spore or zygote into a fully functional and mature organism—a process recapitulated in spectacular fashion during the embryogenesis<sup>23</sup> of every present-day multicellular life form.

To summarize, an abridged account of the major evolutionary transitions of life discussed so far was thusly proposed by Grosberg and Strathmann:<sup>24</sup>

<sup>18</sup> Carroll, 2001; and King, 2004

<sup>19</sup> Bonner, 1974; Bonner, 2009; and Kaiser, 2001

<sup>20</sup> Buss, 1987; and Hammerstein, 2003

<sup>21</sup> Kirk, 2005

<sup>22</sup> Solari et al., 2006

<sup>23</sup> TODO: Reference to the biogenic law and Gould's "*Ontogeny and Phylogeny*".

<sup>24</sup> Grosberg and Strathmann, 2007

(a) replicating molecules become compartmentalized, yielding the first cells; (b) replicating molecules coalesce to form chromosomes; (c) DNA becomes the conveyor of heredity and, together with RNA and proteins, the agency of the genetic code; (d) symbiotic cells consolidate to generate the first eukaryotic cells containing chloroplasts and mitochondria; (e) sexual reproduction emerges involving the production and fusion of haploid gametes through meiosis; (f) multicellular organisms evolve from unicellular ancestors; and (g) social groups composed of discrete multicellular individuals become established.

All throughout these transitions, major forces were at play knitting the tapestry of life. Prime among which was, of course, natural selection. The forces driving this striking set of changes are noteworthy themselves. Notes on natural selection, best put by Darwin himself:

There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator<sup>25</sup> into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.

How ironic that one of the best models to understand this order of things is actually one of its most harrowing violations: cancer.

## *Cancer*

CANCER IS A DYSFUNCTION OF

## *Microarrays*

<sup>25</sup> This oft-cited final passage of *On the Origin of Species* is frequently quoted stripped of this reference to a “creator”. Such a revisionist stance appears even more bizarre in the light of the fact that it was Darwin himself who added the reference in editions two through six—arguably to appease both the public and his wife (Thompson, 2003). A touch of candour from the man who “politely changed the way we see the world forever” (Rutherford, 2008).

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