

Patterns of information processing in living world

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Life is extraordinarily complex: it is an extremely complex network composed of huge numbers of different chemical reactions continuously creating an enormously complex matrix composed of bewildering numbers of different chemicals involved in these reactions. Additionally, awfully large numbers of interactions between non-living and living worlds contribute to life complexity. Although our knowledge on the diversity of chemical reactions and chemicals in living world grows progressively, our understanding of how they integrate to generate life-relevant structures and functions is still far away from being complete. Here, I show that the investigation of life from information processing perspective allows recognition in living world of complete hierarchy of universal life patterns and many important specific life patterns making the understanding of life complexity amazingly easy.

Traditionally, chemical reactions are considered as steps of mass, impulse (momentum), and energy processing. From this perspective, their integration in living world is usually described in terms of networks composed of pathways which refer to routes of mass, impulse, and energy transfer. Different sources in environment label start points of these pathways. Initially separated, pathways usually become more and more intricately interwoven, but then divide anew into many branches whose end points are marked by waste products. Although many patterns have been discovered within such networks, they do not make the understanding of life complexity easier. At all, it becomes increasingly apparent that the investigation of life from the perspective of mass, impulse, and energy processing is not enough for understanding of how chemical reactions in living world integrate to generate life-relevant structures and functions.

Alternatively, chemical reactions may also be considered as steps of information processing. From this perspective, their integration in living world may be described in terms of networks composed of pathways which refer to routes of information transfer. It is important to note that information processing is not restricted to any limited subset of chemical reactions – as usually assumed – but absolutely all the reactions are involved in it. Although information concept remains in focus of hot debates in philosophy of sciences in general (for review see, for example, Capurro R and Hjørland B 2003) and in philosophy of biology in particular (Adami C 2004, Barbieri M 2003, Emmeche C 1999, Godfrey-Smith P 2000, Griffiths PE 2001, Jablonka E 2002, Manson NC 2006, Sarkar S 1996, 2000, Smith JM 1999, 2000, Sterelny K 2000, Winnie JA 2000), it continues to be an indispensable concept in modern sciences. Moreover, it actually becomes a central concept in the conceptual framework of contemporary biology. At all, it becomes increasingly apparent that information processing must be treated as a major theme in living world and biology must be viewed as an informational science (Auffray C *et al* 2003, Ideker T *et al* 2001). The reason for this is that, in contrast to sources of mass, impulse, and energy, the information source is appointed not in environment but rather in the living world itself and, more concretely, in the DNA molecules. Information stored in DNA molecules is just what makes living world autonomous from the environment even if the dependence on sources of mass,

impulse, and energy makes it sensitive to changes in environment. This suggests that the investigation of life from the information processing perspective may also contribute to the understanding of life complexity as well.

Indeed, investigation of life from information processing perspective allows recognition in living world of complete hierarchy of universal life patterns and many important specific life patterns (Tirjatkin N 2005a, 2005b, 2005c, 2007, 2008) making the understanding of life complexity amazingly easy.

Complete hierarchy of universal life patterns

Multilevelness is the key characteristic of life complexity: living world is actually a hierarchically organized system of systems (Andrianantoandro E *et al* 2006, Emmeche C 1997, Grizzi F and Chiriva-Internati M 2005, Mesarovic MD *et al* 2004, Valentine JW 2003, Van de Vijver G *et al* 2003, Zylstra U 1992). An important attribute of the hierarchy is the gradual integration of systems from the bottom level to the apex so that upper levels are said to emerge out of the lower levels. To determine particular level in biological hierarchy, it is necessary to know a corresponding universal life pattern which variability would underlie the diversity of systems at this level. However, just in this respect, our knowledge is woefully incomplete. The only universal life pattern recognized is the cell (Mazzarello P 1999). All other known life patterns are doubtlessly specific. Recently, the list of familiar subcellular and supercellular (supracellular) life patterns such as organelle, tissue, organ, organism, etc. has been significantly extended through various structural and functional units referred to as modules, motifs, etc. (Alm E and Arkin AP 2003, Alon U 2003, Csete ME and Doyle JC 2002, De Silva E and Stumpf MPH 2005, Huang S 2004, Oltvai ZN and Barabási AL 2002). However, no one of them can be accepted as universal life pattern. Therefore, the presentation of their hierarchy as “life’s complexity pyramid” (Oltvai ZN and Barabási AL 2002) is an overestimation of their significance. Thus, the biological hierarchy composed completely of universal life patterns lacks. This big gap in biology foundation hampers progress within the “era of biology” significantly.

Meanwhile, the investigation of life from information processing perspective allows recognition in living world of many new life patterns (Tirjatkin N 2005a, 2005b, 2005c, 2007). Some of them seem to be universal (Tirjatkin N 2008).

Subcellularly, the information processing involves two tightly coupled reactions: genome expression and genome replication. During genome expression, information is converted first from DNA into RNA (transcriptome) form by DNA transcription, then from RNA into polypeptide (proteome) form by RNA translation, and finally from polypeptide into metabolite (metabolome) form by catalysis. It is important to note that the genome is a limited set of genes and each gene is usually expressed separately to be fully converted into the corresponding element of the cell structure or function. For each gene, its own sequence of DNA transcription, RNA translation, and catalysis can be determined. This directed sequence of chemical reactions is the most basic universal life pattern which can be called a gene expression network, abbreviated GEN. Its variability is virtually unlimited. Additionally, in some GENs, the obligatory sequence of chemical reactions can be restricted or extended. So, in many GENs, end products are

polypeptides functioning always as substrate molecules and never as catalysts. In many other GENs, end products are RNAs that never become translated into polypeptides, but function always at the level of RNA as substrate molecules. On the other hand, in many GENs, products of DNA transcription or RNA translation undergo post-transcriptional or post-translational processing respectively. The cell itself can be considered as a highly regular composition of interacting GENs which can be called GENome. Whereas gene and genome are notions that refer to how information is stored in the cell, GEN and GENome refer to how the gene and genome work. During information processing in particular GEN, it is just the job of other GENs to provide necessary elements for gene expression machinery. Collectively, GENs in GENome work to replicate the complete genome so that the life history of the single cell begins with one cell but ends with two. In particular cell, the GENome is suited to specific subset of sources of mass, impulse (momentum), and energy to produce their usable forms essential for the cell life. Thus, subcellularly, all chemical reactions are organized highly regular: first into GENs and then into GENome.

Supercellularly, the information processing involves other two important reactions: genome multiplication and genome diversification. Mechanism of genome multiplication is always the same: the genome replication by genome expression. On the contrary, mechanisms of genome diversification differ greatly ranging from the spontaneous sequence mutation to the highly regulated sequence transfer. Progressive genome replication is usually associated with progressive cell propagation producing a sequence: one cell, two cells, four cells, eight cells, and so on. This sequence can be called cell (GENome) progression. The whole cellular world is only one cell progression which arose from one single primordial cell and has 3 or 4 billions years of uninterrupted history. It can be called general cell progression. The present-day biosphere is merely a tiny slice from it, a visible top of iceberg in ocean of time. The ancient part of this gigantic life pattern leaves very scarce traces. Although all cells of the general cell progression should be theoretically identical to each other genetically, this is not the case in the nature: genome diversification produces cell progressions each of which is specified by a particular individual genome and can be called individual cell progression. Respectively, the general cell progression can be considered as a growing composition of an increasing number of individual cell progressions. Individual cell progression is universal life pattern with virtually unlimited variability. Spatiotemporal organization of a particular individual cell progression mostly depends upon whether the cells divide symmetrically or asymmetrically, whether the asymmetric cell divisions occur occasionally or regularly, whether the asymmetric cell division is associated with symmetric or asymmetric kinetics of the cell propagation, whether the cells will be rather randomly dispersed in space to become autonomous in behaviour or remain in an association to form cell colony (primary, secondary, etc.), whether the cell association grows continuously or is a steady state system, and so on. Thus, supercellularly, chemical reactions are organized highly regular too: first into individual cell progressions and then into the general cell progression.

So, from information processing perspective, all chemical reactions in living world fall into three categories: DNA transcription, RNA translation, and catalysis. They are organized in strong hierarchy of life patterns: GENs, cells (GENomes), individual cell progressions, and the general cell progression. The general cell progression occupies the

apex of the hierarchy. Most likely, it is unique and merits its own name (for example, Zoe). Other three life patterns in this hierarchy are doubtlessly universal. Their innumerable variations underlie the life diversity.

Diversity of individual cell progressions in biosphere

The present-day biosphere is merely a tiny slice from the general cell progression, a visible top of iceberg in ocean of time. However, although the number of individual cell progressions in this tiny slice represents only a small fraction of the whole, it is enormous. Much work is needed to describe and systematize this diversity completely. Review of the diversity of individual cell progressions with special focus on formation of cell associations (Tirjatkin N 2005c) can be summarized as follows.

Within some individual cell progressions, the cells will be rather randomly dispersed in space and each cell seems to become autonomous in behaviour. Just the individual cell progressions with this type of cell arrangement are poorly studied while most attention usually was paid solely the single cell. This type of cell arrangement allows different individual cell progressions to superpose each other in space. Additionally, in some individual cell progressions with dispersed cell arrangement, cells can closely aggregate into simplest temporary cell associations. Within other individual cell progressions, the cells will remain in an association, a cell colony, held together in any way. In the individual cell progressions with this type of cell arrangement, the founder cell first gives rise to primary cell colony which body plan is usually a filamentous chain, a hypha, or a globular body, a sphaera. By further cell propagation, an initial primary cell colony usually clones itself giving rise to a number of primary cell colonies respectively. Within a growing individual cell progression, these primary cell colonies may be either dispersed in space or held together in association forming a secondary cell colony of any kind and size and for any period of time under specific environmental circumstances. In turn, an initial secondary cell colony can give rise to a number of secondary cell colonies. Within a growing individual cell progression, also the secondary cell colonies may be either dispersed in space or held together in larger cell association. So, different individual cell progression can superpose each other even at the level of the secondary cell colony. Generally, the cell association has advantageous ability to carry out activities with a complexity not possible by single cell. Within an association, many cells come together to collectively respond to environmental conditions. This collective respond is usually more effective than by a single cell. Some cell associations are continuously growing systems, the others are rather steady state systems whose cell number is balanced in any ways. Different cell associations show a significant variation of degree of integration and coordination among cells. Within an association, the cells will either remain similar or become different. Progressive cell propagation may be accompanied by cell differentiation creating the diversity of specialized cells.

As in most Karyota, life history of an animal individual cell progression begins at the moment of fertilization when two of the most specialized monogenic cells, the egg and the sperm, combine to produce the most specialized digenomic cell, the zygote. The zygote propagates by cleavage so that the cells become smaller and smaller. Then, the cell association grows and develops in a large variety of ways, forming an initial body

with a species-specific primary body plan. This initial body usually clones itself giving rise to an expanding population of primary cell colonies that often remain attached to each other, forming a larger cell association with a species-specific secondary body plan. The secondary cell colony may show differentiation of primary cell colonies. Soon or later, the onset of meiosis is triggered. The tetrads may propagate forming an association of monogenomic cells, but this case is extremely rare. Mostly, the tetrads do not propagate but differentiate into eggs or sperm. The egg usually develops only from one of the tetrads, while the other three become polar bodies and rather degenerate. Each primary cell colony may frequently change from a free-swimming stage to a sessile stage. In addition to the settlement, this change may include more or less dramatic transformation of the primary body plan. The cloning and formation of secondary cell colony may occur from both the free-swimming stage and sessile stage. In some species, the free-swimming stage is restricted to the initial primary cell colony which soon or later settles and irreversibly transforms into the sessile stage. Similarly, each secondary cell colony may frequently change from a free-swimming stage to a sessile stage and this change may include more or less dramatic transformation of the secondary body plan.

While the morphological diversity of animal cell associations seems to be overwhelming, the underlying body plans are nevertheless governed by rather few general principles. The primary body plan is always a sphaera or its derivative. The sphaera which can be topologically described as the simplest closed surface, with two sides and no boundary lines, can give rise to more complex closed surface such as solenoid or even to a system of solenoids, some embedded in another. The secondary body plan is a series of primary body plans. However, the serial arrangement may become not more evident. In contrast to the abstract mathematical surface, the real biological surface is made up not by dimensionless points but by three-dimensional matrix with embedded cells. So, although the biological surface, like the mathematical surface, is with two sides and no boundary lines, it is actually a wall, since there is a distance between its two sides so that these two sides enclose a space with a volume. In other words, whereas a mathematical surface has no thickness, the biological surface does have. The thickness of the wall may have regional differences in magnitude. Additionally, the two sides of the wall can be differently designated according to their orientation to interior or exterior of the body. Thus, it is very important to recognize that the description of the animal body plan can be generally given in terms of a closed and orientable wall, without boundary lines and with two distinguishable sides. That side of the wall which is oriented into the exterior of the body is here designated as an outside, and that which is oriented in the interior of the body is an inside. One must be aware that the space, which seems to be the interior of the body at the first glance, is actually the exterior. Within the wall, some cells may become polarized cells arranged in cell layers. Some cell layers may be described as the closed surfaces, but their local orientation may greatly deviate from the direction of the wall orientation, giving rise to the internal complexity of the wall. Additionally, other cell layers may not be described as closed surfaces at all. So, the underlying principles of surface topology remain valid only at the wall level but not at the level of separate cell layers. The complexity of the primary and secondary body plan enhances gradually at different ontogenetic and phylogenetic stages, providing insight into the most basic directions of animal evolution. According to primary body plan, four major phylogenetic groups can be

distinguished in Animalia. First, there are 3 phyla with sphaera as a primary body plan: Porifera, Cnidaria, and Ctenophora. Second, there is at least one phylum with sphaera-in-sphaera as a primary body plan: Placozoa. Third, there are 11 phyla with solenoid as a primary body plan: Rotifera, Cycliophora, Micrognathozoa, Gnathostomulida, Kamptozoa, Priapulida, Kinorhyncha, Loricifera, Nematoda, Nematomorpha, and Gastrotricha. Fourth, there are 18 phyla with solenoid-in-solenoid as a primary body plan: Bryozoa, Phoronida, Brachiopoda, Sipunculida, Annelida, Mollusca, Nemertea, Platyhelminthes, Arthropoda, Onychophora, Tardigrada, Chaetognatha, Echinodermata, Pterobranchia, Enteropneusta, Tunicata, Cephalochordata, and Vertebrata.

When the secondary body plan is established in Vertebrata, the wall generally involves poorly segmented integumental wall, poorly segmented gastral wall arranged as a common gut, segmented chordal wall arranged as a chain of compact chordal bladders, poorly segmented atrial wall arranged as a pair of atrial ducts, poorly segmented neural wall arranged as an elongated neural bladder, poorly segmented coelomic wall arranged as a coelomic bladder, poorly segmented meningeal wall arranged as a meningeal bladder, segmented somitic wall arranged as paired chains of compact somitic bladders, segmented germinal wall arranged as paired chains of compact germinal bladders.

Diversity of asymmetric cell progressions in Mammalia

It is reasonable to distinguish between phylogenetic and ontogenetic cell diversity. Whereas the phylogenetic cell diversity is a result of the genome multiplication and diversification during life history of the general cell progression, the ontogenetic cell diversity is a result of differential genome expression during life history of some individual cell progressions.

Most regular spatio-temporal pattern of differential genome expression during life history of an individual cell progression is associated with the establishment of asymmetric cell (sub)progressions (Tirjatkin N 2005b). Each asymmetric cell (sub)progression has a stem cell at the base and is therefore characterized by asymmetric kinetics of cell propagation (not to be confused with asymmetric cell division). Stem cells divide very rarely. If stem cell divides, only one daughter cell inherits stem cell property. On the contrary, the other daughter cell becomes a non-stem (bud) cell but propagates rather quickly giving rise to a large number of progeny cells. So, an asymmetric cell (sub)progression consists of a stem cell lineage and a number of cell (subsub)progressions each of which has a bud cell at the base. Whereas the potential to divide seems to remain unlimited throughout the whole stem cell lineage, the progressive propagation of each bud cell is accompanied by a sequential restriction of the division capacity down to the division arrest, terminal differentiation, and death so that each bud cell gives rise to a limited cell (subsub)progression with a limited number of progeny cells. An asymmetric cell (sub)progression is a steady state system. At the base of this system, the asymmetric division of the first (primordial) stem cell yields the second stem cell and the first bud cell. The newly formed second stem cell remains inactive for a long period of time during which the first bud cell progressively propagates producing the first limited cell (subsub)progression. Within a limited cell (subsub)progression, the cells first propagate at the fastest rate producing a growing number of transit amplifying cells. After a critical number of division rounds is reached,

the cells become committed to undergo differentiation into one or more directions of specialization. Differentiating cells propagate at the lower rate and, when a critical number of division rounds is reached, they become mature specialized cells which do not divide and become exhausted by performing their special functions. At certain critical point of the history of the first limited cell (subsub)progression, the second stem cell divides producing the third stem cell and the second bud cell so that the exhausted first limited cell (subsub)progression becomes replaced by the newly formed second limited cell (subsub)progression. Since the potential to divide remains unlimited throughout the stem cell lineage, the asymmetric cell (sub)progression produces unlimited number of limited cell (subsub)progressions which replace each other in consecutive order. So, an asymmetric cell (sub)progression can maintain near a constant number of cells. The establishment of asymmetric cell (sub)progressions during life history of an individual cell progression may result in their diversification as well (as, for example, in Vertebrata including Mammalia).

In Mammalia, the zygote is considered as a truly totipotent cell in the sense that it is the progenitor of all of the four hundred or more ontogenetic cell types and subtypes (Vickaryous MK and Hall BK 2006) which are generated within the cell association during the life history of mammalian individual cell progression. The totipotency is usually retained by early progeny of the mammalian zygote up to the eight-cell stage so that two or more genetically equivalent cell associations may be occasionally formed within the same individual cell progression. Subsequently, the progressive cell propagation gives rise to a growing number of cells with more restricted potential. Traditionally, these cells have been subdivided into two groups: pluripotent embryonic stem cells and multipotent adult stem cells (Anderson DJ *et al* 2001, Gage FH and Verma IM 2003, Petersen BE and Terada N 2001). In mammalian embryo, first the inner cell mass (ICM) cells, then the epiblast cells, and finally the primordial germ cells are pluripotent embryonic stem cells that can be isolated and propagated *in vitro* displaying in culture an almost unlimited proliferation capacity and retaining a relatively normal and stable karyotype and the ability to differentiate into the most broad spectrum of ontogenetic cell types and subtypes (Czyz J and Wobus AM 2001, Eiges R and Benvenisty N 2002, Hadjantonakis AK and Papaioannou VE 2001, Hoffman LM and Carpenter MK 2005, Odorico JS *et al* 2001, Pera MF and Trounson AO 2004, Rossant J 2001, Stojkovic M *et al* 2004, Wobus AM and Boheler KR 2005). In the intact embryo, however, pluripotent embryonic stem cells persist for only a limited number of cell division rounds. This period of expansion of pluripotent embryonic stem cells is accompanied by the generation of primordial multipotent adult stem cells each of which gives rise to an asymmetric cell (sub)progression with cell differentiation in one or more directions of specialization. In this respect, the embryonic stem cells are precursors of adult stem cells. In contrast to traditional view, more recent findings (Anderson DJ *et al* 2001, Hawley RG and Sobieski DA 2002, Kuehnle I and Goodell MA 2002, Lemoli RM *et al* 2005) suggest that adult stem cells retain pluripotency. The only difference between embryonic and adult stem cells is that the propagation of embryonic stem cells is characterized by symmetric kinetics whereas the propagation of adult stem cells is characterized by asymmetric kinetics. Just the transition from symmetric to asymmetric kinetics of cell propagation is essential for establishment of asymmetric cell (sub)progressions within the cell association.

Once established, each asymmetric cell (sub)progression occupies its own domain within the cell association. In such domain, stem cell is usually located in especially carefully protected area, a stem cell niche (Fuchs E *et al* 2004, Li L and Xie T 2005, Ohlstein B *et al* 2004, Spradling A *et al* 2001, Watt FM and Hogan BLM 2000). If the stem cell divides, one daughter cell is retained as a stem cell but the other becomes bud cell and must leave the stem cell niche to enter an area occupied by limited cell (subsub)progressions. Since limited cell (subsub)progressions replace each other in consecutive order, near constant number of cells can be maintained within their area. The newly formed bud cell first enters a section occupied by a pool of transit amplifying cells and proceeds through a number of division rounds at the fastest rate providing a renewal of this pool. The transit amplifying cells are regularly committed to enter the next section occupied by a pool of differentiating cells which propagate at the lower rate. Finally, the differentiating cells are regularly committed to enter a section occupied by a pool of mature specialized cells which become inevitably exhausted by performing their functions. So, each domain occupied by an asymmetric cell (sub)progression consists of two areas: a stem cell niche with one stem cell and an area occupied by limited cell (subsub)progressions. In turn, the area occupied by limited cell (subsub)progressions consists of three sections: a section occupied by a pool of transit amplifying cells, a section occupied by a pool of differentiating cells, and a section occupied by a pool of mature specialized cells. Within each domain occupied by an asymmetric cell (sub)progression, its cells put together a well-proportioned unit. This unit is a very stable dynamic system being able to exist eternally owing to the very fine coordination of the whole cascade of the cell propagation, cell elimination, and cell differentiation events. Using inflow of negative entropy from environment, this unit can maintain sufficiently high degree of organization, so ensuring endless self-renewal. Stem cell lineage plays a key role in this unit. It is namely the source of preservation of genetic fidelity and the source of self-renewal of the whole asymmetric cell (sub)progression. Stem cells remain undifferentiated while simultaneously producing highly specialized cells. The splitting of the stem cell progeny into two separate cell groups that drastically differ in division frequency and division number is assumed as a consequence of a selective pressure in evolution of cell association types to avoid the negative results of mutations. On the one hand, this splitting allows to reduce the division frequency of just those cells that reside permanently in the cell association and so ensures the protection against accumulation of mutations. The division of these cells is very rare and is protected so sufficiently that they may divide unlimited number of times. On the other hand, the splitting allows to reduce the number of cell division rounds in the group of intensively proliferating cells and therefore to minimize the rate of malformation arising out of deleterious mutations. Also non-deleterious mutations in intensively proliferating cells do not accumulate since this progeny of the stem cell soon or later leaves the cell association. So, the splitting provides asymmetric cell (sub)progression with the property to exist beyond the number of cell divisions that leads to a significant risk in deleterious mutation.

After establishment of asymmetric cell (sub)progressions, the cell association consists of four categories of cells: adult stem cells, transit amplifying cells, differentiating cells, and mature specialized cells. Despite considerable efforts, adult stem cells remain the least studied cell category because they are extremely difficult to isolate from the cell association and propagate *in vitro*. Attempts to isolate adult stem cells are hindered by

their extreme rarity in the cell association and by the absence of appropriate markers which can be used to distinguish stem cells from bud cells and transit amplifying cells. Attempts to propagate adult stem cells *in vitro* are hindered by the intrinsic asymmetric kinetics of their propagation (Sherley JL 2002). Therefore, it is not surprisingly that reports on isolation and propagation of adult stem cells are highly questionable and data on studying the behaviour of derived cells *in vitro* or *in vivo* are usually controversial and difficult to interpret. Nevertheless, more recent findings (Henson NL *et al* 2005, Young HE 2004, Young HE *et al* 2005) provide data that allow to assume that adult stem cells are embryonic stem cell-like with respect to their unlimited potency to proliferate and differentiate *in vitro*. Transit amplifying cells show unlimited potency to proliferate but are restricted in their potency to differentiate. Differentiating cells are restricted in their potency to proliferate and are characterized by further restriction in their potency to differentiate. Mature specialized cells divide very rarely, if any, and are usually terminally differentiated. Different asymmetric cell (sub)progressions look alike when compared by their stem cells or transit amplifying cells. Differences between asymmetric cell (sub)progression types become first apparent by the examination of differentiating cells.

Asymmetric cell (sub)progressions superpose each other within the cell association and convert it into a steady-state system which balances cell propagation, cell elimination, and cell differentiation events to maintain the numbers of stem cells, transit amplifying cells, differentiating cells, and mature specialized cells, allowing the cell association to rapidly grow at the same time it is developing structurally and functionally.

Finally, the establishment of specific pattern of interactions between different types of asymmetric cell (sub)progressions within mammalian wall and regional diversification of this pattern contribute to the complexity of mammalian cell association. To describe this pattern, Mammalian Wall Formula is proposed (Tirjatkin N 2007).

Conclusions

Above, I have shown that the investigation of life from information processing perspective allows recognition in living world of complete hierarchy of universal life patterns and many important specific life patterns making the understanding of life complexity amazingly easy.

Living world – an extremely complex network composed of huge numbers of different chemical reactions continuously creating an enormously complex matrix composed of bewildering numbers of different chemicals involved in these reactions – becomes at once comprehensible as soon as one becomes familiar with how such basic chemical reactions as DNA transcription, RNA translation, and catalysis arrange in strong hierarchy of such life patterns as GENs, cells (GENomes), individual cell progressions, and the general cell progression.

Formation of cell associations during life history of animal individual cell progressions becomes more comprehensible if a notion of a closed and orientable surface is used. In contrast to abstract mathematical surface, the real biological surface is made up not by dimensionless points but by three-dimensional matrix with embedded cells. So, it is

actually a closed and orientable wall, since there is a distance between its two sides. The thickness of the wall may have regional differences in magnitude. Additionally, the two sides of the wall can be differently designated according to their orientation to interior or exterior of the cell association. To avoid confusion, one must be aware that the wall is not a boundary of the cell association but just its body.

Ontogenetic cell diversification during life history of mammalian individual cell progressions becomes at once comprehensible as soon as one becomes familiar with how the most regular spatiotemporal patterns of differential genome expression – asymmetric cell (sub)progressions – emerge and diversify. Additionally, it becomes more comprehensible if Mammalian Wall Formula is used which describes how specific pattern of interactions between different types of asymmetric cell (sub)progressions within mammalian wall emerges and diversifies regionally.

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