



BIOMORPHOGENIC PRINCIPLES OF CELL-MATRIX BIOLOGY: A PLECTICS INSIGHT

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INTRODUCTION

Student – Latin, *studeo* – devoted to do something;
studium – eager, passion, study.

To be a teacher is profound responsibility.

Paraphrasing **Emily Dickinson**

In 2002, the great physicist and Nobel laureate Murray Gell-Mann wrote: “The subject that I call *plectics* is the study of simplicity and complexity. At the Santa Fe Institute we deal to a great extent with matters of simplicity and complexity. I arrived at the name, *plectics*, in the following way. The word „complex” comes from *plexus*, originally meaning braided, and *com-*, meaning together, hence braided together. „Simple” comes in a similar way from roots meaning once folded; and the Latin words for „braided” and „folded” both owe their ultimate origin to the Indo-European root *plek-*. In Greek, that root gives rise to *plektos*, meaning braided. So, in using the word *plectics* we are describing the subject of simplicity and complexity without committing ourselves as to whether we are talking about something simple (once folded) or something complex (braided together)” (1).

Reductionism, which has dominated biological research

for over a century, has provided a wealth of knowledge about individual cellular components and their functions. Despite its enormous success, it is increasingly clear that most biological phenomena arise from complex interactions between the cell’s numerous constituents, such as structures (organelles), proteins, DNA (deoxyribonucleic acid), DHA (docosahexaenoic acid), RNA, glycans, lipids, and small molecules. Therefore, a key challenge for cell biology in the twenty-first century is to understand the dynamics of the cell-to-cell and cell-to-extracellular matrix (ECM; briefly, matrix) interactions that contribute to the biological life (2).

PRINCIPLES OF CELL-MATRIX BIOLOGY

Imagine a world in which everyone knows only part of the alphabet.

Jamey Marth (3)

The language of cell biology has its own “alphabet”, words, terms, and syntax - rules for the arrangement of words in sentences for the life of cells.

From Latin *principium* means “first, foremost”. Hence, that is the foundation of one’s knowledge (2-4). Of course,

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we should know the scientific facts, but I believe that they are required primarily to embed them into hypotheses, principles and knowledge. (Quite similar to how molecules incorporate their properties into the structure they build up and properties become structure's function.) Also, *"if you give a man a fish, you feed him for a day. If you teach him to fish, you feed him for a lifetime"* - **Chinese saying.**

Shift away from the traditional focus on descriptive details and towards a more integrative and conceptual view of cell-and-matrix Molecules, Structures and Functions (MSF) (Fig. 1), my didactics is based on both stream of associations (Fig. 2) and KISS (Keep It Short and Simple; also *KISS gene* – encoding for kisspeptin-1, a biomolecule involved in reproductive and cancer biology).

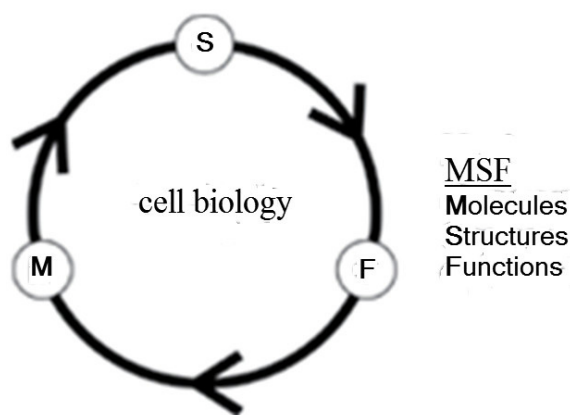


Figure 1. A drawing showing MSF-based teaching Cell Biology. This may enable students understanding the triarchic nature of the cell life. All figures of the present "lecture" are from (2).

My devotion is to teach medical students how information becomes knowledge and a conceptual and intuitive way of thinking in biomedicine. To feel the knowledge, like they would feel their mother tongue. I strive to enable a transformation of the knowledge of MSF into the knowledge of Disease-Prevention-Therapy (DPT). That is, to facilitate a Translational, Bench-to-Bedside (BtB) Cell Biology logic.. Cells are Molecules they synthesize, Structures they build up, and Functions they perform. A combination of MSF distinguishing one type of cells from another is the cell differentiation.

Among all the microscopes used in studying the cell, the brain microscope only has heuristic potentials.

Students learning Cell Biology have to ask Qs and give As:

Which Molecules, How, Where (cell, extracellular matrix, tissue, organ), When (interphase, mitosis), What Structures they form, and What Function perform. Hence, the more the Students know MSF, the better they may understand DPT – the mission of the physician (MD).

I will not be ashamed to say "I know not", nor will I fail to call in my colleague when the skills of another are needed for a patient's recovery.

From the Hippocratic Oath, a modern version

I shall now introduce briefly some novel Biomorphogenetic Principles (BMP) for teaching Cell Biology.

STREAM OF ASSOCIATIONS

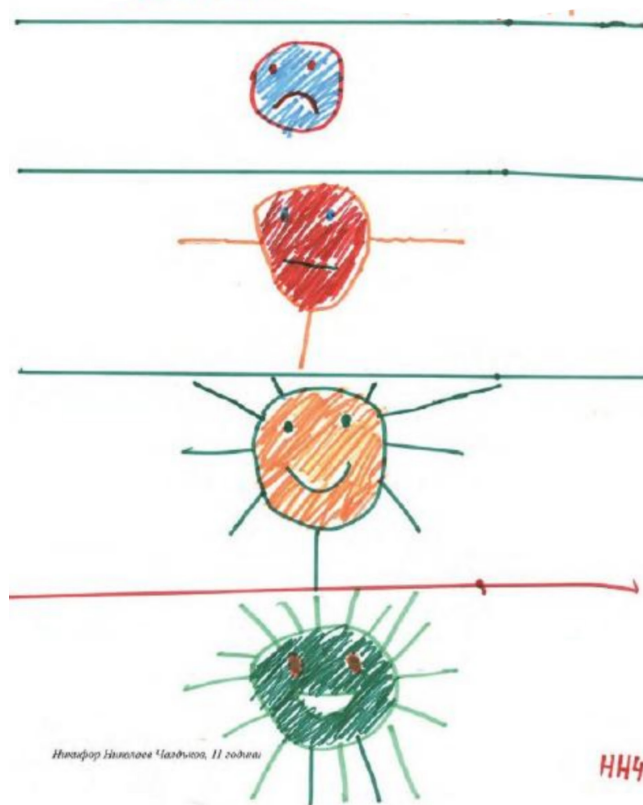


Figure 2. A drawing by my grandson Nikifor (when being 11 years old) presents Stream of Associations as "emblem" of my associative teaching method.

The First Biomorphogenic Principle:

Membrane compartmentalization (Fig. 3).

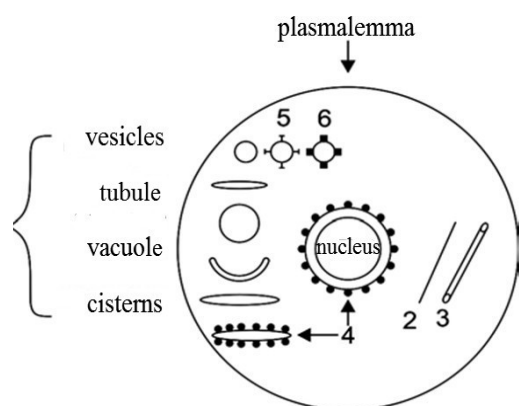


Figure 3. Schematic illustration of Biomorphogenic Principles I. Plasmalemma (plasma membrane), Nucleolemma, Endomembranes (1), and Exomembranes (see Fig. 4). Cytoskeletal structures: 2 – filament, 3 – microtubule. 4 – polysomes (polyribosomes) attached on the surface of cistern of rough endoplasmic reticulum and of outer nuclear membrane. 5, 6 – coated vesicles..

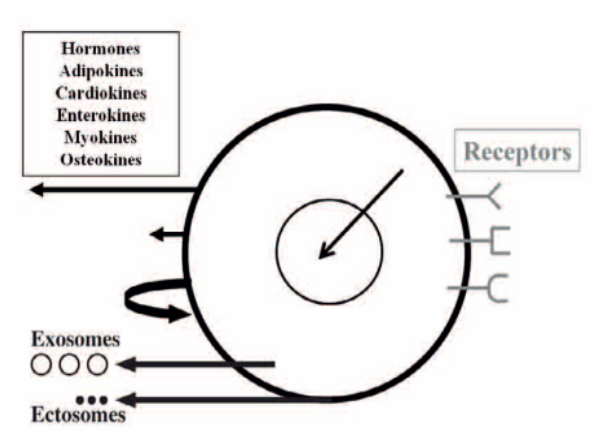


Figure 4. Schematic illustration of a cell viewed with its receptive activity (right side) and secretory activity (left side) – from up-to-down, long arrow indicated endocrine, small arrow - paracrine, curved arrow - autocrine, two parallel long arrows - extracellular vesicles (exosomes and ectosomes) as examples of exomembranes.

The Second Biomorphogenic Principle:

Membrane fractalization

Theory of surface roughness (fractal geometry) founded by the great mathematician Benoît Mandelbrot introduced the word „fractal“, as well as developing a theory of „roughness and self-similarity“ in nature (see 5). If a surface is fractal, its geometry repeats itself periodically at different scales. To be called fractals, biological and/or natural objects must fulfill a certain number of criteria including self-similarity, a high level of organization, and shape irregularity.

A human cell (e.g. hepatocyte) contains: one nucleus, approx. 1700 mitochondria, 400 peroxisomes, 300 lysosomes, 200 endosomes, 20 Golgi complexes – and 110 000 μm^2 total membrane surface, about 30 % belonging to the mitochondrial membrane's fractalization (Fig. 5, Table 1).

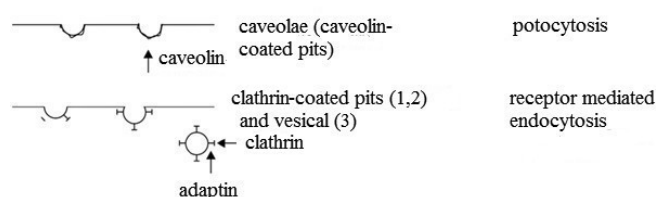
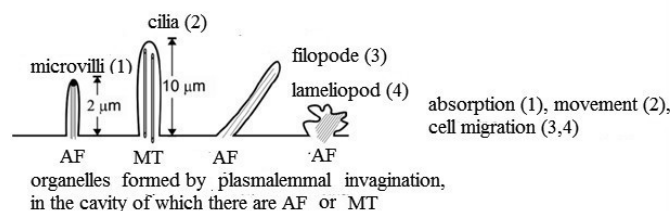
A. ORGANELLES FORMED BY INVAGINATION OF PLASMALEMMMA**B. PLASMALEMMMA-CYTOSKELETAL ORGANELLES**

Figure 5. Schematic representations of membrane fractalization biomorphogenic principle.

Table 1. Fractalsomes, examples.

- Microvilli (PL* + AF* + AAP*)
- Steriocilia (Sreriovilli) (PL + AF + AAP)
- Kinocilia (PL + 9+2 MT** + MAP**)
- Primary (sensory, single, non-motile cilia) cilia (PL + 9+0 MT + MAP)
- Membrane nanotubules (cytonemes) (PL + AF or MT)
- Dendritic spines (PL + AF, MT...)
- Inner mitochondrial membrane
- Sarcolemmal folds at the nerve-muscle junction

* PL, plasmalemma, AF, actin filaments, AAP, actin-associated proteins

** MT, microtubules, MAP, microtubule-associated proteins

The Third Biomorphogenic Principle:

Membrane fission-fusion (Fig. 6, 7).

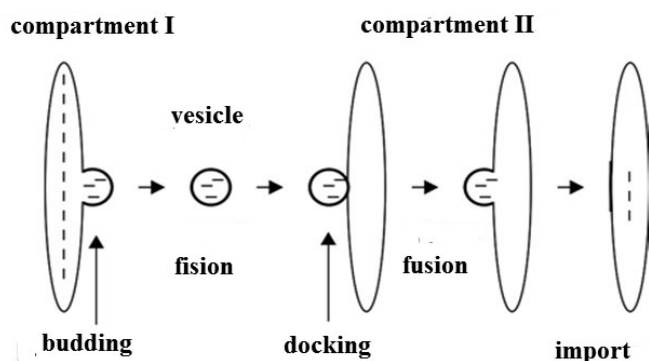


Figure 6. Schematic representations of membrane fission-fusion biomorphogenic principle.

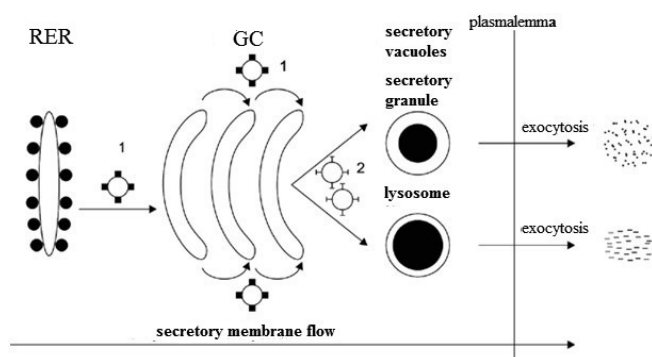


Figure 7. Schematic representations of receptor-mediated secretory membrane flows as an example of membrane fission-fusion biomorphogenic principle. The endocytotic membrane flow is another example of this principle.

To recap, 3Ms: Membrane compartmentalization, Membrane fractalization, and Membrane flow.

The Fourth Biomorphogenic Principle:

Assembly and disassembly (Fig. 8)

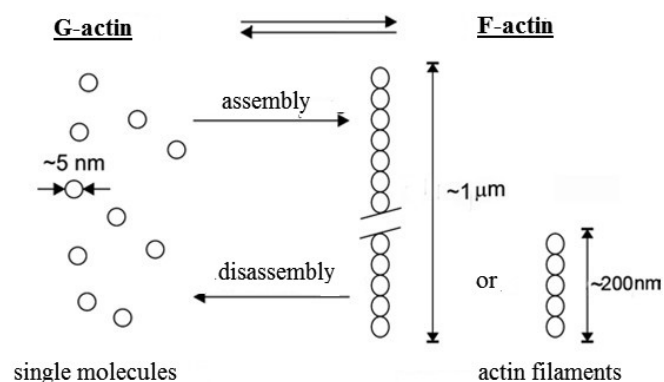


Figure 8. Scheme presenting an example of the fourth biomorphogenic principle: assembly and disassembly of G-actin and F-actin. Not shown are other examples, such as assembly-disassembly of tubulin-microtubules, clathrin and clathrin coated vesicles; caveolin and caveolin-coated caveolae.

The Fifth Biomorphogenic Principle: Assembly and package of matrix molecules to compose matrix structures (Fig. 9).

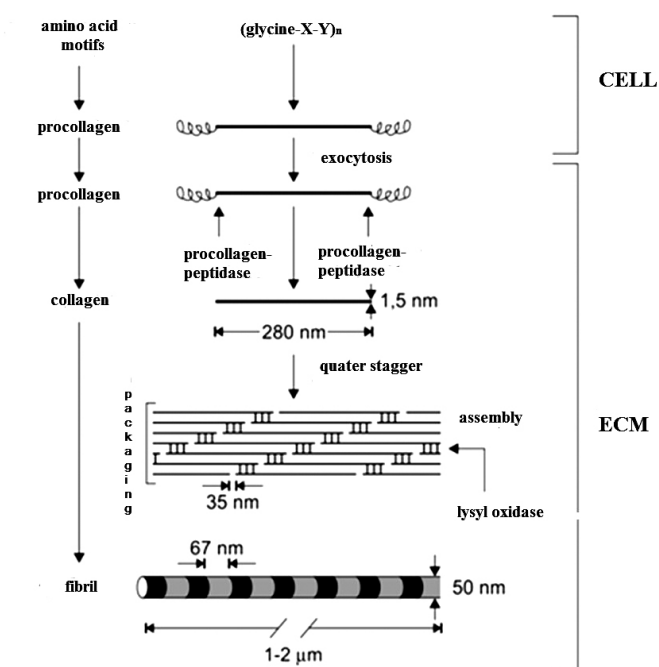


Figure 9. Schematic representations of procollagen-collagen-fibril assembly and package as an example of matrix biomorphogenic principle.

General principle of cell biology: The cells-and-matrix are indivisible units of life of all multicellular organisms

It is taken as axiomatic that life is a function of cells, and so strong is the educational belief that cells are “unit of life” and “building blocks of life”. However, the cells (except blood and lymph circulation cells) are surrounded and linked - both structurally and functionally - with ECM (matrix). When a cell is separated from the matrix, it becomes “homeless” and dies – anoikiya, a type of programmed cell death.

Once again, cell-and-matrix are structural and functional unit of the life of multicellular organisms. Understanding the cells separately from the matrix is conceptually wrong, because not only is the matrix a product of the cell, but it is also connected by the plasmalemma *via* receptor-ligand interactions. In effect, that leads to cell-matrix talk, communication, and signaling with each other (Fig. 10, 11)

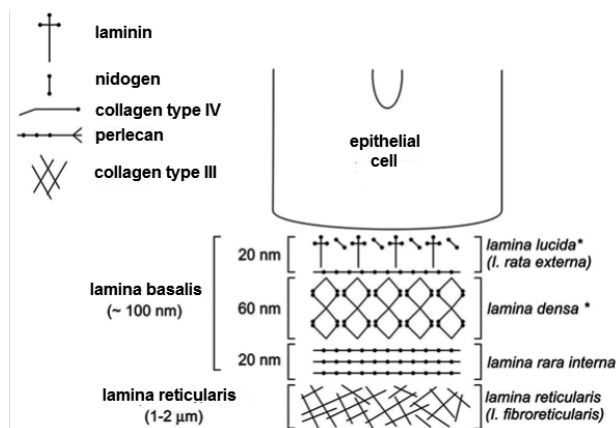


Figure 10. Schematic representations epithelial cell-basal lamina unity. Molecular architecture of basal lamina is depicted. This is also an example of the Fifth Biomorphogenic Principle: Assembly and package of matrix molecules

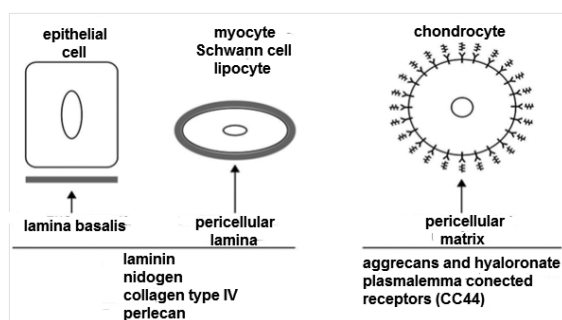


Figure 11. Schematic representations (i) cell-basal lamina unity in epithelial cell, myocyte, Schwann cell, and lipocyte (adipocyte), and (ii) pericellular matrix of the chondrocyte.

In KISS, Cells-and-Matrix are the units of Multicellular Life.

The Cell says: *I am I and my matrix.* Reminding *Yo soy yo y mi circunstancia.*

of José Ortega y Gasset' *Meditaciones del Quijote* (1914):

Also of David Foster Wallace's „*This Is Water: Some Thoughts, Delivered on a Significant Occasion, about Living a Compassionate Life*“.

Herein I paraphrase as follows:

Two young cells swimming in the matrix: “There are these two young cells (instead the original “two young fish”) swimming along and they happen to meet an older “cell” swimming the other way, who nods at them and says „Morning, boys. How’s the water?“ And the two young “cells” swim on for a bit, and then eventually one of them looks over at the other and goes „What the hell is water?”

ACKNOWLEDGMENTS

DECALOGUE FOR THE STUDENT 2019-2020

1. He who learns, he will succeed. (Bulgarian proverb)
2. *Forward! Science is a sun, / which in our souls shines!** – not only on May 24, the Bulgarian National Day of Cyrillic Alphabet and Culture, but continuously throughout life (LLP – Lifelong Learning Program; also, *Laboratory, Library, Pub*; CME - Continuing Medical Education).
3. Follow didactic cascade: from information to knowledge to way of thinking. Feel the knowledge like you feel your mother tongue. Translate the information of cellular molecules, structures and functions (MSF) into knowledge of the pathogenesis of Diseases and their Prevention and Therapy (DPT), that is a creative journey from bench-to-bedside (BtB). *Remember:* There are no departments and clinics within the cell.
4. Learning without thinking is useless. Thinking without learning is dangerous (Confucius). *Be thinker and doer, both.*
5. Human cognitive potential is symbiosis of thoughts and emotions. *Think outside the box.*
6. Imagination is more important than knowledge because knowledge is limited (Albert Einstein) – *stream of associations* is an essential tool of a creative learning.
7. Develop moral reflexes - mutual respect and love for each other, create and enjoy *brain-and-heart friend/ship* (BHF).

8. Follow your parents' advice: WHAT DID I ARRIVE HERE FOR? - to study first, then rejoice - the reverse chronology is meaningless.
9. Healthy lifestyle and good education can ensure your *quality of life* (QoL).
10. Stay tuned, wise and independent (*sapere aude*), have the intellectual courage to cross (at least once) at a red light the road of science to make your own green path on it. To achieve your *Eureka effects*.

Then you can say: ***Vox Studentium vox Dei!***

With respect and hope,
BHF-ly yours,



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