Psychiatria Danubina, 2019; Vol. 31, Suppl. 1, pp S9-S20
Medicina Academica Mostariensia, 2018; Vol. 6, No. 1-2, pp 9-20 *Review*

GRAPHIC MAPPING OF CLINICAL DISEASE PATHWAYS REVEALS A COMPLEX NETWORKING AND CLUSTERING DUE TO NATURAL ETIOPATHOGENETIC INTERCONNECTIVITY*

Zdenko Kovač

Department of Pathophysiology, Medical School University of Zagreb, University Hospital Centre Zagreb, Zagreb, Croatia

received: 29.6.2018; revised: 4.9.2018; accepted: 26.9.2018

SUMMARY

Human physiology is a complex, nonlinear, self-regulated system, in which multiple functional subsystems act within the whole body reactivity. Understanding of physiology and pathophysiology requires integration of both clinical and basic factual knowledge and regulatory homeodynamic concepts. Two integrative methods have been developed to improve understanding of disease processes and natural development. Their features are here shortly presented. Matrix led algorhythmic analysis and re-synthesis puts together patients' clinical data along with a broad academic knowledge which may be relevant to it. Graphic representation enables outlining a multiple interconnections among etiopathogenetic components within the human body. The etiopathogenetic clusters (EPCs) are crossing points, the integrative hubs of disease pathways. Multiple diseases of triggered by independent etiologies often converge to a common EPC, and thus contributing to natural networking of physiological processes in health and diseases. Contemporary biomedical sciences have been daily producing copious amounts of data whose participation in integrative physiology is yet to be explored within the whole body reactivity. Graphic representation and active composition of patho-physiological processes stimulates a synthetic reasoning as a subroutine intellectual habit, critically relevant to both physicians and biomedical researchers. Integrative pathophysiology facilitates anchoring of a whole body and local etiopathogenetic mechanisms. This may be of special importance in contemporary trends of the intensive compartmentalization in medicine.

Key words: *integrative pathophysiology - etiopathogenesis - graph theory - etiopathogenetic clusters - EPC - algorhythms - ISP-Declaration - complexity - etiology - big data*

**Author has recently given lecture on this thematic titled "*Integrative and cognitive tools for tomorrow medicine*";*
*Subtitled: "*Pathophysiological reactivity outlined via algorhythmic networks and etiopathogenetic clusters fits criteria of graph theory*", at the 8th International Society for Pathophysiology Congress, held in Bratislava, Slovakia, Sept 5-8, 2018.*

* * * * *

Advances in molecular methodology and information technology have given a strong impetus towards upgrading and deeper understanding of human health and disease physiology. It has additionally boosted the genuine interest and enthusiasm for a clinical application and patients' benefits. The frontiers of clinical research have been directed and forwarded by new technological advancements in diagnostics and quantifiable data which depict functional states of human body. These molecular data have ignited a reflective and critical evaluation of classical physiological understanding and biological comprehensive visions. In this paper etiopathogenetic clustering and pathways have been portrayed as a reliable consideration of natural processes interconnectivity. Graphic representation of physiological networks in health and disease has an advantage in comparison with traditional narrative descriptions. Disease natural pathways are presented in form of interconnected units which form the algorhythmic maps of reactivity. Physiological relations among acting elements have directionality of action, feedback and feed-forward regulatory loops. Graphic maps outline the parallel pathways and easily put together relevant events of nano-scale analyses with the clinical disease-symptom/sign level. The etiopathogenetic clusters (EPCs) are crossing and integrating points of complexity networks. The network visualization of physiology of disease and health underlying processes places individual mechanisms within the complex interconnectivity and may contribute to explanation of nonlinearity phenomena.

Seven facets of complexity problem in medicine and the ISP-Declaration on the anchoring mission of pathophysiology

Contemporary medicine is faced with a challenging need of transformation both in learning/teaching methodology and cognitive aspects of health and disease physiology. Advancements and new approaches in both cognitive and understanding dimensions of biomedicine are of a critical importance for conversion of reactive into a more pro-active professional profile. A procurement and maintenance of health has growingly become

a pending priority. Predictive, preventive, participatory and personalized medicine vision (i.e. "P4 medicine") was founded and promoted on more intense and reiterative feedback between the practice and the science (Hood 2014, Sagner 2017). The P4 medicine enforces the pro-active approach and assumes a more advanced and deeper interpretation of human body physiology. The understanding of the whole body physiology (i.e. the holistic comprehension, vision and reasoning) is critical for clinical care and for any of the "Ps" of such professional demand. It is not an easy task. It is a tantalizing goal to make a maximal insight into physiological fluxes based on reductionistic data gained in simplified experimental models. The myriads of mechanisms elaborated in controlled conditions are tested for their functionality and their potential placement within the whole body physiology (Vogt 2014, Marcum 2017, Haendel 2018). It is not easy to avoid the phenomenon of a "going beyond the data" within the interpretation of the results. Such trespassing in reasonning is seductive and makes a hidden and misleading traps in building the biomedical integral understanding (Kovač 2014, Hofer 2018). Contemporary physicians and biomedical scientists are asked to overcome the inherent cognitive shortages and to make a proper upgrading of the profession to satisfy the proclaimed demands.

There are at least seven groups of reasons for such professional demand. Firstly, due to explosive increase of the volume of potentially relevant information, understanding of a nature of human body performance in health and disease has become increasingly complex (Kovač 2012, Coveney 2016). Modern research technologies have made the unprecedented revolution in life sciences, both in terms of quantity and quality of experimental data. However, beyond the glittering surface of modern technologies (a research and a diagnostic ones) there is a struggle for a more complete cognitive prospective and comprehensive vision of human body life processes. Understanding of life physiology has become equally complex at various levels of consideration, like, transcriptomics, proteostasis, stem cell physiology, exosome and other ways of horizontal inter-organ communication, cytokine networks, etc (Fröhlich 2018). Secondly, the growing plethora of measurable data ("big data") has still been waiting for a proper integration and their mutual functional relations (like, causality, parallel independent phenomena, etc). The gigantic quantities of data coming out of experimental throughput methodologies seem to be somewhat chaotic material – waiting for a proper theoretical framework (Shah 2018, Zhang 2018). Often they are correlations and miss a causality dimension in between the measurable events. Distinguishing correlation from causality is epistemologically essential to experimental sciences and equally important in interventional (practical) medicine. For a majority of this large scale information a proper place should be figured out within the classical physiological knowledge of body reactivity, including etiology and epidemiology phenomena (Figure 1). Thirdly, the physiological complexity includes nonlinearity of biological reactivity in health and disease. Nonlinear responses of integral body are based on a coordination of multiple subsystems and their intrinsic reactivities. At the same time, the reactivity of each subsystem is nonlinear itself. Principal

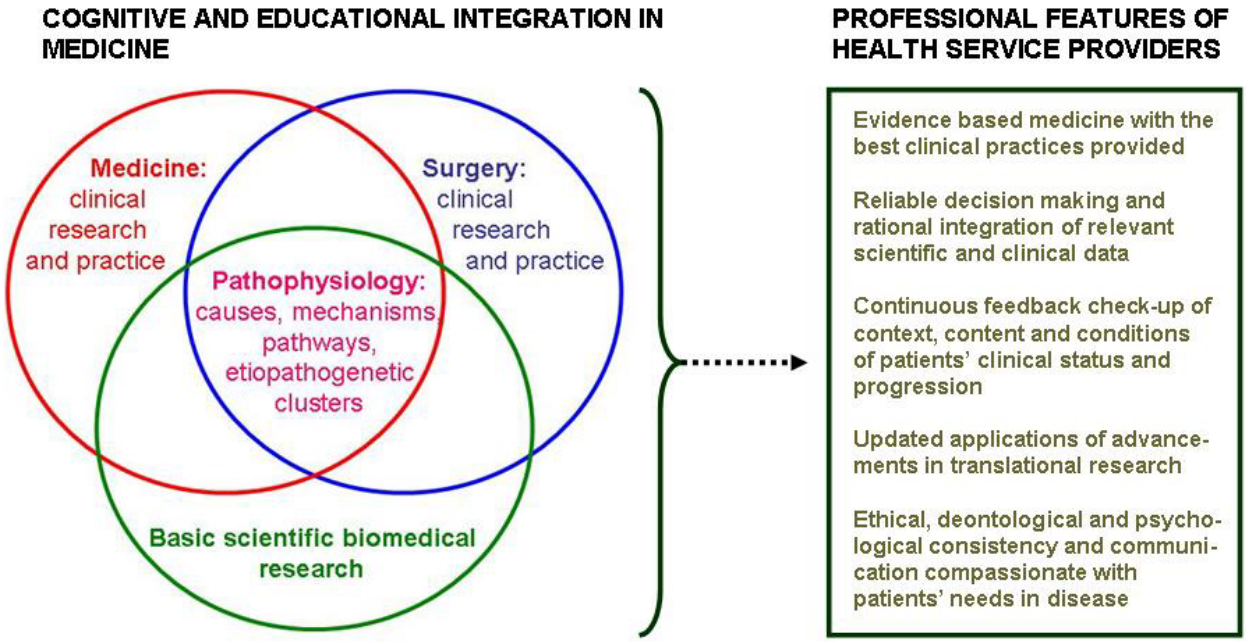


Figure 1. Educational and cognitive advancements are critical for tomorrow medical providers. Venn diagram puts pathophysiology into anchoring position within the three major activities and resources of the science and medicine. The fulfillment of practical role of physicians and other health professionals heavily relay on both research and practice as major sources of knowledge

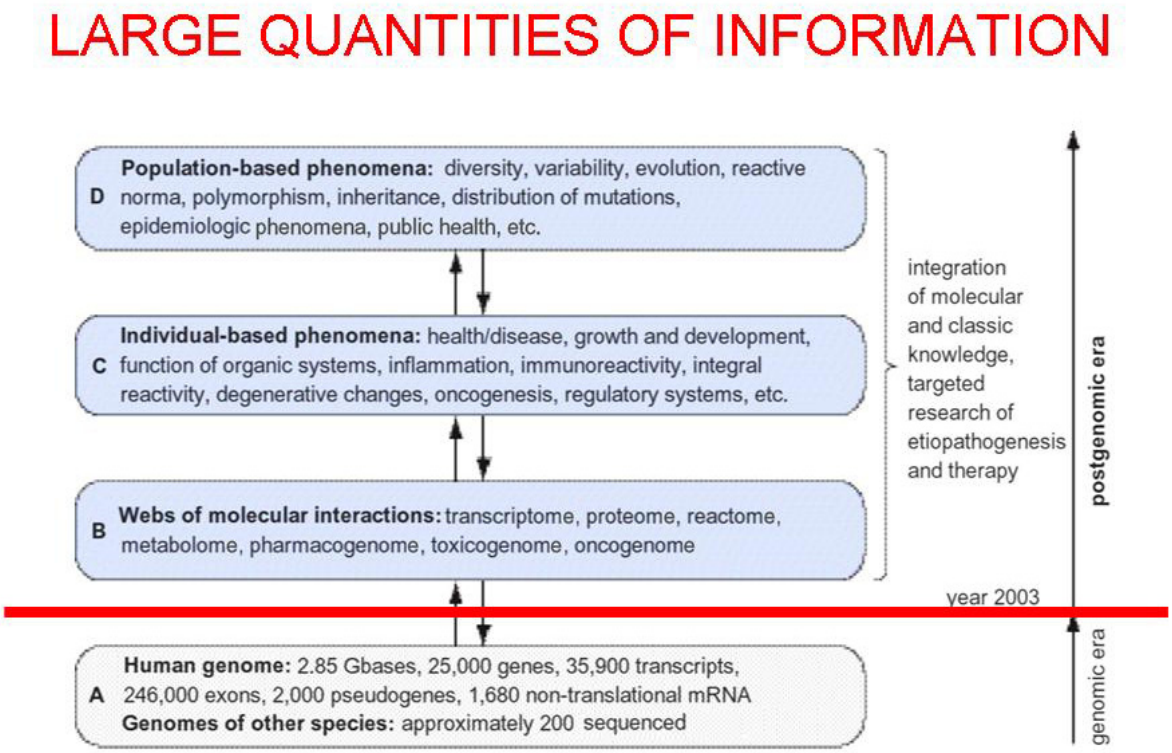


Figure 2. Classical clinical and epidemiological knowledge (source levels C and D) are enriched by exploding quantities of molecular data (source levels A and B) in postgenomic era. Presently, big data of molecular information dominantly represent a "raw material" to be integrated within a reinterpretation of human body physiology and pathophysiology. (Modified and translated /from Croatian/ Figure 1-10 from page 10 of the reference Gamulin 2018, with a consent and kind approval of the author, editors and publisher)

generators of nonlinearity include plateau-type and polynomial-type of doze and temporal relations in individual mechanisms, mirror-j physiology, networking of bio-information and regulatory pathways, etc (Sedlić 2017, Green 2017). Nonlinearity features of physiological reactivity contribute to additional complexity and low whole body predictivity. Fourthly, classical reduction of disease phenomena to a singular analytical pathway has become insufficient. Multiple new pathways (parallel, feed-forward, branching, etc) have come into focus in considering etiology, pathogenesis, manifestations and outcomes of disease states. They contribute to a variability of disease symptoms, dysfunctions and natural development (Joyner 2011). Fifthly, evidence based medicine and translational medicine have founded their strategies on assumption of better and deeper understanding of underlying etiopathogenesis (Figure 2). The etiopathogenesis is figured out as a cross section of basic and clinical knowledge and practice, and thus it may contain a "grey zone" of understanding of processes, like methodology aspects, characteristics of experimental model, etc. Thus those strategies which assume a direct "rational integration of relevant scientific and clinical data" actually ignore a problem of data relevance, which is not always obvious and not easy to be extracted from results coming from various experimental conditions. Re-iterative and manifold reciprocal feedback check-ups along with parallel monitoring clinical phenomena and alignment with basic science data may consolidate understanding of relevant whole-body reactivity. Such approach fosters a better understanding of the mechanisms behind the data and may better address the internal biases of interpretations (Islam 2016). Sixthly, personalized/ precision medicine is a modern trend and general policy of "individualization of medical practice". It is essentially P4 medicine geared to specific individual variations and characteristics of body reactivity. According to screened features, the underlying idea is to tailor as optimal as possible prevention and therapy. Such tailoring would come out of consideration of each and every facet of information belonging to the person considered. It has been developed on several assumptions and facts. Each person has a unique molecular and genetic constitution and reactivity that makes him/her susceptible to certain diseases. In addition to the best response, the highest safety margin is assumed (Carrasco-Ramiro 2017). The scientific breakthroughs will equip the physician with tools to be figure out efficiently the status of the person. Those assumptions, at present time, tend to ignore the complexity-related epistemological issues and shortages of physiology understanding (Kovač 2012). Seventhly, qualitative method. It aims to explore, understand and explain patient's health/disease experiences. Identification medical history taking (family and disease history, life style features) is epistemologically classified as a simple

and description of a symptom have a qualitative notion and based on non-numerical data. Qualitative methods, in general, have been "criticized for lacking rigour, transparency, justification of data collection and analysis methods being used, and hence the integrity of finding" (Hadi 2016, Gallego 2018). It is therefore considered inferior to quantitative scientific methods. This methodological difference is not trivial and should not be ignored.

Understanding of pathophysiological pathways and networking has emerged as urgent demand. Anchoring mission and position of pathophysiology within the cognitive landscape requires methods, professionals and academic strategy to facilitate efficiently with contemporary trends. Such mission implies the potential to deal efficiently with the seven complexity features described above. Understanding of natural interconnectivity of physiological phenomena opens a new dimension of practical medicine (Gamulin 2003, Kovač 2015, Coveney 2016). A fusion of clinical and basic knowledge is enriched by mathematical modeling. Powerful information-managing and computing systems and interactive quantifiable methods have been applied to various aspects of challenging clinical reality (Bellomo 2015). General academic strategies include policies of outcome based programs, a narrowing of the clinical and bench research, building theoretical and practical capacity to integrate scientific knowledge and clinical experience, nurturing a critical inquiry attitude, and learner's ability to self-evaluate and later self-regulate in clinical practice. The next generations of practitioners and learners should increasingly be able to extract and synthesize knowledge.

Training and coaching of future medical practitioners and researchers should be channeled towards such goals. Studying pathophysiology has taken various strategies, scopes and methodologies (Churilov 2015, Kovač 2014, Rall 2016). International Society for Pathophysiology (ISP), in year 2006, proclaimed the necessary steps in teaching/learning as the "powerful tool in the quest to comprehend the pathobiological nature as foundation of clinical reasoning and a proper appreciation of disease" (Declaration text available in Kovač 2017). On one hand, the eight taxative ISP-instructions have imposed the strategic guidelines which may be relevant to "academic policy makers in redesigning and upgrading curricular structure". On the other side, they enforce a building of "a new frame of reference" that may timely bring to fruition of powerful methodology of molecular approaches in clinical medicine. Such frame of reference demands an active role of clinicians, along with biomedical bench-scientist, in incorporation and reinterpretation of classical knowledge of physiology of health and diseases. General goal is an integration of theoretical visions and postulates, relevant scientific data and concepts with practical clinical aspects of the disease in a patient. It deals with fundamental pillars and landmarks of human body reactivity, pathways and spontaneous networking in various states of disease and disorders.

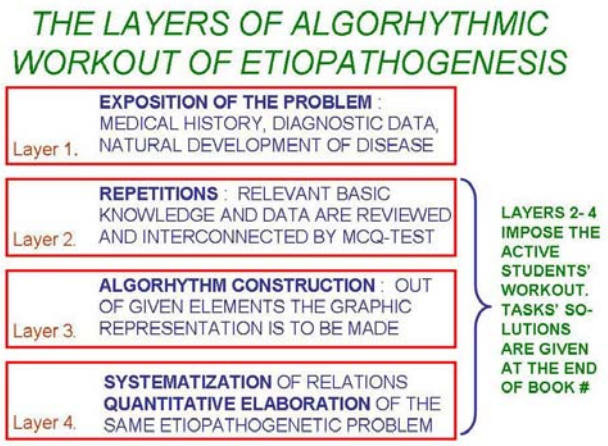
According to the ISP-Declaration medical practice and scientific biomedical research are two major resources of reliable knowledge for pathophysiology. A maximal insight into multiple aspects and facets of medical knowledge requires fusion and formation of a solidified and reliable framework of disease processes. This prospective and integrative mission places the pathophysiology at the central position in a questing of pathobiologic nature of disease. It seems that the most effective study procedure could be achieved by utilizing both analysis and re-synthesis of facts, concepts and visions. Two directional construction of knowledge in medicine stems from multiple facets of information, including medical history, diagnostic data, relevant scientific frame of reference, epidemiological data, etc. Etiologic and pathogenetic interpretation is to be built on wide range of information. It stems from clinical macro-phenomena (a disease history, examination, diagnostics, and therapy effects) and extends to the nano-scale world of ions, genes and molecular forces. It seeks for a deeper insight providing a reliable foundation for rational diagnostic and therapy approach. In clinical reality, pathophysiology provides theoretical tool and an up-to date interpretation scheme for meeting the emerging demands of postgenomic era in medicine.

The ISP recipe takes care of interdisciplinary approach and gives an appropriate position to facets of knowledge generated by close and remote disciplines relative to practical medicine. The ISP declaration holds that organismic level performance is more than sum of all subsystem units. Thus physiology of health and disease can not be correctly reconstructed of reductionistic elements alone. Is should always keep eye on whole-body performance phenomena as a central integrative manifestation of underlying processes.

Biomedical knowledge analysis and resynthesis via a matrix led algorhythmic method

In order to upgrade understanding of disease phenomena we have developed algorhythmic elaboration of disease pathways which include analysis and graphic re-synthesis of relevant information (Kovač 2012, 2013). The method puts together multiple facets of knowledge coming from various hierarchy levels. Clinical macro-scale descriptors of life phenomena are interconnected down to water, electrolyte and macromolecular information, and vice versa. Algorhythmic elaboration enforces the horizontal, vertical and longitudinal integration of patient relevant information. Horizontal integration refers to cross-talks among the organs in health and diseases. Inter-organ communications are maintained via hormones, cytokines, chemokines, mutual functional loads, neuronal networks, metabolic precursors and product concentrations, etc. Those multiple ways of cross communications between the skeletal muscle and the bone include >30 signaling modules (Isaacson 2014, Riley 2017), between skeletal muscle and white fat tissue

>300 (Pedersen 2009, Giudice 2017), between brain and intestine >40 factors (Kennedy 2017), etc. Vertical algorhythmic integration refers to interconnectivity of underlying processes responsible for disease manifestations. Signs and symptoms and macro-scale indicators of disease related dysfunctions are explained though subsystems' alterations, spanning like gene altered functions or electrolyte concentration alterations. Longitudinal dimension refers to time of disease processes, during which secondary processes may be initiated, tissue structure altered, self healing recruited, etc. The pathways and networking of processes are crystallized out of plethora of clinical data (signs, symptoms, hidden dysfunctions, outcomes, etc) and knowledge of sub-systems (nano-molecular, thermal, macromolecular, genomic expression, cellular phenomena, etc.), which are largely acquired via reductionistic methodologies. The matrix led analysis and resynthesis method consists of the four layers (Figure 3). Learner is led to analyze and to re-synthesize the architecture of underlying etiopathogenesis.



Abbreviations: MCQ - multiple choice questions

Z Kovač et al. Pathophysiology. Study Guide Algorhythms – Problem Solver. Book Two. Medicinska naklada, Zagreb, 2014

Figure 3. Four layers of algorhythmic analysis and resynthesis. The stepwise method of etiopathogenetic algorhythms provide and enforces the active students' participation in teaching/learning procedure. It is an open, self-controlled approach, in which a newcomer is led by the matrix of the task through 4 interconnected layers. Analysis, repetitions from various angles, re-synthesis of unit-elements (compare Figure 4), and quantitative consideration are systemically put together in teaching/learning procedure

The first step is the exposition of problem, given in a form of "raw data" is primarily qualitative type of information, usually from patients' medical history. It contains tables of diagnostic laboratory data, illustrations, and explanatory curves and diagrams, when appropriate (Figure 3, Layer 1). Sometimes exposition is enriched by additional information derived from selected publications with experimental data, epidemiological information, etc. Narrative presentation uses natural language and terminology used in practical medicine. Each case study is derived from published reports concerning the given problem. Scientifically it is primarily qualitative type of information mixed with quantitative data whenever it was possible and appropriate. The exposition part gives a study context for the upcoming elaborations within the 2 through 4 step of given problem matrix.

The second step is the repetition of relevant knowledge which re-enforce understanding of given case manifestations within a broader context of relevant knowledge. It is a multiple choice test, that includes statements related to the exposition and referred teaching/ learning materials (Figure 3, Layer 2). Questions and the tasks are designed in a special way to be the most informative and instructive. Namely, the correct answers are the wrong statements, whereas all other statements are essentially truthful descriptions of pathophysiological pathways of the study case from exposition. Such matrix guides a reader towards new facets and through additional layers of considered etiopathogenesis. It is a tacit strategy to provide the solid foundation of declarative knowledge and deeper understanding.

The third step is the algorhythmic workout of the problem presented in exposition and repetitions (Figure 3, Layer 3). It represents an active build-up of cause-consequence pathways of events out of pre-given 25-30 units of etiopathogenesis. Graphic symbolic representation outlines positive and negative feedback loops, as well as parallel and contextual events (Figure 4). In addition student discovers parallel and contextual events and feed-forward coherent and incoherent regulatory loops, as well. The active re-construction of etiopathogenesis out of fragmented elements may be considered as a formal integration of knowledge. The graphic flow of etiopathogenetic pathways interconnects symptoms and signs (as clinically available medical information) with nano-scale molecular/electrolyte data, intrinsic built-in regulations of reactivity, etc (Figure 4B). In addition, algorhytmic graph presentation integrates study contents of various courses of biomedical curricula (Figure 4C). Their expertise and methods are here put together into harmonious and integrative interpretation of disease development and manifestations. Visual graphic re-design helps developing habit of systemic elaboration through a stepwise procedure, which are close to the practical every day activities of the physician - as a subroutine attitude.

The fourth step is the feedback integration of the problem which deals with additional relations, systematization and quantitative aspects of the same problem (Figure 3, Layer 4). This step contributes to a more comprehensive and contextual interpretation. It establishes additional relations in interpretation of disease phenomena, unraveled in previous steps. All four levels of elaboration are focused on the central theme given in the exposition and each new level adds up important facets and aspects. Thus, the integrated take-home message is generated.

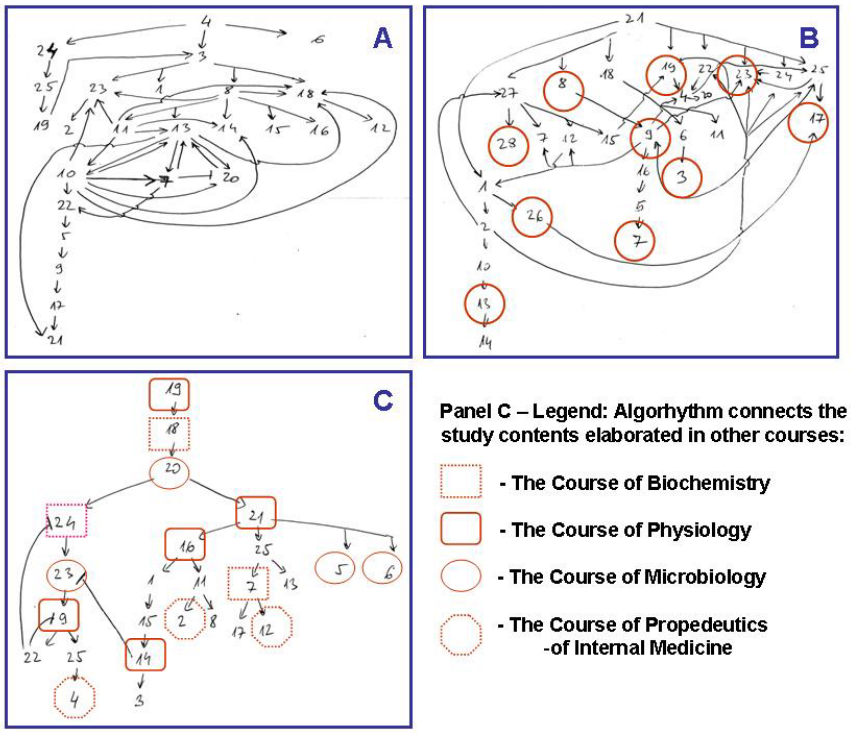


Figure 4. Within A through C panels hand-written basic charts represent the solutions of three different pathophysiological problems, respectively. Those algorhythmic networks are study contents of the layer 3 in Figure 3. Numbers are codes of specified etiopathogenetic units pre-given in the text. Arrows have symbolic meaning of "causing, positive effect, positive permissive effect" of the proximal to the distal unit in sequence of the pathway; whereas, "T-ended" lines mean "inhibition, negative effects, or negative permissive" effects of the proximal to the distal unit in sequence of the pathway. In panel B circled units are clinical symptoms and/or signs presented in the exposition (layer 1 in Figure 3) in given study case. Panel C- Etiopathogenetic algorhythms integrate knowledge which comes from contents of various curricular courses. Students and freshmen in pathophysiology figure out and put together into a coherent graphic representation – pathways of physiological fluxes of disease

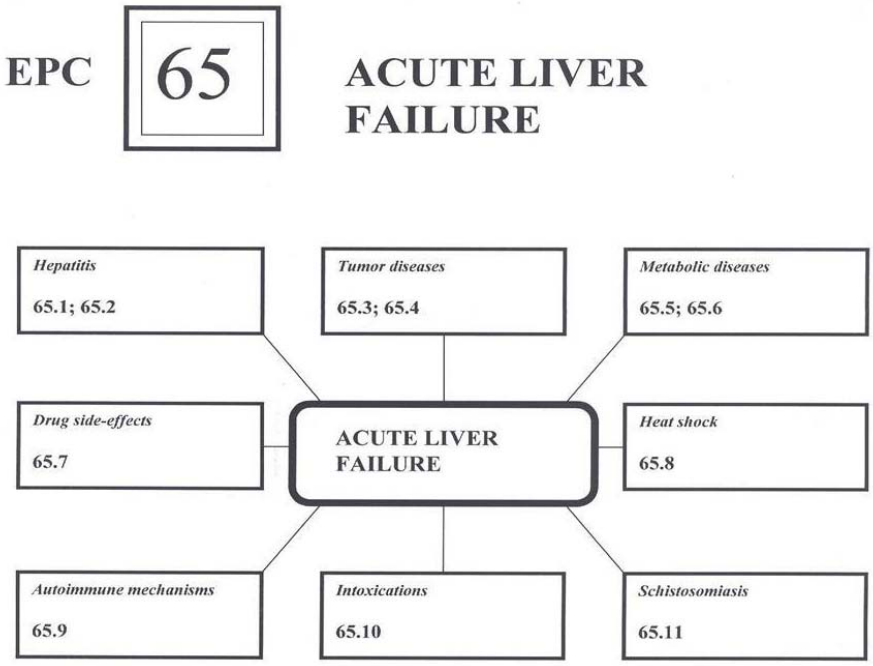
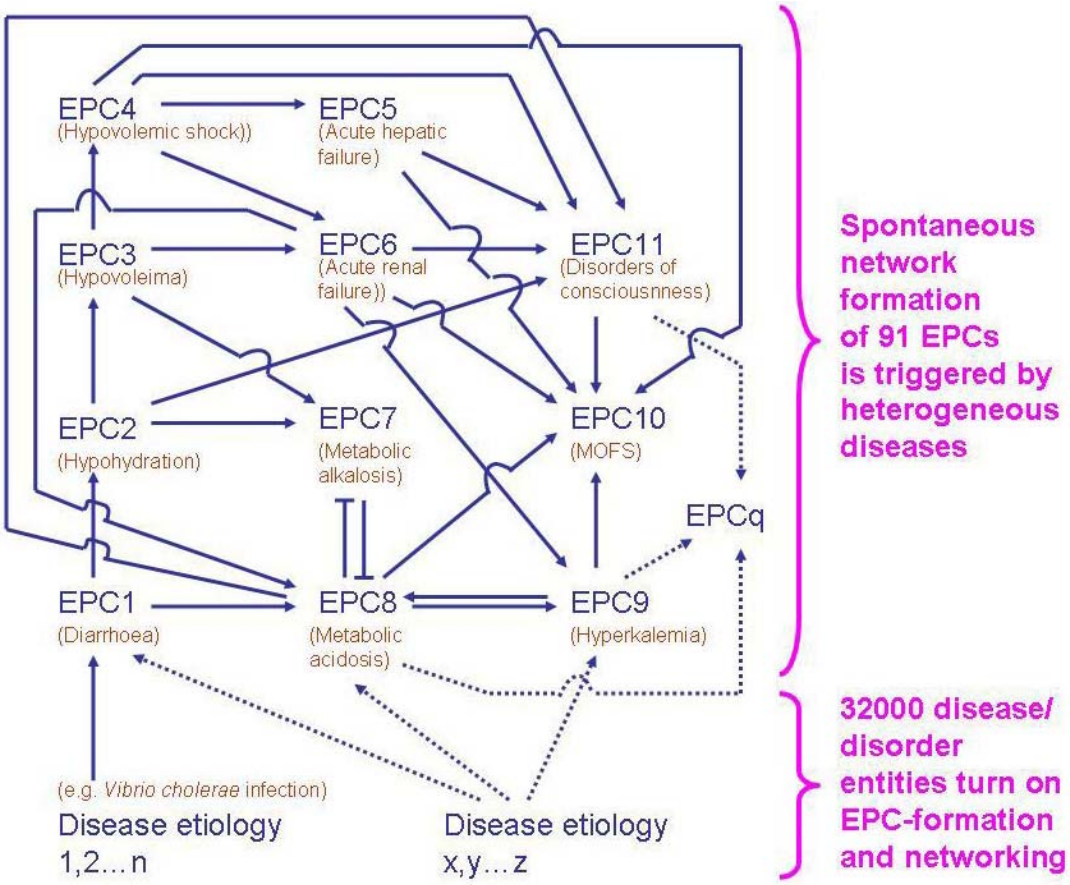


Figure 5. Introductory rosette of the EPC of acute liver failure serves as navigation scheme among multiple groups of conditions. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book. Each cluster out of 91 EPCs has such belonging rosette in a form of undirected graph representation (Modified and translated /from Croatian/ the introductory rosette of the 65th Etiopathogenetic cluster of the reference Kovač 2013, with a consent and kind approval of the author, editor and publisher)



Abbreviations: EPC - etiopathogenetic cluster; n,x,y,z – any real number of 1-32000; q-any real number of 1-91

Figure 6. Multiple nosologies (the etiopathogenesis of individual disease entities) spontaneously trigger the EPC-network formation represented by directed graph relations among clusters. In parentheses the example of cholera development is outlined. The insights into etiopathogenetic EPC networking may help both physicians and researchers in their appreciation of systemic nature of pathobiology of disease/disorders (Reproduced Figure 3 from page 22 of the reference Kovač 2015, with a consent and kind approval of the author, editor and publisher)

Etiopathogenetic clusters as elementary units of natural networking of disease pathways

Algorhythmic pathophysiology elaboration has revealed a natural tendency to form common crossing points of reactivity of heterogeneous pathways. The pathways spontaneously converge and form etiopathogenetic clusters (EPCs). EPCs integrate multiple inputs and multiple exits. They look like natural integrators, the common „hubs“ of human body response in various diseases (Figure 5). 91 EPCs have been identified at multiple levels of hierarchy of human body disease reactivity. EPCs are shared in natural development of heterogeneous conditions and they show tendency to form a network (Figure 6). Among the EPCs connecting pathways serve as “the EPC-driving force”. Thus, the EPCs may be seen as “a new emerging feature” of pathophysiology foundation of disease. Case study approach within the EPC-context simplifies consideration of 32,000 diseases/disorders listed within human medicine agenda. We published the EPC-based book that comprises 1165 case studies connected to 91 etiopathogenetic cluster (Kovač 2013). It is problem solver four volume book in which each patient case is elaborated form medical history, through basic etiopathogenetic pathways and clustering points and branching to secondary processes. Those 91 EPCs are formed at various hierarchy levels of human body physiology. Disorders of electrolytes are identified as 12 EPCs, including hypokalemia, hyperkalemia, hyponatremia, hypochloremia, etc. Disorders of fluids and osmolality cover 7 EPCs (hypohydration, hyperhydration, hypovolemia, hyperosmolality, hyperosmolality, ascites and edemas). Acid-base disorders are presented with 6 EPCs, whereas heat and energy metabolism include 14 clustering points. There are 9 cellular, lipid and protein disorders-centered EPCs. The remaining 43 EPCs are formed at physiological subsystems’ dysfunctions, like the EPC of acute renal failure, the EPC of heart failure, the EPC of autoimmunity, etc.

The EPCs concept and approach has an importance in practical medicine. Namely, they are targets of the therapy interventions. As natural functional integrative points – the EPCs are used as a controlling and/or correcting levels of medical treatment. One can easily recognize clinical beneficial effects in following examples. The EPC of hypoglycemia is target of a glucose

infusion therapy and very efficient prevention of hypoglycemic coma development in diabetic patients with insulin over-dosage. Timely conversion of ventricular fibrillation into normal heart rhythm prevents progression of the EPC of cardiogenic shock. The infusion of saline will stop and/or revert progression of the EPCs of hypohydration and the EPC of hypovolemic shock syndrome and save the patient life in massive cholera infection. In each of those cases a correction of clustering position brings about functional improvement in all pathways connected to that EPC, and therefore leads to a fast clinical betterment. Therefore the EPCs are seen as "biomarkers" of disease processes networking and points to be monitored and controlled by a therapy. This kind of reasoning holds true for a majority of 91 EPCs indentified in natural disease networking.

Ever since algorhythmic re-synthesis method and etiopathogenetic clusters were introduced generations of students have accepted it with enthusiasm and have given the positive feedback appreciation. In quality survey more than 3000 students have graded the method 2.3 times better in comparison to classical seminar methodology. Many of them described it as a "student friendly". Some of them recall later on that they have adopted "a useful approach of considering the every-day problems in professional life". Those methods were described by many teachers and students as inciting, challenging and powerful tool. It enforces the three-dimensional integration of the etiopathogenetic problem and keeps attention on both dominant and concomitant processes at the same time. It clearly depicts etiopathogenetic pathways and networks of interconnected elements within the hierarchy of the entire system. Three-dimensional integration of knowledge may be considered as appropriate method for a proper appreciation of the nature of diseases. It provides a unifying framework to integrate biophysical, biochemical, morphological (and other) aspects of disease processes with clinical signs, symptoms and dysfunctions (compare Figures 4, 5 and 6). At the same time, the modular system of this methodology opens an easy way to deal with the cutting edge of relevant research and up-to-date insights and discoveries. Namely, newly discovered facts can be easily placed within the appropriate segment of reactivity represented by network interconnections, as presently understood and comprehended. Reviewers evaluated and gave their opinions on these two methods. It was claimed that power of the approach is due to fact that two methods "*...put together contemporary understanding of both basic and clinical sciences' data. Those methods facilitate physicians' integration and make a bridge over the gap in contemporary medicine. They provide reliable foundations for rational diagnostics and therapy…*" (Poljak 2014). Similarly, a power of this approach attributed to "*...integrative relations of macro-world and nano-world of molecules and forces…*" (Rukavina 2014). In term of understanding biological principles of health and diseases the EPCs were described as "*…mosaic blocks, interplaying in all nosological forms, like elements of Mendeleyev's table adjoined in any substance, so they give strong impetus to systemic autonomous analysis of clinical and pathophysiological problems by students…*" (Churilov 2015). It seems that two methods have come close to fulfillments of demands specified in the ISP Declaration.

Pathophysiological interconnectivity outlined by the formalism of graph theory

The graphic representation of algorhythmic resynthesis and clustering phenomena, as it bas been rightly reflected by one of the reviewers "*...gives sense of mathematization of medicine (…) and medical knowledge is systematized and integrated along the logical pathways (the algorhythms)…*" (Švagelj 2016). Unlike majority of narrative interpretations in medicine, these two methods convert study contents into units, quanta of physiological elements of disease, and, the follows the resynthesis of elements. Mutual relations between the two connected units are causal (stimulatory, permissive, inhibitory, and like). Such exercise has a form of non-numerical and non-metric mathematical reasoning. An application of a symbolism of graph theory, a branch of topology, was found to be very suitable for representation of those real etiopathogenetic units and their relations. Unlike reductionistic simplifycations to less complex models, algorhytms and EPCs deal with the integral system. Since etiopathogenetic units are components of different function subsystems, they include both quantitative and qualitative data, involve various organs, they cross and connect various disciplines (compare Figure 4C), etc – such chimerical synthesis required the appropriate representation scheme. Leonard Euler (1707-1783) invented graph theory for such purposes. He says of his graph theory: "*…this part of geometry deals with relation dependent on position alone, and investigates properties of the position; it dose not take magnitude into consideration, nor it does involve calculation…*". With these features, graph theory is useful concept for nonlinear complex systems. It describes a complex system as a net of multiple events, seen as a whole. It seems appropriate for integrative human physiology and reactivity in health and disease. In our case, directed links in-between elements of algorhythm do indicate a "physiological flux", mutual oriented influence, and/or cause-consequence relations (see Figure 4 and 6), with no identifiable quantity within the relation. At the same time individual units of the algorhythm may represent a mechanism whose physiological features could be quantified. Graphic outline also forms tree-like branching points in etiopathogenetic pathways' networking. Some of them we named the EPC, the clinically relevant hub points of networking (see above). Undirected links in the EPC- rosette serve as indicator of certain, non-specified type of association (see Figure 5).

Spontaneous networking of disease processes, pathways and EPCs, presented with help of graph theory symbolism may facilitate our understanding of throughput biological data. Graphic representation outlines and makes visible a contextual events including regulatory feedback loops (positive and negative ones), feed-forward loops (coherent and incoherent ones) and parallel pathways. The complexity of etiopathogenetic processes' network is graphically given as clear communications among multiple elements, some of which are at diagnostic reach, whereas the others are clinically "invisible" (i.e. theoretical and/or non-measurable), yet important components of the etiopathogenesis of disease. Unlike narrative presentation of etiopathogenesis the graphic schematization has the advantage of a symbolic simplicity which pulls together a multiplicity of pathophysiological facets at the same time. It dose not ignore a non-dominant or a "weak" contributors in development of a disease/disorder. The upcoming era of medicine seeks for more efficient cognitive and educational armamentarium. Deepening of understanding of connections (established and new ones) of local and whole body physiology may be useful in bridging the gaps of contemporary medicine.

Physicians' approach to whole body will always remain the major referent concept and orientation in medicine, despite a progressive compartmentalization into narrow fields of interest (specializations, sub-specializations). The algorhythmic analysis/synthesis and the EPCs may be considered as a counter-response to the real challenge of the plethora of information. They are an appropriate simplification of data plethora and justified level of "granulation" of knowledge for practical physicians. At the same time, it may be useful to biomedical researchers in navigation within the clinical world and medical healing/preventing pragmatism, disease variability and the imperative to act within not-to-wide time framework. A broader panorama of knowledge management is presented in Figure 7. Our methodology provides and enforces top-down and bottom-up knowledge integration. It is always kept in mind that clinical medicine and biomedical research are two major pillars for the integrative physiology. Bridging the basic science and clinical application gap is materialized by the two methods. Those methods make visible etiopathogenetic interconnectivity of disease pathways and clusters and take into account the standpoints of human brain reasoning and knowledge processing.

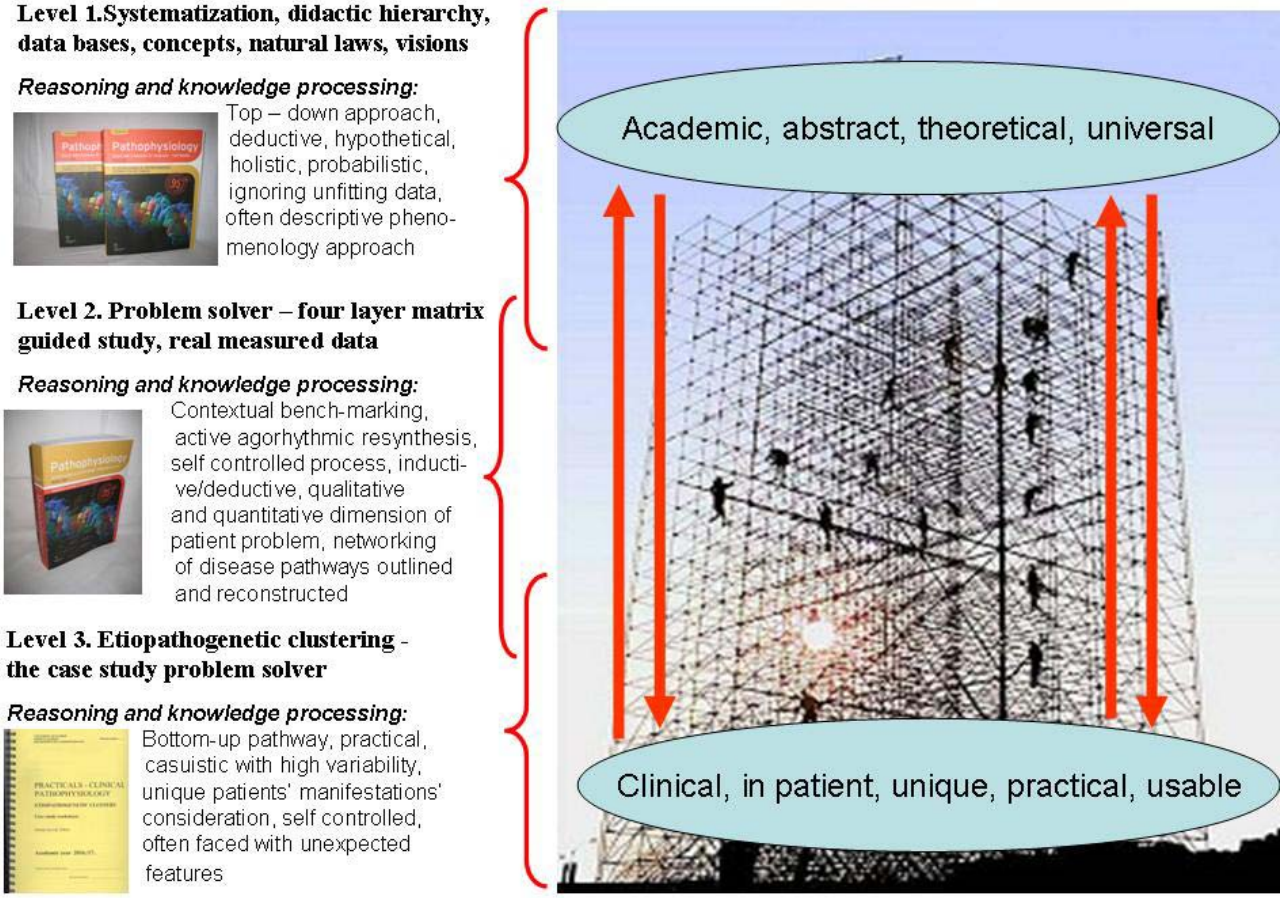


Figure 7. Zagreb School of Pathophysiology elaborates curricular subject contents by using three different teaching/learning and knowledge processing standpoints. Written materials are designed in a way to enforce an active student participation and integration of clinical and theoretical dimension of disease. Two methods are useful in bridging heterogeneous facets and quality of information (Modified and translated /from Croatian/ Figure 1-13 from page 17 of the reference Gamulin 2018, with a consent and kind approval of the author, editors and publisher)

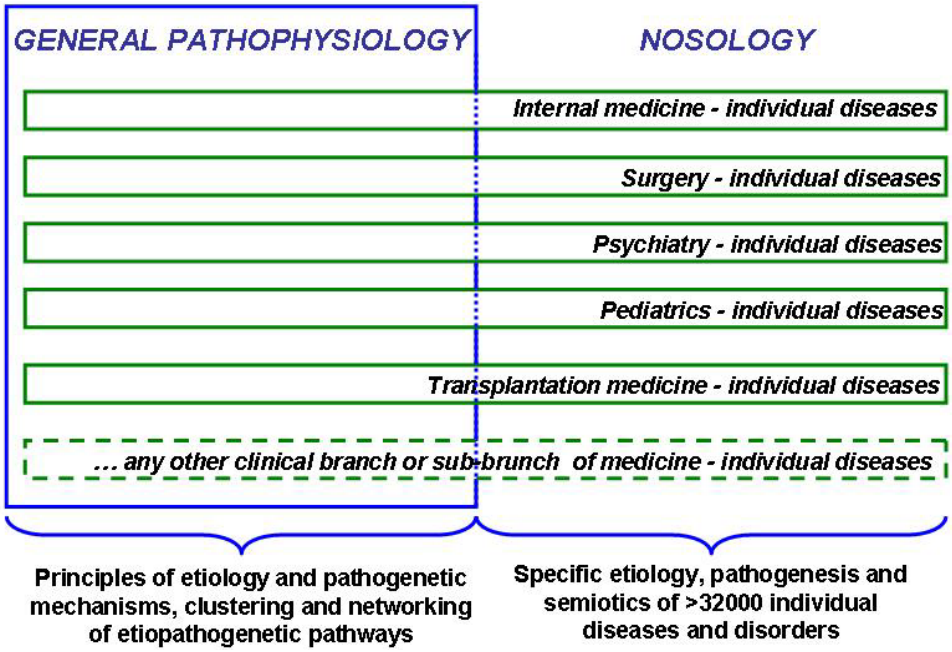


Figure 8. Natural overlapping relations of general pathophysiology and nosology (a special pathophysiology of individual disease). Pathobiological aspects common to multiple groups of diseases/disorders are subject of general pathophysiology. Nosology deals with processes underlying signs, symptoms and dysfunctions of particular clinical entity. Since body has a limited types of reactivity, processes triggered by heterogeneous etiological factors may lead to common pathogenetic pathways and networking

Matrix algorhythmic approach, as apposite to classical textbooks "*...starts from real data and leads to understanding of individual patient case within the context of general knowledge. (...) Algorhythmic elaboration of etiopathogenesis is a purposeful type of interconnecting of basic knowledge of genomic, proteomics, metabolomics and other – omicses and understanding of phenomena which includes the manifestation of disease*..." (Gamulin 2016).

The improvement and better efficiency of teaching/ learning and understanding is permanent silent need in clinical medicine. Navigation among big data and complexities, a usage of tacit knowledge within the routine daily work may make confusion and ask for a deeper understanding of etiopathogenesis and network reactivity. The graphic representation outlines the hidden networks, according to which natural spreading, communications and clinical patterns of diseases are formed. A newcomer in the field may re-discover that what has been known and practiced in medicine as a standard, now seen from a broader pathobiological perspective. Two methods may be useful to students, researchers and physicians in attempts to cross the major epistemological problem (reductionism versus integral view) in dealing with complexities of human body reactivity. Therefore other branches of medicine which are focused, among other issues, on nosologies of diseases, appreciate a common background of human body reactivity in various diseases (Figure 8). Many nosologies "use" identical parts of spontaneous networking of etiopathogenetic processes. Despite the heterogeneous etiologies many diseases - they share some common pathways and clusters.

Conclusion – graphic representation facilitates the integrative understaning of natural etiopatogenetic interconnectivity

Understanding of integral human body functioning is based on a maximal insight into heterogeneous research methods and data in parallel with equally well understanding of clinical dynamics of disease etiology, pathogenesis and outcomes. The power of graphic symbolism gives a useful simplification and presentation of etiopathogenetic reasoning in form of graphic networks. Two major pillars of understanding of a complex pathobiology in human medicine are clinical accumulated knowledge of nature of disease and experimental biomedical data and theoretical concepts. Presented methods of algorhythmic analysis and resynthesis of pathways and regulatory loops interconnect the EPCs. The EPCs are functional units and integrating points of reactivity in disease development. Pathophysiological foundations of disease phenomena are reduced to the interconnected elements of natural body reactivity. Such reasoning brings together researchers and practical clinicians in their attempts to improve understanding the nature of health and disease. The graphic mapping of pathways and the EPC enables consideration of various levels of "granularity" of knowledge (e.g., levels of electrolytes, gene expression, macromolecules, symptoms, outcomes of disease, etc), and its integration into unifying network of processes. This approach may fill some gaps caused by general trends of compartmentalization of practical medicine.

Acknowledgements: None

Conflict of interest: None to declare.

References

1. *Bellomo N, Elaiw A, Althiabi AM, Alghamdi MA: Mathematics toward systems biology and complexity: reply to comments on "On the interplay between mathematics and biology - hallmarks toward a new systems biology". Phys Life Rev 2015;12:85-90. doi: 10.1016/j.plrev.2015.02.006*
2. *Carrasco-Ramiro F, Peiró-Pastor R, Aguado B: Human genomics projects and precision medicine. Gene Ther 2017; 24:551-561. doi: 10.1038/gt.2017.77*
3. *Churilov LP: From physiology of disease to systemic pathobiology. History and current trends in pathophysiology. Med Acad Most 2015; 3:2-22*
4. *Coveney PV, Dougherty ER, Highfield RR: Big data need big theory too. Philos Trans A Math Phys Eng Sci 2016; 374:1-11. doi.org/10.1098/rsta.2016.0153*
5. *Fröhlich H, R Balling, N Beerenwinkel, et al.: From hype to reality: data science enabling personalized medicine. BMC Medicine 2018; 16:150 doi.org/10.1186/s12916-018-1122-7*
6. *Gallego G, Nørgaard LS: Qualitative Methods in Pharmacy Research. Pharmacy (Basel). 2018; 6. pii: E79. doi: 10.3390/pharmacy6030079*
7. *Gamulin S: Impact of Molecular Medicine on Pathophysiology, Medical Practice, and Medical Education Croat Med J 2003; 44:374-385*
8. *Gamulin S: Kovac's algorhythms in upcoming era of precise medicine. Liječ Novine 2016; 149:70-2 (in Croatian)*
9. *Gamulin S, Marušić M & Kovač Z: Pathophysiology. Textbook. Book One, The 8th Edition. Medicinska naklada, Zagreb, 2018 (in Croatian)*
10. *Giudice J, Taylor JM: Muscle as a paracrine and endocrine organ. Curr Opin Pharmacol 2017; 34:49–55. doi:10.1016/j.coph.2017.05.005*
11. *Green RM, Fish JL, Young NM, et al.: Developmental nonlinearity drives phenotypic robustness. Nat Commun 2017; 8:1970. doi: 10.1038/s41467-017-02037-7*
12. *Hadi MA, José Closs S: Ensuring rigour and trustworthiness of qualitative research in clinical pharmacy. Int J Clin Pharm 2016; 38:641-6. doi: 10.1007/s11096-015-0237-6*
13. *Haendel MA, Chute CG, Robinson PN: Classification, Ontology, and Precision Medicine N Engl J Med 2018; 379:1452-1462. doi: 10.1056/NEJMra1615014*
14. *Hofer IS, Halperin E, Cannesson M: Opening the Black Box: Understanding the Science Behind Big Data and Predictive Analytics. Anesth Analg 2018; 127:1139-1143. doi: 10.1213/ANE.0000000000003463*
15. *Hood L, Flores M: A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. N Biotechnol 2012; 29:613-24. doi: 10.1016/j.nbt.2012.03.004*
16. *Isaacson J, Brotto M: Physiology of Mechanotransduction: How Do Muscle and Bone "Talk" to One Another? Clin Rev Bone Miner Metab 2014; 12:77–85. doi:10.1007/s12018-013-9152-3*
17. *Islam R, Weir C & Del Fiol G: Clinical complexity in medicine: A measurement model of task and patient complexity. Methods Inf Med 2016; 55:14–22. doi:10.3414/ME15-01-0031*
18. *Joyner MJ: Giant sucking sound: can physiology fill the intellectual void left by the reductionists? J Appl Physiol 2011; 111:335–342. doi:10.1152/japplphysiol.00565.2011*
19. *Kennedy PJ. JF Cryan, TG Dinan et al.: Kynurenine pathway metabolism and the microbiota-gut-brain axis Neuropharmacol 2017; 112:399-412. doi.org/10.1016/j.neuropharm.2016.07.002*
20. *Kovač Z: 95th Anniversary of pathophysiology in Croatia. Psychiatr Danub 2017; 29(Suppl. 4):S720-S741; Med Acad Most 2017; 5:2-23*
21. *Kovač Z: Integrative clinical pathophysiology – algorhythmic disease consideration and etiopathogenetic clusters (EPC). HAZU Rad 2015; 524. Medical Sciences, 42:15-33*
22. *Kovač Z: Pathophysiology of teaching/learning as reliable pathway towards integrative Clinical reasoning. Bulletin Sankt Peterburg Univ 2014; 11:237-58*
23. *Kovač Z et al.: Clinical pathophysiology - Etiopathogenetic clusters. Book three (Four volumes). Medicinska naklada, Zagreb 2013 (in Croatian)*
24. *Kovač Z: Pathophysiological foundations of personalized medicine. Etiopathogenetic clusters as integrating units of clinical pathophysiological pathways and networks. In „Person in medicine and heathcare-From bench to bedside to community". Editors V Đorđević, M Braš, D Miličić. Medicinska naklada, Zagreb 2012, pg 57-64*
25. *Marcum JA: Multimorbidity, P4 medicine and holism. J Eval Clin Pract. 2017; 23:213-215. doi: 10.1111/jep.12588*
26. *Pedersen BK: The diseasome of physical inactivity – and the role of myokines in muscle–fat cross talk J Physiol 2009; 587:5559–5568*
27. *Poljak Ž: An introduction into Zagreb model of etiopathogenesis consideration. Liječ Novine 2014; 128:34 (in Croatian)*
28. *Rall JA: The XIIIth International Physiological Congress in Boston in 1929: American physiology comes of age. Adv Physiol Educ 2016; 40:5–16*
29. *Riley LA, KA Esser. The Role of the Molecular Clock in Skeletal Muscleand What It Is Teaching Us About Muscle-Bone Crosstalk Curr Osteoporos Rep 2017; doi: 10.1007/s11914-017-0363-2*
30. *Rukavina D: Integrative relations of clinical macro-world and nanoworld of molecules and forces in etiopathogenetic algorhythms and clusters. Liječ Novine 2014; 134:34-5 (in Croatian)*
31. *Sagner M, McNeil A, Puska P et al.: The P4 Health Spectrum - A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan. Prog Cardiovasc Dis 2017; 59:506-521. doi: 10.1016/j.pcad.2016.08.002*
32. *Sedlić F & Kovač Z: Non-linear actions of physiological agents: Finite disarrangements elicit fitness benefits. Redox Biol 2017; 13:235-43*

33. Shah ND, Steyerberg EW, Kent DM: Big Data and Predictive Analytics Recalibrating Expectations. JAMA 2018; E1-E2
34. Švagelj I: An essay on „The Zagreb model of etiopathogenesis exploration". Liječ Novine 2016; 149:72 (in Croatian)
35. Vogt H, Hofmann B, Getz L: The new holism: P4 systems medicine and the medicalization of health and life itself. Med Health Care Philos 2016; 19:307-23. doi: 10.1007/s11019-016-9683-8
36. Zhang L: Big data and medical research in China. BMJ 2018; 360:j5158; doi: 10.1136/bmj.j5158

Correspondence:

Prof. Zdenko Kovač, MD, PhD
Department of Pathophysiology, Medical School University of Zagreb
University Hospital Centre Zagreb
Kišpatićeva 12, 10000 Zagreb, Croatia
E-mail: zkovac @mef.hr