

# **PATHOPHYSIOLOGICAL BODY REACTIVITY AND INTERACTIONS IN COMORBIDITIES Synergism Versus Antagonism of Disease Pathways and Etiopathogenetic Clusters in Comorbidity Conditions**

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## **SUMMARY**

*Complexity, variability, nonlinearity and adaptive alterations in human health and disease are considered within the integral body physiology. Sokolić's principles and Koshland's pillars of life are referred as a conceptual frameworks for the whole-body performance. Disease pathways and etiopathogenetic clusters (EPCs) form networks. Due to EPCs, pathways and networks body reactivity gets reduced, and may lead to latent insufficiencies, a decompensation and death. Networking can be triggered by various etiologies. Overlapping of one disease network with the other simultaneous ones may lead to interferences of a disease development and manifestations. Comorbidity effects may be synergistic, and thus it leads to a more severe disease state. On the other side, antagonistic interaction of the two diseases may lead to improvement and/or prevention. 20 comorbidities of each type are outlined in this paper.*

**Key words:** *etiopathogenetic clusters (EPC) - Sokolić's principles - Koshland's pillars - reactivity - comorbidity - synergism – antagonisms*

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## **INTRODUCTION**

Human body physiology in health and disease is a dynamic adaptive system with continuous matter/energy and bioinformation exchanges with environment and within itself. It is a complex open dissipative system with a nonlinear activity feature (Buchman 2004, Bartsch 2015). Nonlinear behavior essentially means that system considered - may respond in different ways to the same input - depending on their own state, context and condition (Descalzi 2019, Kondepudi 2017). The nonlinearity itself stems from the system complexity, implying multiple simultaneous interactions (genomic, cellular, proteomic, etc.), which are not easily controllable and identifiable, and, thus, the behavior of the system cannot be easily inferred from its properties. Yet, general physiological performance exerts regularity and physiological stability in self-maintenance and interactions with the environmental challenges. Maintenance of dynamic stability is procured by numerous of feedback negative and positive loops and feed-forward mechanisms (coherent and incoherent ones), which often act in a parallel and redundant mode (Svenningsen 2020).

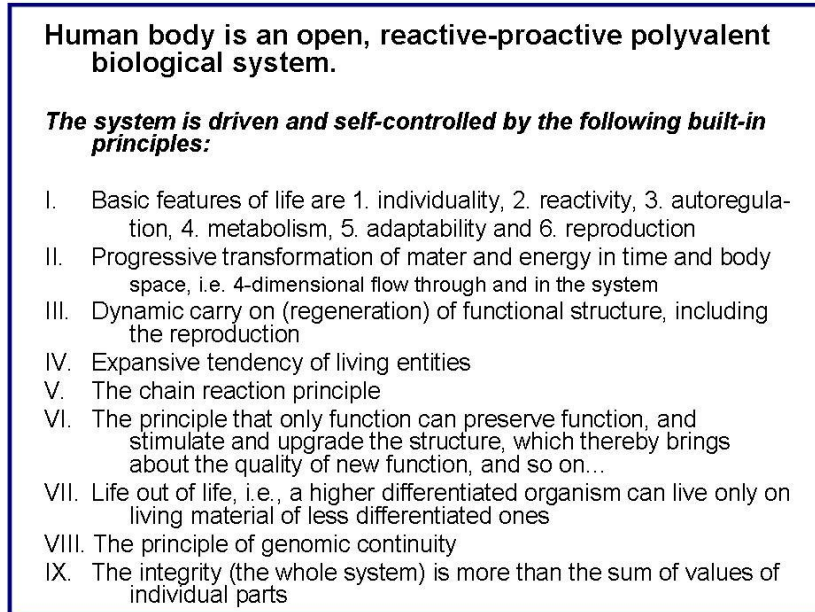
Following the basic mission and nature of medicine, physicians are always taking care of the individuum, not just a segment of the body. Even very narrow subspecialists standpoints are directed towards understanding and improvement the whole-body performance. In this paper some features of two integrative scenarios are

presented, seven Koshlands' pillars of life, and nine Sokolić's principles of physiological systems. These integrative frameworks are relevant attempts of putting together the plethora of data coming both from clinical and basic science research and practice. Body reactivity alterations during health and disease can be analyzed following the etiopathogenetic pathways. In disease development pathways tend to form etiopathogenetic clusters (EPCs), as hub points of multiple pathways. Networking of various EPCs reduces body reactivity, that contributes to latent insufficiency and decompensation. Heterogeneous etiologies trigger the overlapping networks and may lead to interferences of two or more simultaneous disease processes. Several examples of comorbidities synergism as well and antagonisms are outlined in this paper.

## **TWO CONCEPTUAL INTEGRATIVE SCENARIOS IN BIOLOGY – THE NINE SOKOLIĆ'S PRINCIPLES AND THE SEVEN KOSHLAND'S PILLARS**

Professor Pavao Sokolić (1907-1977) at University of Zagreb had defined the human body as „*the open reactive-proactive polyvalent biological system (...) which acts according to nine built-in principles*“ (Gamulin 2021, Kovač 2017). His principles listed in Figure 1, mold the physiological complexity into a simple vision, whose general integrative features could

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**Figure 1.** Nine principles of human body physiology in health and disease as defined by Professor Pavao Sokolić

be defended as valid, even after 70 years of their circulation in academic community. His „basic features of life“ are thought as indivisible landmarks of human physiology as living organism. Those features are mutually supportive, homeostatically interregulated and their integral performance is the whole-body phenomenon. Thus, Sokolić's first principle could be considered as valuable starting point for a theory-of-organism-to-be, which is still at a nascent and fragmentary stage in physiological science (Rosslenbroich 2016, Pepper 2008).

In contemporary physiological language his principles could be rephrased as follows. Body intrinsic features are powered by genomic blueprint instructions, bioenergetical fluxes which are dependent on exogenous resources, and a self-regulated individuality. Such living unit has got a spontaneous structural and functional regeneration and maintenance, and it is prone to a reproduction and growth. In addition to these „proactive“ and self-maintaining features, human physiology in endowed with an adaptive and re-active capacity to both exogeneous and internal stimuli. The „adaptive“ feature implies a body capacity to change and to learn from an experience. Sokolić's 6<sup>th</sup> principle implies an epigenetic „talk“ of one physiological function to other physiological subsystems (their induction, expansion, etc). Related to the whole-system physiology Sokolić stresses that a capacity of integral complex system is larger than what could be predicted from its functional units (the ninth principle). Indeed, it holds true. Namely, the advent of powerful molecular research, especially in the postgenomic era, has brought a clear light into myriads of physiological mechanisms. High level of certainty of scientific proof is, by large, achieved by simplified and strictly controllable study conditions of the scientific question considered. Yet, a „reconstruc-

tion“ of integral physiology out of those elemental insights is not a straightforward undertaking. It seems some aspects of integral body physiology have been lost due to methodology applied. Translation medicine has been experiencing a similar problem (Place 2017, Gentry 2020).

Nine narrative principles give a macroscopic scale conceptual framework of body physiology performance. Physicians find them useful, as a general vision, in putting together laboratory, clinical manifestations, diseases natural development and other diagnostic data. Their conceptualization and clinical reasoning starts from the whole-body disease manifestations that is followed by the search for orderly and lawful dysfunctionality events which may be responsible for patients' complaints.

In the year 2006 Daniel E Koshland (1920-2007), biochemist and Editor in chief of journal Science, published his concept of the seven pillars of life, acronymed PICERAS. The term comes from P(rogram), I(mprovisation), C(ompartimentalization), E(nergy), R(egeneration), A(daptability), S(eclusion) (Koshland 2002). These pillars are „the essential elements - thermodynamic and kinetic - by which a living system operates“. His insightful vision integrates seven function/ structure domains applicable primarily to the cell the level. Four pillars PERA contain recognizable contents which correspond with some contents of Sokolić's nine principles. Although they were written from different professional backgrounds and performances, authors came to common basic foundations. Therefore, without going into further details of these four pillars – attention and some elaboration will be devoted to Koshland's pillars of „C“, „S“ and „I“.

Compartmentalization (the “C” pillar) is a fragmentation of body volume into subunits which are prerequisites for maintenance of appropriate concentrations of

ingredients for body chemistry, and may be protective against potential intoxication. Such limited volumes within the body are formed at cellular level (like, cytoplasm, nucleus, other organelles, etc.) and supracellular level (organs, groups of cells, etc.). Confined and limited volumes may be critical for life kinetics (like, a prevention of dilution, an avoidance of toxicity, an appropriate localization of enzymes, etc.). Functional compartmentalization is phenomenon of a tissue/organ specialization and centralization within the larger organisms. In addition to Koshland's attributes assigned to compartmentalization phenomenon, one could add a gradient formation as its important consequence in human body physiology. Namely, body gradients across compartment limits of the physiological barriers (like, fluids' pressure gradients; diffusion of gasses and metabolic reactants and products; osmotic-, oncotic-, and electrochemical-gradients; etc.), Once formed and maintained those gradients serve as a smooth drivers of given life functions. Disorders of compartments may lead to reduction/loss of those gradients which are regularly pathogenic or thanatogenic processes. Thus, the concept of compartment can be incompatible with the life biological phenomena.

The Seclusion (the "S" pillar) refers to individual enzymatic specificity for its substrate and enzymatic unique catalytic process which enables biochemical pathways to be performed regardless of other substrates and other enzyme in the same compartment. Similar "secluded" patterns occur in specificity in DNA and RNA interactions. Koshland says "*this property is like insulating an electrically conducting wire so it isn't short-circuited by contact with another wire*". The seclusion principle, based on ligand/receptor like specificities may contribute to feedback and feed forward messages and regulation. In addition, contemporary physiology may identify many examples of this life pillar. Cellular phenomena of phagocytosis/ exocytosis, autophagy, cellular transporting systems, and proteasome catabolism contain a seclusion principle, driven by specific and selective mutual affinities of given components of individual pathways.

The Improvisation feature of life (the "I") is ability to change its program in some way - in order to cope with demands of vicissitudes of its environment. Koshland emphasizes "*a process of mutation plus selection that allows programs to be optimized for new environmental challenges that are to be faced*". That concept is supported by factual data related to some body functions. For example, the acquired immunity in response to environmental antigenic challenges activates a massive increase in mutation rate in targeted region of the T cell receptor genes and antibody DNA blueprint (15). Yet, on the other side, if it were the only group of mechanisms this pillar of life could have been reduced back to „A“ (the adaptation) and „P“ (the program) pillars. However, this „I“ pillar, in human physiology

may be considered, in a broader sense, as redundancy of reactive pathways and mechanisms, including, polygenism, biological reserve, homeostatic/ allostatic regulatory modes, etc. The interplay and alterations in intensity of those physiological reactive patterns appears as real „improvisation „with a strong adaptive capacity.

Both Sokolić's principles and Koshland's pillars are valuable theoretical visions of a life phenomenology. They have tried to put together vast areas of knowledge, with idea of figuring out the common denominators of life phenomenology. Both of them were aware that life phenomena are not straightforward reduction to physical and chemical laws, principles and patterns. Both of them strived towards an integration of fragmented knowledge and scientific data. This problem has, later on undergone the exponential growth in recent *omics*-era of scientific research (Manzoni 2018, Noriega 2018). Both of them influenced and inspired basic and clinical research which paved way towards the whole-body physiology.

## **INTEGRATIVE BODY REACTIVITY IN HEALTH AND DISEASE**

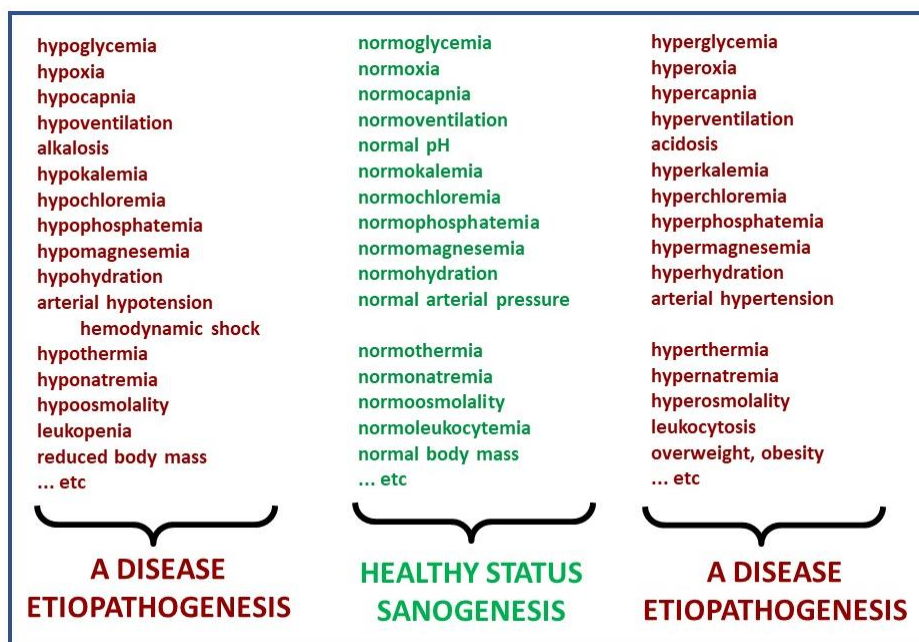
In his first principle Pavao Sokolić introduced the concept of reactivity, as a necessary clinical descriptor of functional performance states of human body physiology. He insisted on a fusion of experimental and non-experimental evidence in establishing the physiological status. He considered clinical observation and physical examination, disease medical history, statistical descriptors - as equally important as morphological, dynamic and static tests in diagnostic procedure. Sokolić had defined human body reactivity as „*a functional-dynamic capacity of the organism to react to a given stimulus in any time-point of life*“ (Gamulin 2014a). As practicing physician, and integrative pathophysiological he strongly felt a need to grasp and to integrate the all-possible clinical facets, even very discrete ones, of patient's condition. His meticulous diagnostic procedure (with a usage of a simple diagnostic tools of his time) turned to be highly efficient. He was aimed to build a comprehensive physiology of disease processes which will take into account all known and relevant physical, chemical, biological and psychological aspects of life. His credo was that integrative understanding of pathophysiology is only reliable pathway for rational therapy. Such conceptual framework has been revived in postgenomic era and 4P-medicine campaign (Alfonso 2019, Khakimova 2020). In those semiologic efforts Sokolić achieved a unique level understanding and unprecedented clinical efficiency.

His concept of body reactivity was a simple estimate of integral functionality that is influenced by many components of the system. The reactivity is „*the capacity and type of reaction which is manifested as a set of qualitative and quantitative organismic responses*„, and it „*is the result of a combination of inherited and*

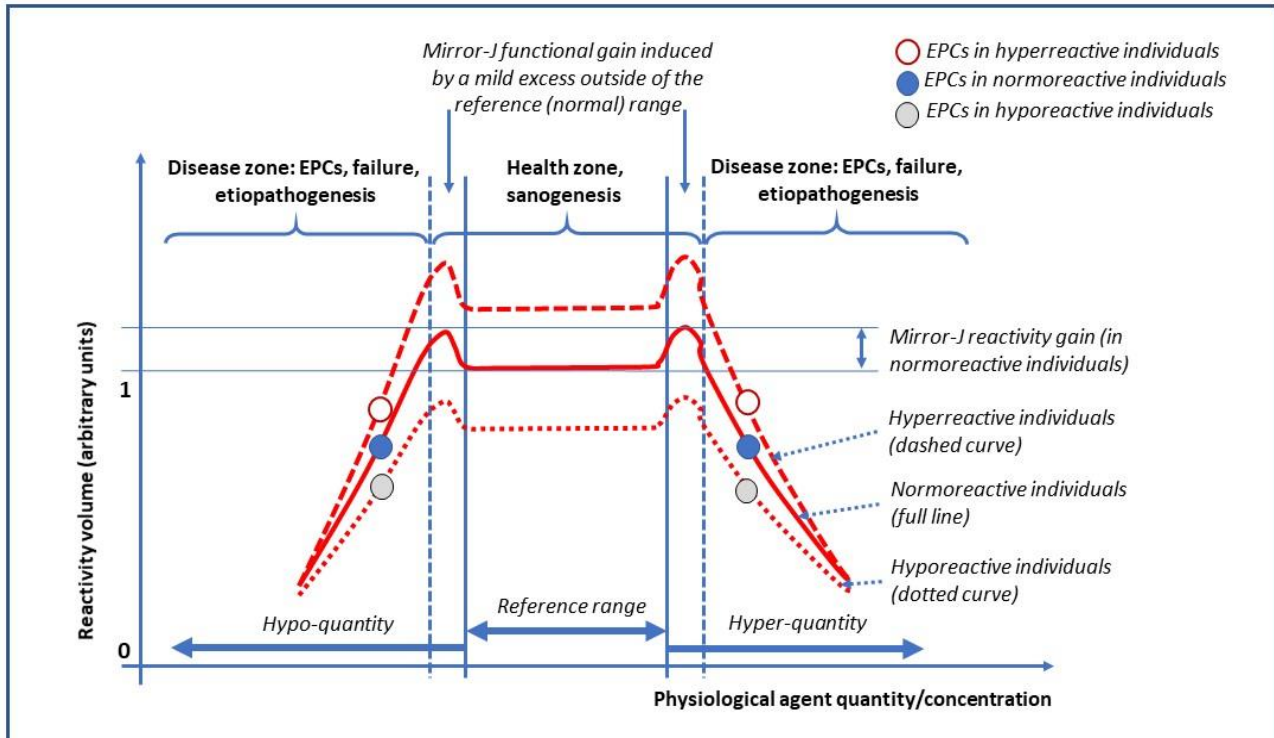
acquired characteristics, and the overall physiological experience up to that point of time“ (Gamulin 2014a,b). In nowadays terminology Sokolić's body reactivity can be considered as a composite and synchronized execution of individual reactivities of functional subsystems and their mutual interdependence and interactivities. Each functional subsystem maintains and adjusts its physiological component used by any subsystem. For example, the glucostatic subsystem (let it be called the subsystem „A“) procures normoglycemia (its physiological component „a“, that), as the necessary precondition for energy metabolisms of other subsystems and glucostatic subsystem itself. Since energy demands alters through the time (an increase, a decrease, a futile turnover) the glucostatic subsystem permanently buffers demands for the glucose supply as the energy substrate. Similar mode of action applies to other subsystems, like oxygen-delivery-subsystem, hydration-regulation subsystem, thermostat, pressostat, ponderostat, etc. (let them be called subsystems B, C, D, E, F, respectively, and so on). Physiological subsystems are mutually dependent and maintenance of their physiological component within a given range – provides appropriate feeding into the other subsystems. Hypofunction (or failure) or hyperfunction of the subsystem affect the performance of other subsystems. For example, hypoglycemia due to dysfunctional subsystem A directly leads to dysfunction of pressostat subsystem and hypoglycemic shock and coma (Hagar 2017, Patil 2020). Maintenance of physiological parameters within the normal range enables sanogenetic processes and healthy status and performance (Figure 2). Mild alteration of physiological body parameters indu-

ces body responses which increase the volume or reactivity in form of mirror J hormesis-like patterns (Sedlić 2017). Normoreactive, hyperreactive and hyporeactive individuals follow similar reactivity boosting due to mild and short physiological agents oscillations (Figure 3).

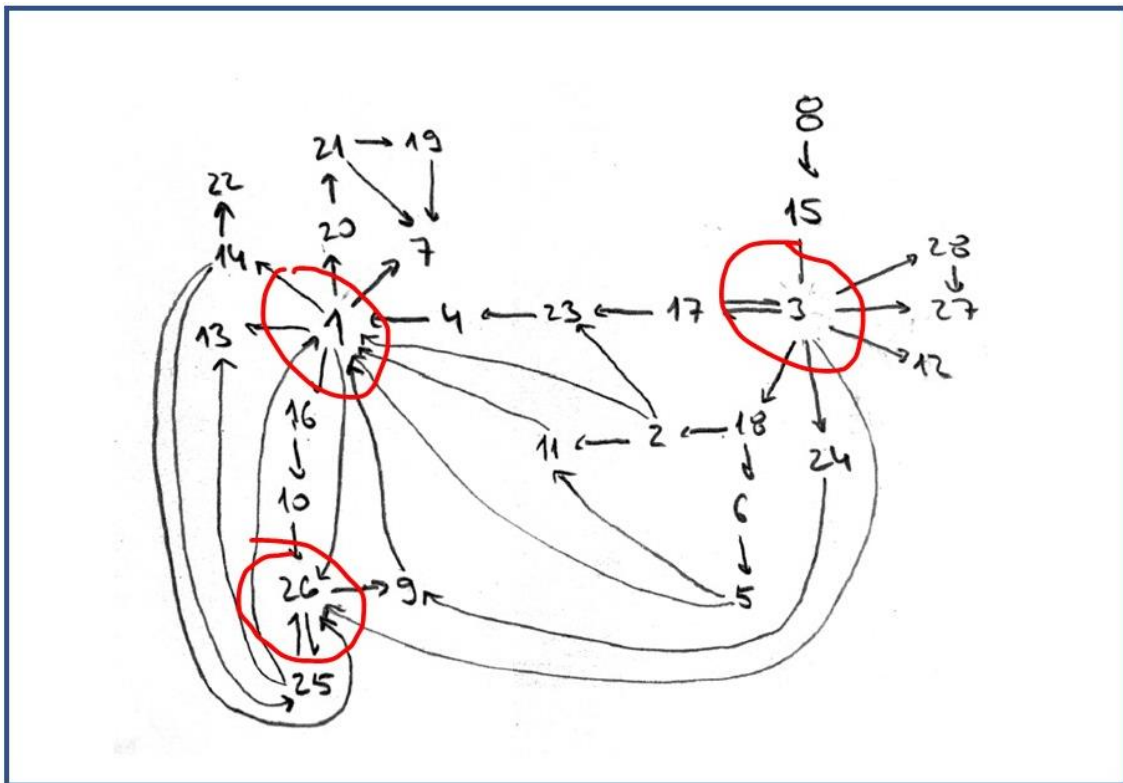
The reactivity of any functional subsystem includes a certain degree of autonomy, a sensing and working capacity, homeostatic regulation and depends on genetic. Please note that physiological subsystems are composed of multiple components. For example, a locomotor subsystem consists of skeletal muscles, bones, joints, tendons, blood perfusion, etc. In a complex body physiological performance many subsystems contribute to overall body reactivity. For example, the sport performance of athlete is contributed by the reactivities of locomotor subsystem, hemodynamic subsystem, respiratory subsystem and mental-neurologic as major executive components. At the same time hydration-regulation subsystem, thermoregulatory subsystem, acid-base regulatory subsystem, (etc.) are much involved as permissive limits-defining subsystems. Shortly, in healthy individuals subsystem A procures the optimal functional component „a“ to subsystems B,C, D etc. and to itself (the subsystem A); subsystem B, likely, procures the optimal functional component „b“ to subsystems A,B,C and so on, and so on. The reactivity of each subsystem emerges from inherited and acquired characteristic, combined. In can be increased by *anabiotic processes* (like, anabolism, hypertrophy, regeneration, etc.) and reduced by *catabiotic processes* (like, atrophy, cachexia, catabolism, etc.) in comparison to reference (normal) range (Gamulin 2014c).



**Figure 2.** Healthy body performance is harmonic balancing of basic functional components and their maintenance within or close to the reference range. Potent groups of mechanisms take care of each component (eg, glucostat, pressostat, thermostat, etc) and thus keeping the sanogenic physiology. A significant deviation of any basic component, in principle, triggers a certain etiopathogenetic pathway, thus leading to a reactivity reduction and a disease manifestation



**Figure 3.** Excessive hypo- and hyper- deflections of the physiological parameter outside of its reference causes a reduction of reactivity and triggers given etiopathogenetic clusters. Hyporeactive and hyperreactive individuals have a pattern of disease manifestation similar to the normoreactive ones. Mild deviations, however, induce a limited functional gain according to mirror-J response pattern and thus boosts the health physiology (see Sedlić 2017)



**Figure 4.** Etiopathogenetic analysis and resynthesis of disease components, outlined in form of a graphic chart, reveals the natural hubs of pathways, called the etiopathogenetic clusters (the EPCs) (circled in red). An emergence of the EPCs shows a regularity, a spontaneous networking and multiple loops of self-regulation. In this handmade algorithm each Arabic number codify the given etiopathogenetic element which is used as unit block of disease architecture

## NETWORKING OF ETIOPATHOGENETIC PATHWAYS AND CLUSTERS AS NATURAL BASIS OF DISEASE

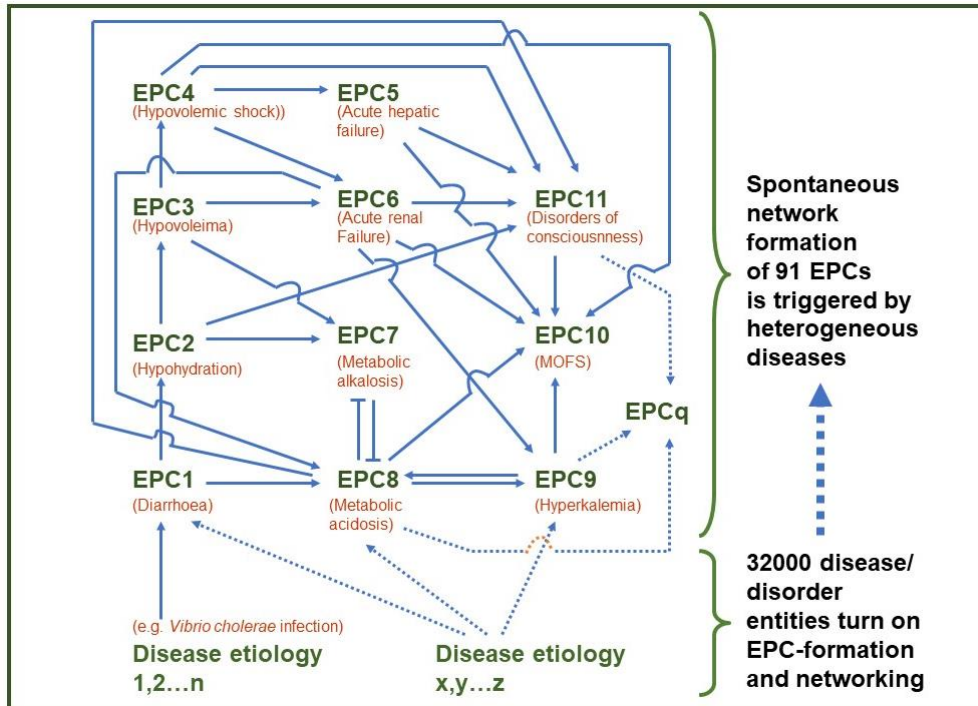
Claude Bernard (1813-1873) introduced experimental research and methodology into studies in medicine. He made a scientific revolution in biomedicine and was duly honored as the founder human physiology. His concept of internal steady state (French *milieu interieur*) anticipated self-regulated maintenance of constancy of various body parameters like, body temperature, glycemia, kalemia etc. – to be of a critical importance for the multicellular organism. In his words “*the fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated.... All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment*” (Bernard 1865, 1974). At his time real mechanisms of dynamic stability of *milieu interieur* naturally were far from basic identification and quantifications. It was theoretical construction with a high probability to be valid in multicellular living bodies. Bernard opened a brand-new conceptual framework for the upcoming age of physiology research and understanding. Later on, following the Bernard’s legacy, Walter Bradford Cannon (1871-1945) in the year 1926 coined the term homeostasis which has become a central pillar of modern physiology. Homeostasis with feedback and feedforward loops and allostasis have become a central organizing principles of physiology. Homeostatic and allostatic principles are applicable and applied from the nano-scale world of water and electrolyte regulation within the living body, up to clinical macro-scale organismic level.

Physiology of health and disease is a continuum. Steady state of functional agents in the *milieu interieur* in healthy individuals is maintained within a pertinent reference range. Body adaptive responses follow nonlinear patterns. Switching from health to disease, and vice versa, represent alterations of multiple steady state elements. Nonlinearity stems from several levels of body functional organization. They include macromolecular functional features (e.g., enzyme kinetics, molecular turn-over), cellular level (e.g., integration of multiple signals, triggering division versus death pathways), tissues levels (e.g., remote effect of hormones/cytokines) and regulatory levels (e.g., endocrine/neural homeostasis, mirror-j physiology), etc. (Sedlić 2017). Nonlinearity contributes to complexity patterns of natural responses in health and disease. The complexity of human body physiology, additionally, stems from parallel pathways, multiplicity of regulatory homeostatic/homeodynamic loops (feedback and feedforward), biological redundancy, genomic variability, interdependence on physiological gradients, chronobiological alterations of reactivity robustness and plasticity of function/structure maintenance (Kovač 2012).

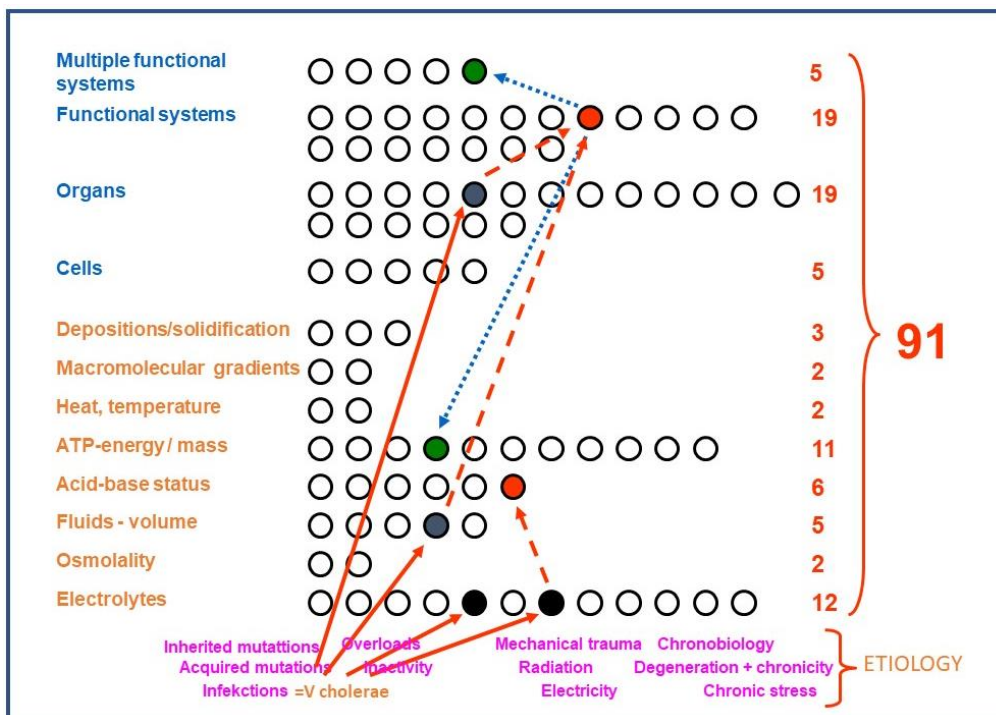
Etiopathogenetic analysis and resynthesis of both clinical and basic data relevant to pathophysiology of particular disease revealed multiple pathways, self-regulatory feedback loops and feedforward coherent and incoherent adjustments. These relations are graphically represented as disease natural algorithms, that connect etiology, internal body events with symptoms, signs and dysfunction of the disease (Figure 4). Such disease matrices showed general tendency to form hubs, called etiopathogenetic clusters (Kovač 2012, 2015). The etiopathogenetic clusters (EPCs) are crossing points, the integrative hubs of disease pathways. EPCs are nodes in which multiple pathways are joined together, and, at the same time some other pathways are initiated. „*There is general natural tendency of etiopathogenetic pathways to form common crossing points of reactivity. Etiopathogenetic clusters are the points where, very often, many unrelated pathways converge to the common units of pathogenesis*“ (Kovač 2015). Units 1, 3 and 26 in Figure 4 have characteristics of EPCs. These EPCs represent the extreme deviation of physiological parameters out of reference range, like hypokalemia, hypohydration, hyperhydration, etc. (compare Figure 2). Functionally EPCs themselves are reductions of specific subsystem reactivity, which additional limits the reactivity of other subsystems (compare Figure 3). Consequently, whole body reactivity progresses to latent insufficiency and decompensation.

Among EPCs there is a spontaneous networking with a certain regularity of patterns of responses. Etiopathogenetic pathways belonging to heterogeneous types of diseases tend to group together into given EPC (Figure 5). Medical conditions of unrelated etiologies are joining together through the EPCs, which do emerge in their natural development. In addition, those EPCs develop at various function/structure levels in human body (Figure 6). This analytic-synthetic description of etiopathogenesis arouse broader interest. It was referred to as „*...around 100 of mosaic blocks, interplaying in all nosological forms, like elements of Mendelejev’s table adjoined in any substance, so they give strong impetus to systemic autonomous analysis of clinical and pathophysiological problems by students...*“ (Churilov 2015).

Body reactivity has been reduced down to 91 EPCs and their interconnecting pathways (Kovač 2012, 2013). Two or more disease being developed at the same time have a certain probability to interfere with each other at some steps of their development. There are three theoretical possibilities; the first – no interference, the second-mutual amplification (a disease synergism) and third-mutual inhibition (a disease antagonism). The first possibility is likely to exist, by it is not easy to be scientifically proven. Here we shall discuss literature data that fit the other two predictable possibilities.



**Figure 5.** Etiopathogenetic clustering is triggered by heterogenous etiological mechanisms. Among the EPCs there is a regulatory trade-off which modifies overall body reactivity. Since EPC-networking stems from individual disease initial pathways one can expect mutual influences of various diseases at the level of networks. (*Basic etiopathogenetic components of cholera are given in parentheses, as example of disease etiopathogenetic spreading within the body*). This is modified Figure 3 from reference Kovac 2015, included in this paper with kind consents of Editor and publishing house



**Figure 6.** EPC networking occurs at various function/structure hierarchy levels within the human body. Etiological factors trigger primary EPC(s) which lead to secondary EPC(s) (marked with red dashed arrows), and so on. In principle, involvement of more and more EPCs in the networking means more severe disease and progressive functional loss. Total 91 EPCs were identified in etiopathogenetic networking triggered by various etiological factors (Kovač 2012, 2013, 2015)

## SYNERGISTIC COMORBIDITY CROSS TALK: DISEASE „A” AGGRAVATES DISEASE „B”

Clinically, comorbidity has been defined as “any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study” (Feinstein 2015). Statistically comorbidity was defined as „the presence of separate illnesses in the same patient at a frequency greater than would be expected by chance” (Joshi 2017). Coexistence and co-development of two or more diseases is an increasing clinical reality (Vetrano 2019, Nicholson 2019). Prevalence of multimorbidity was estimated 55% up to 98% in general population over 60 years of age (Marengoni 2011, Makovski 2019).

According to algorithmic analysis/resynthesis two diseases in the same body are expected to synergize in etiopathogenesis. For simplicity, one can imagine that the EPCs of the two parallel diseases may happen to be of the same type, and thus the morbidity and mortality should be higher in those cases of those two coexistent diseases. The synergy/adding up effects at the EPCs level

would additionally trigger the synergy/adding up effects at the network level. In table 1 there are listed 20 published pairs of the index diseases (conditions marked with “B”) which are worsened by the comorbid state/disorder/disease (conditions marked with “A”). For example, selenium and zinc deficiencies increase the COVID19 mortalities (Majeed 2021, Jothimani 2021, Joachimiak 2021). These facts at clinical levels at present time are not fully explained at etiopathogenetic pathways and EPC-level. Reduced protective reactivity in those deficiencies, and, on the other side, sanogenic therapeutic effects of supplementation (Alexander 2020) support the assumption of their permissive role in natural antiviral reactivity. In table 1 there are examples of comorbidity diseases which aggravated different index diseases. For example, the body status of obesity synergizes with the incidence of mountain sickness (San Martin 2017), breast cancer (Goodwin 2013) and male breast cancer (Keiman-Borker 2017). Diabetes mellitus contributes to incidence and severity of acute ischemic stroke (Akhtar 2018), acute kidney injury (James 2015) and lower extremities arterial disease (Nativel 2018).

**Table 1.** Disease “A” worsens disease “B”. Examples of natural synergism of etiopathogenesis of one disease/disorder/condition with the etiopathogenesis of other disease/disorder/condition reported in biomedical literature

Etiopathogenesis of disease/condition - “A”	Etiopathogenesis of disease/condition - “B” synergized by the “A”	Reference
Obesity, overweight	Acute mountain sickness	San Martin 2017
Adolescent obesity	Male breast cancer	Keinan-Borker 2017
Obesity	Breast cancer	Goodwin 2013
Advanced age and related pathologies	Increased COVID-19 mortality	Chen 2020
ACE2-hyperexpression conditions*	Increased COVID-19 sensitivity and mortality	Fang 2020, Zuin 2020
Selenium deficiency	Increased COVID-19 mortality	Majeed 2021, Moghaddam 2020
Zinc deficiency	Increased COVID-19 mortality	Jothimani 2020, Joachimiak 2021
Diabetes mellitus	Acute ischemic stroke	Akhtar 2018
Diabetes mellitus	Acute kidney injury	James 2015
Diabetes mellitus	Lower extremity arterial disease	Nativel 2018
High salt intake	Arterial hypertension	Frispli 2012, Ma 2015
Reduced potassium intake	Arterial hypertension	Stone 2016, Aburto 2013
Atrial cardiopathies	Cryptogenic stroke	Yaghi 2017
Atrial fibrillation	Thromboembolism	Huang 2018
Arterial hypertension	Cardiovascular diseases	Soliman 2017
Arterial hypertension	Acute kidney injury	James 2015
Heart failure	Acute kidney injury	Gudoorkar 2019, Vilacorta 2008, Ronco 2019
Chronic diseases**	Chronic disease anemia (CDA)***	Gangat 2013
Anemia	Acute heart decompensation	Caughy 2014
Heart failure	Anemia	Westenbrink 2008

Abbreviations: COVID-19 - Corona Virus Disease; ACE - Angiotensin Converting Enzyme;

\*ACE2 expression is upregulated by ACE-inhibitors, thiazolidinediones and ibuprofen.

*Diabetes mellitus* increases the ACE2 expression, as well.

\*\* Including chronic infections, autoimmune disorders, chronic renal insufficiency, malignances, etc.

\*\*\* Synonymically called „Anemia of chronic inflammation”



Some pairs of diseases show mutual both directions harmful effects. Anemia and heart failure aggravates each other (Caughy 2014, Dunlay 2018, Vilacorta 2008). In these cases, due to reduced oxyphority there is an additional demand on hemodynamic system to maintain a tissue oxygen supply. Thus, the etiopathogenesis of the index disease of „acute heart decompensation” is accelerated by the additional function demand caused by comorbidity condition of anemia (which may be of any etiology (Caughy 2014, Dunlay 2018). In the opposite situation, index disease of „anemia” is aggravated by the heart failure as comorbidity state due to both substrate (macronutrients, micronutrients) and oxygen delivery reduction (Vilacorta 2008). In addition horizontal communications among tissues, via cytokines, chemokines, myokines, (...etc.), may contribute to a synergistic comorbidity pathologies (Duggal 2019, Arnoldussen 2014). Those simultaneous cross talks via myriads of tiny contributions may be responsible for reactivity loss synchronization in mutually harmful comorbidities (Hughes 2020, Ruan 2020).

## ANTAGONISTIC COMORBIDITY CROSS TALK: DISEASE „C” PREVENTS/ELIMINATES/IMPROVES DISEASE „D”

The second type of hypothesis is a mutual antagonism of the two disease, and thus their beneficial effects to the patient’s condition. Namely, one would expect that in some cases comorbidities should be mutually protective, as well. It is a clear-cut expectation and assumption that comes from the etiopathogenetic framework and EPCs-networking patterns. In table 2 twenty index conditions are listed with reported antagonism by other comorbidity disease. Those paired diseases have a non-identical etiologies, and yet they show mutual protective/healing properties. Monogenic heritable disease of cystic fibrosis protect individuals against tuberculosis (Maindl 1987, Crawford 1972) and secretory diarrhea caused by *V. Cholerae* and by *E coli* (Quinton 1983); measles reduces incidence of nephrotic syndrome (Janeway 1948); schistosomiasis is protective against malaria caused by *Plasmodium falciparum*, etc.

**Table 2.** Disease “C” attenuates disease “D”. Examples of natural antagonism of etiopathogenesis of one disease/disorder/condition versus the etiopathogenesis of other disease/disorder/condition reported in biomedical literature

Etiopathogenesis of disease/condition - “C”	Etiopathogenesis of disease/condition - “D” antagonized by the “C”	Reference
<i>Giardia duodenalis</i> parasitosis	Bacterial mediated intestinal diseases	Manko 2017, Manko-Prykhoda 2020
Schistosomiasis ( <i>S haematobium</i> )	Malaria ( <i>P falciparum</i> )	Lemaitre 2014
X-linked agammaglobulinemia	Lymphoma caused by Epstein-Barr virus	Faulkner 1999
Cystic fibrosis	Tuberculosis	Meindl 1987, Crawford 1972
Cystic fibrosis	Secretory diarrhea ( <i>V Cholerae</i> , <i>E Coli</i> )	Quinton 1983
Embryo/fetus-mother ABO.-incompatibility in pregnancy	Rh-sensibilization and Rh-hemolytic disease	Levine 1943, Ascari 1969
Intermittent fasting	Insulin resistance	Mattson 2018
Caloric restriction	Metabolic syndrome	Normandin 2017
Caloric restriction	Verbal memory loss	Witte 2009
Caloric restriction	Tumor growth and immunotolerance	Petriciola 2016
Inherited chemokine receptor allele <i>CCR5delta32</i>	AIDS	Stephens 1998
P-antigen deficiency ( <i>pp-phenotype</i> )	<i>Erythema infectum (parvo-virus B19)</i>	Young 2004, Brown 1994
Individuals with Duffy negative blood group	<i>Plasmodium vivax</i> malaria*	Bray 1956
Measles	Nephrotic syndrome	Janeway 1948
Ketogenic diet and severe caloric restriction	Seizures	Swink 1997
<i>Thalassemia major et minor</i>	Malaria ( <i>P falciparum</i> )	Weatherall 1948, Haldane 1997
Ascariasis ( <i>A lumbricoides</i> )	Malaria ( <i>P falciparum</i> , <i>P Vivax</i> )	Naher 2002, Naher 2011, Stefani 2012
Malnutrition	Cerebral malaria	Naher 2002
Hepatitis G	AIDS	Tillmann 2001, Xiang 2001
Hepatitis A	Hepatitis C	Deterding 2006

Abbreviations: CC - chemokines; AIDS - Acquired Immunodeficiency Syndrome

\*Those individuals are susceptible to other types of *Plasmodia* infections and diseases

Additionally, there are examples of comorbidity diseases/disorders/conditions which improve different index diseases. For example, caloric restriction was shown to improve metabolic syndrome (Normandi 2017), verbal memory loss (Witte 2009) and it reduces the tumor growth (Petriciola 2006).

Despite complexity of human body physiology in initiation, development and outcomes of disease antagonistic comorbidities cross talk of two diseases can be considered as a sort of natural experiment at the level of human population. Etiopathogenetic antagonism may be seen as the mutual inhibitory interplay at disease pathways and the EPCs, that improves body reactivity and clinical status. Such natural experiment proves the concept and emphasizes importance of integration of knowledge related to whole body reactivity and reconsideration of relevant reductionistic data and their contributions within the whole-body reactivity.

## CONCLUSION

Interpretation and understanding of complexity, variability, nonlinearity of human health and disease may be guided towards integration by Sokolić's principles and Koshland's pillars of life. Disease pathways and etiopathogenetic clusters (EPCs) are useful tools and natural pathophysiological elements for monitoring the disease processes. They form networks which are responsible for the reduction of reactivity during the disease. Networking gets triggered by various etiologies. Overlaps of one disease network with the network of other simultaneous disease causes mutual interferences. These interferences may be synergistic, and thus it leads to a more severe disease condition. On the other side, antagonistic interaction of etiopathogeneses of the two diseases may lead to improvement and/or prevention. Searching of literature reveals multiple examples of various disease comorbidities. 20 example pairs of each type (i.e., disease worsens the other disease, versus, disease improves the other disease) are outlined in this paper.

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