Exploring Biocomplexity in Cancer: A Comprehensive Review

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Abstract

Living objects have complex internal and external interactions. The complexity is regulated and controlled by homeostasis, which is the balance of multiple opposing influences. The environmental effects finally guide the selforganized structure. The living systems are open, dynamic structures performing random, stationary, stochastic, self-organizing processes. The selforganizing procedure is defined by the spatial-temporal fractal structure, which is self-similar both in space and time. The system's complexity appears in its energetics, which tries the most efficient use of the available energies; for that, it organizes various well-connected networks. The controller of environmental relations is the Darwinian selection on a long-time scale. The energetics optimize the healthy processes tuned to the highest efficacy and minimal loss (minimalization of the entropy production). The organism is built up by morphogenetic rules and develops various networks from the genetic level to the organism. The networks have intensive crosstalk and form a balance in the Nash equilibrium, which is the homeostatic state in healthy conditions. Homeostasis may be described as a Nash equilibrium, which ensures energy distribution in a "democratic" way regarding the functions of the parts in the complete system. Cancer radically changes the network system in the organism. Cancer is a network disease. Deviation from healthy networking appears at every level, from genetic (molecular) to cells, tissues, organs, and organisms. The strong proliferation of malignant tissue is the origin of most of the life-threatening processes. The weak side of cancer development is the change of complex information networking in the system, being vulnerable to immune attacks. Cancer cells are masters of adaptation and evade immune surveillance. This hiding process can be broken by electromagnetic nonionizing radiation, for which the malignant structure has no adaptation strategy. Our objective is to review the different sides of living complexity and use the knowledge to fight against cancer.

Keywords

Complexity, Networks, Small-World, Genetic Mutations, Self-Organizing, Self-Symmetry, Energetic Balance, Entropy, Nash Equilibrium, Games, Evolution, Cancer, Therapy

1. The Biological Regulation—Homeostasis

Living systems are open, dynamic structures performing random, stochastic, self-organizing processes. Together with the space arrangement, they create a temporal self-similarity [1] and follow the dynamic equilibrium in homeostasis [2]. The temporal self-similarity forms an intrinsic self-time of the living objects [3].

The openness of the biosystems is sensitive to environmental influences, which trigger some internal processes keeping homeostasis in the human body Figure 1. Adynamic hierarchical structure characterizes the biosystems.

The hierarchy is not one-directional. Every level interacts with all others, allowing the physiological control to react to all the environmental challenges, keeping homeostasis stable. The living system forms dynamic interactions between the various parts (like molecules, cellular compartments, cells, tissues, and organs), ensuring the spatiotemporal control of homeostasis and balancing multiple opposite regulatory feedback. The promotion and inhibition are activated in parallel "like

twins" in the homeostatic balance [4]. The vibrant "competition" of suppressor-promoter pairs have an essential role in the homeostatic balance dynamic regulation Figure 2. The chemical principle governs the balance of the promoter-suppressor pair in the complex equilibrium of homeostasis like the Le Chatelier-Braun principle: a perturbation in the system in equilibrium has an opposite effect of the perturbation, balancing the equilibrium.

Promoter suppressor balance forms a transition probability instead of strict determinism. The transition depends on the overall conditions and their fluctuations.

While these pairs may not have the same "promoter-suppressor" terminology used in genetics, they serve similar balancing functions. Here are some examples:

1) Agonist ↔ Antagonist. In physiology, agonists are molecules that activate a receptor or cellular response, while antagonists are molecules that inhibit or block the receptor or response. For example, neurotransmitters and their receptors often have agonists and antagonists that help regulate neural signaling.

2) Activator ↔ inhibitor: This pair is similar to the genetic promoter-suppressor concept. Activators enhance a specific process, while inhibitors hinder or slow it down. For instance, enzymes can have activators and inhibitors to control their activity.

3) Stimulator ↔ Repressor: In various biological contexts, stimulators promote a particular response, while repressors dampen or reduce that response. Hormonal regulation often involves stimulators and repressors.

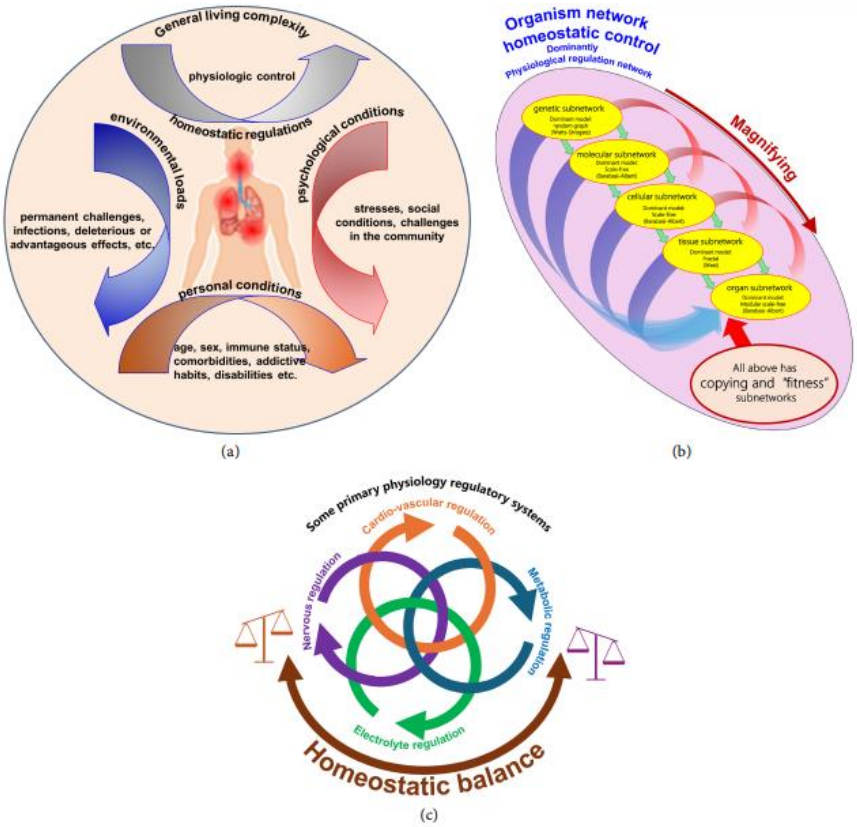


Figure 1. Physiologic networks in human living complexity.

a) The external and internal impacts induce processes to keep equilibrium in the human body.

b) The organism network has various interdependent complex subsystems, which could have different evolutional principles (random, scale-free, copying, fitness) and produce hierarchical networking.
c) The homeostatic balance controls physiological regulatory systems, which are also interconnected and deeply connected to the subnetworks in (a). The four physiological feedback loops shown regulate the most important feedback loops, but these are not alone; six more have multipurpose systematic effects, and further regulatory loops exist with less complexity.

4) Pro-inflammatory-Anti-inflammatory: In the immune system, pro-inflammatory molecules (e.g., cytokines) promote inflammation as part of the immune response, while anti-inflammatory molecules (e.g., cytokines and prostaglandins) help resolve inflammation and maintain tissue homeostasis.
5) Excitatory-Inhibitory: In neuroscience, excitatory neurotransmitters and receptors promote neuronal firing and signal transmission, while inhibitory neurotransmitters and receptors suppress neuronal activity.

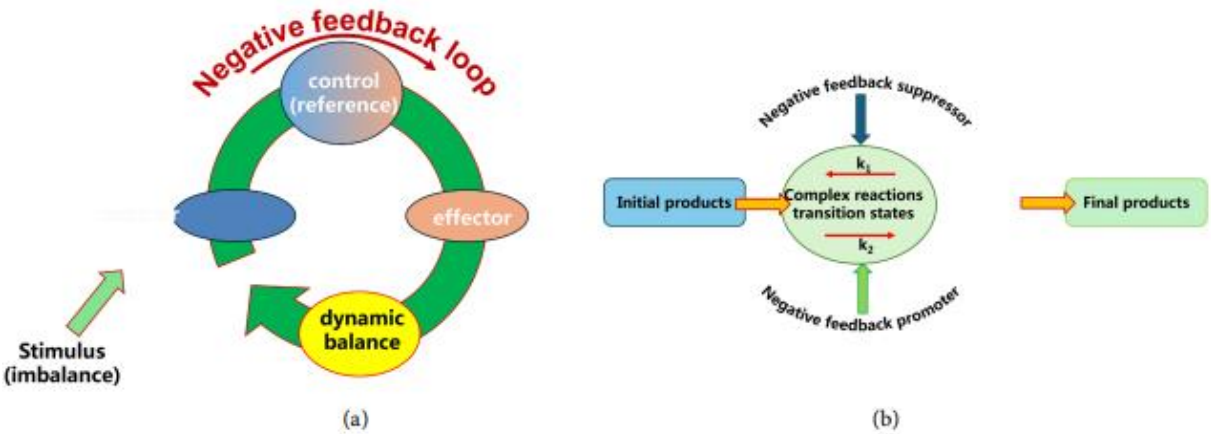


Figure 2. The feedback mechanisms (a) the negative feedback loop controls the dynamic balance. (b) The dynamic balance of the suppresser and promoter effects defines the equilibrium through transition states

We use the promoter-suppression effector-pair in general meaning. The promoter-suppressor negative feedback balance typically refers to a regulatory mechanism within biological systems where specific molecules or genes act as promoters to increase the expression of a particular gene. In contrast, others act as suppressors to inhibit that expression. The goal is maintaining a dynamic equilibrium or balance between these opposing forces. Both effectors in dynamical equilibrium (promoter and suppressor) evaluate the cost/benefit ratio and fluctuate around the optimum for both when the cost of further steps is higher than the benefit of the result. The negative feedback process regulates the cost/benefit ratio.

The negative feedback in every promoter-suppressor balance makes fluctuations Figure 3. The fluctuations appear even in the simplest molecular bonds, where the temperature and the bond

strength oppose and balance. In chemical reactions, the two-way reaction direction represents the opposing driving forces. The biological processes are more complex, and the overall negative feedback processes tune the equilibrium. The fluctuations are "chaotic" [5], [6] which means that no deterministic temporal prediction of the subsequent opposing steps exists. The chaos in physiology has a special meaning [7]. The "constrained randomness" [8] is usual in physiology, and its study is a valuable tool to understand its mechanisms as well as recognize the deviation from "normal".

By the essential fluctuations around the equilibrium, the life is on the "edge of chaos" [9] [10]. It has a self-organized criticality [11], which is widely used in biological perspectives [12] [13]. The control of the regulation compared to the reference value is ensured by the feedback mechanism within a predetermined range. The system does not require precise adjustment. The proportional feedback mechanism driving forces on the opposing actors realize an automatism, keeping the system in equilibrium. Fuzzy logic may model it. It evaluates the "degrees of truth" instead of the "true or false" choices [14].

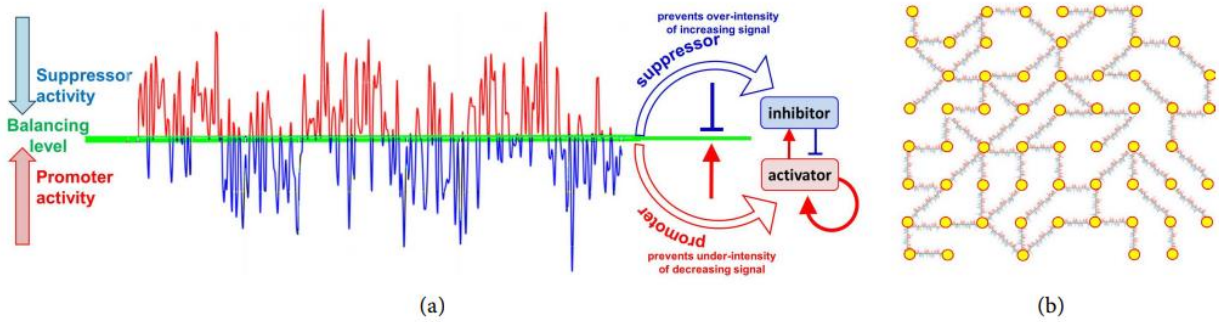


Figure 3. The permanent dynamic changes cause a never-rest situation. (a) The dissipation consumes the energy, while the energetically open conditions drive the process. When a promoter increases the growth of the signal (energy, info, etc.), the opposing suppressor becomes active to avoid the overshot of the change. The same happens with the suppressor, which is limited by the promoter in the opposite direction. The opposing activity of the promoter-suppressor pair creates fluctuation around the equilibrium level. (b) The connections between the various parts dynamically fluctuate at all levels of the organizational structure (A hypothetical part of the network connection is shown for clarity).

The fuzzy logic directs the homeostatic control of the entire spatiotemporal arrangement of the living systems. This distribution results from the strongly interconnected negative feedback loops, which regulate the balances in all ranges, stabilizing the dynamic system. Each step of dynamic equilibrium is based on the interconnected balance of suppressor-promoter pairs of the regulatory homeostatic process [15]. The complex dynamic equilibrium drives the living regulative activities from genomic to global adaptation to environmental challenges [16]. The time-dependent processes realize the observed signal with a probability as the actual exposition from the possibilities of the fluctuations of the measured signal. These phenomena request a stochastic approach instead of deterministic descriptions [17]. The deterministic reductionism can mislead the research. The stochastic approach is fundamental in biological dynamism [18] [19]. The vivid dynamic equilibrium forms a stable system with active fluctuations in the predetermined range. This self-regulatory system is complex; every process in the system is involved in multiple interactions and embedded in the network of numerous other functions. The homeostatic

equilibrium induces compensatory strategies against every external influence and activates backlash mechanisms. In this way, any drug therapies, together with their targeted effect, cause an opposite compensatory process, developing resistance against the impact of the drug. This simple rule appears in chemistry (Le Chatelier-Braun principle) and fits the Darwinian selection rules. Reacting to the environmental challenges, the regulative activities are tuned by the complex dynamic balance of the living systems from genomic to global adaptation [16]. Instead of conventional deterministic changes, the dynamic events request a stochastic approach, introducing a time-dependent probability of the processes [17].

Biological complexity is a well-proven fact based on physical and physiological principles [20] [21]. Darwin developed a non-deterministic idea through the theory of evolution that introduces probability in biological species development, having uncertainties as consequences. This idea drives biological development everywhere. The environment drives the Darwinian selection and whose the easiest adaptability to the changed conditions. This is a complex mechanism. Contrary to the complexity of human organisms, the paradigm of modern medical research does not deal with the consequences of complexity [22]. Misinterpreting the complexity, some research uses homeostasis as a static framework for effects [23]. The biological dynamism is fundamentally stochastic [18]. The observed complex phenomena cannot be studied in isolated parts [24]. "A living thing cannot be explained in terms of its parts but only in terms of the organization of these parts" [25]. Living complexity has a logical incompleteness [26], discovered in the mathematical application a century ago [27]. Incompleteness in biology means there are no answers to valid questions, which have complex feedback with self-reference, like the "classical" question: what was the first, the hen or the egg? The answer needs evolutionary thinking, and determinism is not applicable. A similar question in the complex homeostatic stability has no direct answer: what existed first: the promoter or the suppressor? The feedback needs developmental, non-deterministic, and non-linear consideration. The complex system is regulated and controlled primarily by negative feedback loops with Darwinian law, having incompleteness, which is a challenge in theoretical biology [28].

2. Self-Organization

Self-organization characterizes the living organism in its spatiotemporal arrangement at every level of the structure [29] [30]. The self-organized complex feedback processes compensate for the extended number of perturbations and secure the system's stability. The self-organizing procedure is defined by the spatial-temporal-fractal structure, which is self-similar in space and time [31]. The self-similar construction of the living objects statistically repeats the same building block (template), connects them with forming a network [16], and creates a self-similar harmony. Self-similar harmony is dominant in life. The self-organized hierarchical clustering has robust stability against internal and external noise. The constructional template repetition makes a similar structure by some orders of magnitude magnification. Self-similarity characterizes the time set of different interactions and energy exchanges.

The random unicellular life structure vividly functions when the cells have plenty of energy for their life, so their environmental dependence is marginal. However, when the living mass grows, the resources become limited, and the cells must organize themselves to survive. The organization

needs to "sacrifice" a part of the individual energy budget in exchange for the possibility of joint survival. The driving force of the limited resources to the direction of collectivity is observed in starving slime molds [32] [33]. The collective actions help distribute the available, limited energy intake to share between the parties on their needs and, in this way, satisfy the group's survival. Those cells that give up their independence and are connected to other cells by work division share the available resources and thus ensure their survival. Collectivity balance appeared in evolution [34]. The size of the colonies of cooperative cells is matter [35]. The accidentally created more adaptive subjects have evolutional advantages and start the complexly self-organized building of the living structure. The goal of group formation is cooperation, which optimizes energy input. The driving force of the limited resources to the direction of collectivity is observed in starving slime molds [32]. Such collective strategy appears not only in the case of living subjects but also in animal or human societies, where self-organized connections help individuals survive environmental fluctuations. Interestingly, the grouping protective survival strategy is more general than the energy-sharing triggers, which is a driving force for the collective actions of some prey animals against the predators. Artificial intelligence models show the advantage of collectivity [36] and among many others in ant colonies [37] [38].

2.1. Energetics

The transition state at the biological reactions creates significant fluctuations in the transition energy. The system tries to keep the utilized energy as low as possible, but the independent "environmental" energy quanta nondeterministically interact and make the regulation process noisy. Homeostasis guarantees the local stability of living objects and compensation for the effects of internal and external noises. The homeostasis is a dynamic process adjusted to the energetically open system. The dynamic processes are self-organized [30], driving the system's evolution [39] in a non-linear way [29]. The dynamic complexity ensures the robust stability of living objects following homeodynamic processes rather than a homeostatic one. It continuously interacts with its environment, cross-transporting energy, materials, and information, and during these processes, both parties have dynamic modifications.

The environment and the entire organism with its subunits (like cells, tissues, and organs) have open energy trade with each other in the living system. The self-organized process with self-similar rules develops fractal structures [40], which characterize the clustering of the cells well distinguished from the pathological forms [41]. Homeostasis optimizes the energy expenditure of the system, maximizing its efficacy. The efficacy maximum means a minimal dissipation loss of working energy. Entropy production increases energy dissipation loss, meaning the energy is manifested in heat instead of creative structural utilization. Entropy characterizes the system's disorder, referring to the lost energy already being used for disordering the structure. The activation energy (molar enthalpy) of a process linearly depends on the molar entropy [42] [43], connecting the invested energy and limiting its efficacy by the non-active energy part.

Healthy homeostasis maintains a stable internal environment and minimizes entropy production, trying to limit the increase in entropy with regulative feedback, efficient resource utilization, and adaptation and repair. The idea of the minimum entropy production in a system was introduced by Prigogine [44], [45]. His theorem was generalized in a dynamic equilibrium of stationarity [46], trading with the stability of the stationer systems [47] [48]. Normal cellular division and organization in a balanced energy flow inherently involve some entropy production generating metabolic heat.

Cancer cells have metabolic alterations and higher entropy production than normal cells. The excess entropy production results from uncontrolled proliferation, leading to increased energy expenditure and disorganized growth patterns, developing a higher lesion temperature. Cancer is a typical entropy producer with its uncontrolled proliferation and the energy demand to supply it. The disrupted protein function by genetic alteration and the modified cellular regulation contribute to disordered energy flow and increase entropy production. Network structure plays a crucial role in determining the overall entropy production of a complex system. Efficiently arranged networks with optimal flow paths can facilitate processes with lower entropy generation compared to poorly connected ones. However, the minimal entropy production is not a universal law and doesn't always apply to all complex systems. Specific system properties and external constraints can influence the dominant principle governing entropy production.

Homeostasis and minimal entropy production are intricately connected concepts that shed light on how living systems maintain stability and efficiency amidst the constant flux of the world. Homeostasis maintains the internal environment in dynamical equilibrium, while entropy production is a universal trend toward disorder. Homeostasis minimizes entropy production. Living systems constantly defy the tendency towards increasing entropy by actively maintaining homeostasis. The balancing process involves negative feedback loops. The balances are used judiciously to maintain vital processes, take care of the energy and matter resources, and minimize waste and dissipation. Some note worthy examples of how homeostasis works with minimal entropy production.

- The metabolic enzymatic processes in pathways are arranged and regulated to optimize energy extraction and minimize waste production.
- Sweating and shivering are examples of how the body minimizes entropy production by maintaining a stable internal temperature.
- The immune system identifies and eliminates foreign invaders, preventing cellular disorganization and maintaining tissue integrity.
- Systems with homeostasis can adapt to changing conditions and repair damage, preventing entropy from gaining a foothold. The interplay between homeostasis and minimal entropy production offers a fascinating lens to understand living systems' remarkable resilience and efficiency.

The minimal entropy production, which is connected to the optimal use of energy resources, is slightly connected to the Darwinian evolution principle, which governs the long-term evolution of the species. The species that can manage minimal entropy production have advantages due to better energy utilization.

Network structure plays a crucial role in determining the overall entropy production of a complex system. Efficiently arranged networks with optimal flow paths can facilitate processes with lower entropy generation compared to poorly connected ones. Specific network properties, like modularity, redundancy, and feedback loops, can contribute to minimizing entropy production. Modular systems can isolate inefficiencies, while redundancy ensures continued function despite disturbances. Feedback loops can regulate processes and optimize resource utilization, reducing waste and entropy generation.

In a simple energy exchange, the energy intake linearly depends on the mass, so the mass of the living object linearly defines the metabolic energy. This exchange distributes the metabolism equally and proportionally to the metabolic mass. The most straightforward situation for average distribution is when the cells are entirely independent, with no interaction, and the energizing nutrients are unlimited. Such a situation happens in well-supported cell cultures, where the medium has plenty of nutrients for all the cells. All cells metabolize equally, so the individual metabolic rate is equal, independent of how many cells are involved [49]. The specific energy usage (the basal metabolic rate (BMR) of a unit mass (M) of the living object B BMR M 0 ∝) shows the efficacy of the energy utilization in the resting state. Experiments clearly show the difference between individual satisfaction with energy supply and collective optimization. The in vitro cell cultures provide plenty of nutrients in the supporting medium where the cells are living. In this case, there is no cooperation and no self-organization among the cells, so their intaking metabolic power is equal, B0 = const. independent of the number of cells involved in the experiment [49]. Optimizing energy distribution is unnecessary when the environmental conditions may be unlimited to ensure the nutrients for life energy. There is no self-organizing; all cells participate equally in the unicellular setup. The challenge of individuality starts when the resources are limited. The limit of natural resources soon begins to develop a competition between the neighboring living fellow-subjects for the resources. Similar individuals, having the same "body mass" compete intensively with relatively equal chances to win. However, when a more massive object appears by accidental variation of cellular contacts, its chances to adapt to the challenges and survive increase. The equality of the participating cells is broken; they specialize in various tasks in the collective, which mainly depends on their position in the structure and participation in the energy and information transfer. The adaptation maximizes the use of resources, like when starving the object maximizes the material payoffs [50], as we had seen in molds where the starting multicellularity realized the available maximum.

Living objects have enormous heterogeneity. Their parts are not similar in their form, shape, size, structure, behaviors, properties, physiologic parameters, living preferences, etc. Due to these features being universal for living creatures, space and time similarities of living organisms ("allometry") are observed [51]. Various concepts of metabolic studies may use allometry [52]. However, the selforganizing of their integrity and the energy sharing of the metabolic process is common, giving the possibility of allometry [53]. Irrespective of their evident and enormous differences, self-organized self-similarity is general for all kinds of life realization. In the complex self-organized order of cells, the power intake in unit mass ($BB0$) follows an allometric scaling [54].

$$B_0 \propto \frac{BMR}{M} \propto M^{-\frac{1}{4}} \qquad (1)$$

It is a clear tendency: when the mass is more significant (the unit has more individuals cooperating), the requested basal metabolic rate decreases the specific energy utilization and efficacy. The reason for these relations is rooted in self-organizing and self-similarity [55]. Allometry has a role in self-organized evolution [56]. In this way, the allometry preferring the larger mass for optimal use of the available energies has an additional preference in the evolution process. Optimal energy management may limit cellular tumor thermogenesis. Suppressed thermogenesis reduces entropy production. This change is one of the reasons the animals with large masses, despite having more cells and a higher probability of cellular divisions, have less cancer prevalence [57]. Homeostatic

control and minimal entropy production optimize energy utilization, which could have a pivotal role in cancer prevalence. Random genetic mutations offer a linear expectation of cancer incidence but have a power law function, indicating that several sequencing mutations lead to cancer. The minimal entropy production, interspecies allometry, and homeostatic control show living systems' adaptive strategies and intricate organization, including the deviations leading to cancer. Deviation from physiological optimization and resource utilization could hint at the mechanisms of cancer development. The disruption of the optimizing principles (including the deviations in the homeostatic regulation) contributes to malignant conditions. It builds a therapeutic strategy to restore homeostasis and minimize entropy production in dysregulated states. The predictability of gene interactions could be a great addition to personalized medicine with a better estimation of the risk of the malignancy and increase the treatment efficacy. Scaling, a power function dependence like (1) is fundamental in living processes. The relative changes are generally proportional in a complex system [58]. Consequently, when a parameter $\wp$ depends on the parameter g, then $\left(\frac{\Delta \wp}{\wp} \text{ and } \frac{\Delta g}{g}\right)$ are proportional by an empirical factor z:

$$\frac{\Delta \wp}{\wp} = z\frac{\Delta g}{g} \tag{2}$$

Integration of (2) we get

$$\wp = qg^{z} \tag{3}$$

The deviation from the randomness is connected to the self-similarity of the living objects [59] [60], and the fractal geometry may describe the assembly of the biological structures [61]. The self-similarity of the fractal geometry is connected to the scaling behavior. A large category of living systems and processes may be described with scaling laws [62]; even the metabolic power and its fluctuation behave universal scaling [63]. The living organism has to grow in collective harmony, and the relative growth of parts must be proportional [64], so the basic scaling (2) is well applicable to growth processes. The scaling allometry focuses on the ideal nutrient supply and homogeneous resting state in stationary equilibrium where the metabolism of the unit mass becomes optimal. With the growing number of "individuals," nutrition starts to be limited. When the nutrients are scarce, like, in many cases of cancer development, the scaling power differs. In this stage, some cooperation features at least perish the weak or internal members of the "colony", appear, and the suboptimal alimentations develop increased demand for intensive transports.

The bio-signals have self-similarity and correlate with their earlier value at time-lag τ . Autocorrelation is how the signal correlates with its earlier values. The τ characteristic of temporal self-similarity originates from the repeated regulatory signals in the organism. The autocorrelation carries information about the dynamism of the microstates, showing the preferences of possible variants of the molecular reactions [65]. The homeostatic balance defines autocorrelation of the set of signals of biological changes [66] [67]. The induced collective noise of homeostasis has particular noise when the noise power and the frequency have a reciprocal relation (1/f noise) [68] [69]. The self-similar signal is one of the hallmarks of collectivity, well described in fractal physiology [70], [71], it is a time-fractal in the living organism [72]. The time fractal makes organized "chaos" in physiological signals [5], which is a stochastic phenomenon, and knowing its origin, it is entirely manageable [73]. The 1/f noise is like a "song" in the dynamic system [74], and it can be

corrected when the cancer deviates its "tune" [75]. The song's harmony also describes the biosystems in popular literature [76]. The cancer genetic sequencing generations have a 1/f power-law distribution of mutant frequencies [77] [78], showing a self-organized adapting behavior of gene organization. This 1/f "noise" has a high complexity with the highest information content and best memory (autocorrelation) [79] Figure 4.

2.2. "Democracy" and "Autocracy" in the Living Complexity

The self-similar self-organizing process is collective [80] and relates to the scaling [81]. Terminals of a circulatory system that supply an organ adjacent to the cells are equivalent and supply the cells with the same functions equally. Collectivity subordinates the individual needs to the groups and optimizes the energy distribution for the best survival with the lowest energy consumption. This energy-sharing works like a kind of democracy [82]. This "democracy" is regulated by general biophysical rules, governed by the competition for resources in micro and macro phenomena. The various species fit the evolutional development when the given living object adopts the different environmental conditions, develops a multicellular structure with individually characteristic "democratic" distribution of the available sources, and forms species-character of the homeostatic regulation.

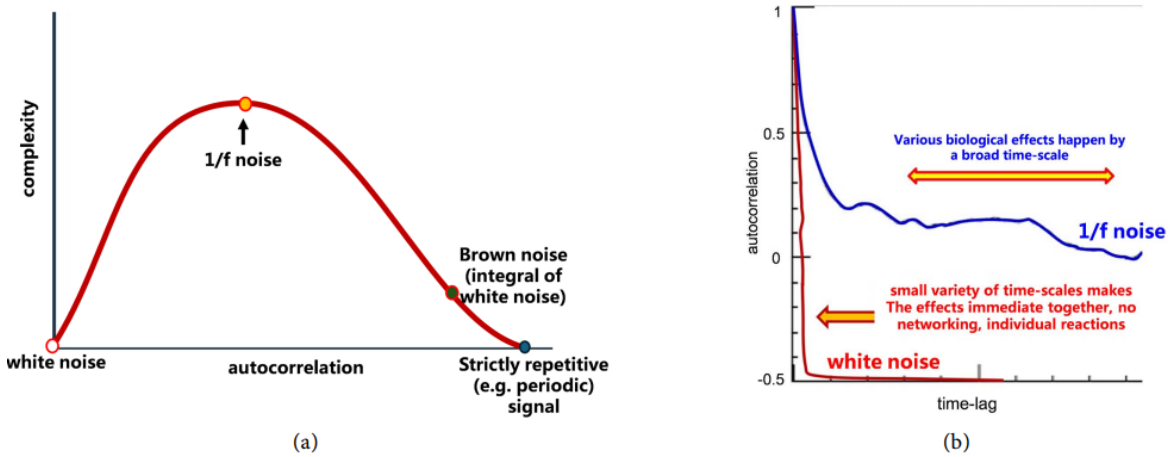


Figure 4. The autocorrelation function is related to the self-similarity parameter of an integrated time series. (a) The complexity is maximal in 1/f noise. Complexity gradually vanishes at lower or higher autocorrelation values. (b) The autocorrelation vs. time-lag.

The unified principle of developing the homeostatic control and the unified dynamic internal "democracy" found the interspecies allometric scaling of metabolic rates versus mammalian body size [83]. This general complex phenomenon also justifies the validity of the comparative study of cancer in the species [84] [85] [86], giving a tool to study comparative oncology [87]. The "democratic" idea looks more general than the energy supply. The "democratic" distribution characterizes the information distribution, too [88].

The cells use different amounts of energy depending on their function, so the "democratic" distribution of energy between all cells equally obviously does not work. However, another kind of "democracy" works: the cells have well-controlled and balanced energy part depending on their function in the collective. The structure of the entire system optimizes the energy distribution. The

energy balance realizes a variation of the transport network supplying the demand variations. This directly involves the fractal structure of transport not being unified as a structure in the system but formed by homeostatic demands.

The balancing of autocracy and democracy characterizes the evolution when the "selfish gene" [89] tries to dominate all processes, but the environment-dependent self-organization requests democratic decisions. Otherwise, the process blocks the complexity of the system. The competition with two actions to cooperate or defect well approaches the biological interactions [90]. Such alternating action strategies are sometimes more relevant than synchronous processes [91]. The balancing of autocracy and democracy characterizes the evolution when the "selfish gene" [89] tries to dominate all processes, but the environment-dependent self-organization requests democratic decisions; otherwise, the process blocks the system's complexity. Complex homeostatic control shows the balance of feedback mechanisms. The negative feedback interactions are tuned to keep the actual state comparative accurate value, determined by the self-organizing system. Nevertheless, the system is energetically open, which is the mandatory condition for life, so the positive feedback mechanisms compulsively push some reactions, determining the metabolic processes in both directions (catabolism and anabolism). These obligatory constraints indeed derive an autocratic line when the probability of responses drives the defined direction of the processes. Such necessary autocratic strategies can be beneficial for exerting control over asymmetric interactions [92]. The regulatory networks have many commonalities from microbes to humans [93]. The regulation of collaboration and cooperativity massively boosts the democratic character with overall genomic complexity. The complex regulatory effects tend to a partnership supporting the democratic structure, whereas others regulate primarily in isolation, in a more autocratic fashion [94]. The degree of collaboration forming autocracy in opposition to democratic behavior is a particular characteristic of the complexity of the open living systems.

The meaning of living efficacy had changed drastically due to a shortage of resources and other existing inequalities. These turn mass-production strategy into survival preferences, and later, more complexly, not only individual survival but the inheritance of successful capabilities to the next generation, transferring the appropriate genetic code. Due to its energetical openness, the individual living object needs internal operative distribution of the incoming energy. Its parts' survival determines the object's overall survival, so optimizing energy distribution is crucial. The "democracy" of distribution is based on a strict competition for the species' survival, making evolutionary selection. The selection mechanisms are strict "autocrats" [95], eliminating the non-optimal creatures; only the best, the most adaptive to the environment, could survive. In this way, an overall driving force appears in the background. The general systems theory [96] was one of the early efforts to show the complexity of open living systems, focusing on the deep embedment of its processes in environmental interactions. Due to the environmental actions, the physical laws work well to explain the evolutionary processes [97]. Life is a collective phenomenon together with its environmental conditions. The energetically open living system intensively interacts with its environment, exchanging molecules and various thermodynamic and electromagnetic parameters. Simply put, our focus differs from living motility to energy transfer. Instead of the monkey's migration through the forest, we concentrate on how the forest migrates (flows) through the monkey, like the environmental energy source.

The environmental determinant is flexible. The developing living organization could counteract and balance the ecosystem in a dynamic interaction, so the situation manifests the complexity again: the environmentally determined evolution drives the self-organization, which in feedback guides the evolution [98].

2.3. Morphogenesis

The mutual interactions of malignant cells with their host tissue form a frame of cancerous development. The generation of the developed forms (morphogenesis) sculpts a single cell into the intricate and diverse shapes of living organisms, independent of their size and lifestyle, equally applicable to such extreme masses as drosophila and whales. Morphogenesis is one of the fundamental pillars of developmental biology. Morphogenesis drives the development of forms in biology [99] with an activator and inhibitor generating repetitive patterns from differential diffusivities and nonlinear reaction terms. Morphogenesis intricately balances genetic instructions and environmental influences. Genes provide the blueprint, but external factors like nutrients, light, and mechanical conditions can influence an organism's shape. The morphogenetic interactions and its acting "field" and "waves" were first proposed as early as 1904 [100]. The morphogenetic field is a group of cells responding commonly to discrete, localized biochemical signals. Shared interactions can develop morphological structures. morphogenesis became one of the focuses of developmental biology. The fractal description of the spatial irregularities of living objects allows for objectively comparing complex morphogenetic differences [101]. The morphogenesis may reprogram the cells, like malignant cells transforming to normal when transplanted to a healthy environment [102] [103], and vice versa. The specific mechanisms of morphogenesis vary greatly depending on the organism and the organ or tissue being formed. Morphogenesis is essential for the proper functioning of organisms.

The complexity of cancer has structural and dynamic components that destroy the healthy homeostatic spatiotemporal arrangement of the host tissue. The developing microenvironment of malignant cells forms a "morphogenetic field," which evolves the structure described by fractals [104]. Generally, scaleinvariant, and statistically self-similar structures form fractals. The irregular, non-self-similar structures could be affine fractals when they can be characterized with a power function or are not fractals, mostly with exponential character [105].

Morphogenetic models with diffusion-like and cellularly inductive methods [106] showed that the frequency of the activated avalanches vs. the number of activated genes in the random gene model has a power-law of 1.25 power, so the high frequency of the avalanches is paired with a low number of activated genes. The development of a small number of spatial patterns was observed to be linked to the minimal genetic networks. The reaction-diffusion system (activator-inhibitor balancing Figure 5) depends on the concept of a chemical prepattern developing before cell fate decision and emphasizes the ability to induce pattern formation. It works like a promoter-suppressor from an allegedly homogeneous initial state. The reaction-diffusion model in morphogenesis [107] could be extended with electrodiffusion in cancer development [108]. Analysis of morphogenesis needs self-organization principles and network analysis of biological structures.

The morphogenetic field can show a significant loss of the intercellular connections with redistribution of the E-cadherin/$\beta\beta$-catenin complexes. Still, the shape modification could force a

transition of the metabolic pathway and rearrange the healthy oxidative signals [104]. This reversing reconnection of the nonconnected malignant cells could be observed in experiments [109] [110], where the electro-diffusion was used in the reaction system.

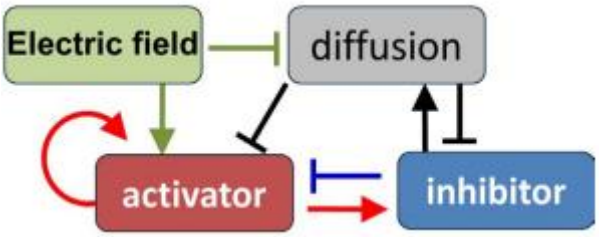


Figure 5. The activator-inhibitor balance is usually modified with diffusion and electric field. These effects are intensively interacting.

2.4. Networking in Living Objects

The complex network may be interpreted where each element is a node, and relationships (connections) between them are represented with links. A graph may represent the network, where nodes are vertexes connected with edges. There are different concepts to build up a network, and these characterize various actual structures.

Erdos-Renyi's evolution of random networks [111] [112] is widely used as a starting reference for network development. Here, each pair of nodes is connected with p probability. It randomly makes approximately pN(N -1) number of links. The Erdos-Renyi (ER) network graph is a discrete distribution function with binomial character [113], which is well approximated by the Poisson distribution. The nodes have an average degree ⟨k⟩, which exponentially decreases at high ⟨k⟩ , showing that the significant deviation from the average is rare. Here, the clustering coefficient is constant, and the network size (N , the number of nodes) is a power function of the mean path length $(\mathcal{L})$: $N \propto \mathcal{L}^d$, so $\mathcal{L} \sim \ln(N)$. ER follows a power-law which is characteristic for all self-organized and self-similar structures (like many biological phenomena) [114].

The links between the network nodes have the primary role in the interactions, information exchange, and transport. A milestone model was elaborated by Watts and Strogatz [115], showing possible extra connections (shortcuts of the links) in the complex social network, which forms "cliques" where the links describe relations between the nodes. The Watts-Strogatz model (WS) [115] starts with a regular lattice, where each node is connected to its nearest neighbors. The network development rewrites the connections randomly, breaks "old" links, and creates new ones. Increasing the rewiring probability $\wp$ from zero, the developing network begins to have a characteristic value of random long-range connections $(\mathcal{L})$, creating a small-world (SW) network, with shortcuts lowering the access path between nodes. The SW networks have local clustering, which is more likely to be connected to other nodes in their near vicinity and have high global connectivity also because of the high probability of being connected to nodes that are further away. SW structure has high local clustering yet a short average path length between any two nodes, supporting direct information transfer in the entire network. The SW feature transition is a crossover, not a phase transition. It depends on the network size N and the degree of disorder $\wp$. The earlier calculation showed the size of the crossover is $N^* \sim \wp^{-2/3}$ [116], which is later corrected to

$N^* \sim \wp^{-1}$ [117] [118]. The existence of the SW was experimentally proven [119] [120] and later, its first theoretical examination gives a hint of how it forms the "small world" in society.

The increasing rewriting connections of the regular network construct regulatory subnetworks. In this way, both the local and global properties of the subnetworks depend on $\wp$. Small-world networks exhibit a property where the characteristic path length between nodes remains relatively small. In low clustered ($\wp \approx 1$), nearly entirely random SWs, the path length is typically logarithmic of the size: $(\mathcal{L}) \sim \ln(N)$), and so $N \sim e^{\mathcal{L}/\mathcal{L}_0}$ where $\mathcal{L}_0$ is a characteristic length. The exponential dependence of N from $\mathcal{L}$ does not follow the power law, so the small world is not self-similar. The critical insight from the WS model [115] is that it demonstrates how random rewiring of a regular lattice can lead to networks with small-world features, where the path length between nodes is $(\mathcal{L})$ short on average, even in large networks. When the radius of the graph $(\mathcal{R})$ is defined by the average distance between the highest degree node (central node, hub) and other nodes, then define the size of the graph as it has d diameter, when $\mathcal{R} \leq d \leq 2\mathcal{R}$ [121]. In the partially random networks like the SW, we have $d \sim \ln(N)$, which slow increase of d by even large N justifies the small world behavior. The small-world nature is crucial in understanding various real-world networks, like such complex systems as social networks and the internet, neural networks, power grid, computational power, epidemic disease spreading, synchronicity, cellular automata, genetic algorithms, and complex biological processes, etc. where local and long-range connections exist, allowing for efficient communication between distant nodes. The small-world concept [115] is well-proven in the epidemiology of infectious diseases [122] [123] [124]. It has a role in the human genome, too [125]. Small-world networks strike a balance between local redundancy and global reach. High clustering promotes information sharing within tightly knit communities, while short path lengths enable efficient signal transmission across the entire network. This combination can reduce transmission costs compared to regular lattices or random networks. Information propagates quickly through localized clusters, minimizing the need for long-distance transmissions and associated energy expenditure. Entropy production could be minimized through small-world features. It may reduce the signal transmission overhead. Efficient information flow reduces energy consumption for transmitting signals and maintaining network connectivity. This translates to minimizing entropy production associated with signal transmission processes. SW enhances the robustness of the network. The redundancy of clustered connections provides fault tolerance. Damage to individual nodes or links is less likely to disrupt global signal transmission than less-redundant networks.

This resilience minimizes entropy production by preventing cascading failures and the need for extensive repair processes. Small-world networks often exhibit dynamic rewiring capabilities, helping adaptive optimization. Links can be formed or removed based on usage patterns, allowing the network to adapt to changing conditions and optimize its efficiency over time. This dynamic optimization can further minimize entropy production by eliminating unnecessary connections and streamlining information flow. However, the relationship between small-world networks and minimal entropy production is context-dependent. The specific network dynamics and operating conditions can influence how small-world properties minimize entropy production. Besides small-world characteristics, other network features can also contribute to minimizing entropy production. Factors like modularity, feedback loops, and node heterogeneity can all play a role. Another network-developing concept was established: the Barabasi-Albert (BA) model, [126]). This

network chooses the nodes by their high degree [114], which are more likely to be attractive than other nodes. The driving force of this process is the Matthew effect of accumulated advantage [127]. The attractive motifs are the high degree are more likely to be valuable to other nodes; they may have access to information or resources that other nodes need; they are more likely to be trusted by other nodes. The distribution of the degree of vertices essentially deviates from the Poisson distribution. It has a scale-free, selfsimilar power-law degree distribution. The probability p (k) that a node has k links is:

$$p(k) \approx c \cdot k^{-\gamma} \qquad (4)$$

where c is a normalizing parameter and α is the degree of the exponent. The $\mathcal{L}$ probability of a highly connected node in BA is statistically more significant than in ER graph. A relatively small number of highly connected nodes (hubs) often determine the BA networks. The BA model is scale-free, characterized by the degree exponent $\gamma = 3$. The power law is scale-free because of the change of scale of k in (4) by g scale factor; the power function does not change: $(gk) \approx c\cdot(gk)^{-\gamma} = c\cdot g^{-\gamma}\cdot k^{-\gamma} = c'\cdot k^{-\gamma}$. The BA network has no inherent modularity, so its clustering coefficient is also constant. The complex systems intensively use scale-free behavior in their networks' large category of spatiotemporal arrangements [128]. The power-law probability theorem has some problems in its evaluation, namely by the value of the exponent α in (4). In the case when $2< \gamma < 3$, the distribution has a finite mean value and infinite variance, but when $1 < \gamma \leq 2$, both its characteristic values are infinite [129]. Most biological networks have a power degree $2< \gamma < 3$, for example, $\gamma = 2.2$ for Escherichia coli. The BA [130] describes many real-world networks well, even complex ones like the World Wide Web and social media. It is a valuable tool for the generation of real biological networks having a few fundamental biological processes [131] [132] [133] [134]. The $\gamma > 3$ range shows the ~ ln(N) similar to the random networks. When $\gamma = 3$ (and the lower cut-off the distribution is larger than 2), then $d \sim \frac{\ln(N)}{\ln(\ln(N))}$, when $\ln(\ln(N)) \gg 1$ [135].

(Note, in case the lower cut-off distribution is 1, the d ~ ln(N) [136].) A new kind of network development was also introduced for ultrasmall-worlds [137], where $\gamma = 1$, named "Mandala network". This deterministic development uses shells of the network. The nodes belonging to a given shell have intra-shell and inter-shell links, with the nodes with the highest degree in the center. The network development is realized by a recurrently expanded addition of a new shell. The mean shortest path in this network is below 3, and remains constant when ln(N) became higher than 10^4 (ln(ln(N)) ≈5).

Various scale-free features of the spatiotemporal structure of living systems appear, like the neural network of the nematode worm C. elegans [138] [139], protein interactions [140] and robust genetic stability [141] of yeast, organizing of the metabolic networks in various species [142], and its connection to the survival certainty [143]. Most proteins interact with few partners, forming a significant proportion of proteins serving as 'hubs', which attract interaction with many collaborator proteins [144]. The degree of separation of the small-world in yeast proteins could be calculated by knowing 1379 proteins in 3.6 average degrees [144]. Hence the d degree of separation gives the small-world $3.9^d = 1379$, so $d \cong 5.95$. The random protein removal from the scale-free networks does not change its stability, but the network is susceptible to the targeted removal of hub proteins. For example, removing a hub-encoding yeast gene causes significantly higher lethality than removing a non-hub [145] [146]. These observations turn our focus from molecular

biology to complex, network-based molecular networks. These mainly molecular subnetworks could overlap in biosystems, and study them by various complex network grouping like metabolic, transcriptional, and protein interactions [134], or according to other aspects. The system is completed with other systemic subnetworks governed by homeostasis. These systemic regulatory action subnetworks (systemic circles like the cardiovascular, respiratory, nervous, lymphatic, endocrine, etc.) regulations, together with the immune surveillance, and many other systemic actions (like renin-angiotensinaldosterone system, kallikrein-quinine system, hypothalamic-pituitary-adrenal axis, etc.) or the subsystem of different organs., all are interconnected and representing enormous complexity of the human body. Small-world formation is a common rule in these networks [115]. The small world involves a logarithmically growing diameter [147]. The formation of the giant component of the random network characterizes the percolation transition, which is close to the random graph [148] (Note that the infinite cluster below the percolation threshold is a fractal, but it behaves as a normal d-dimensional object above this level). A real space renormalization of a network produces smaller groups unifying the next-neighboring connections as a domain, using as a node of the renormalized network, similarly made like in the renormalization of the spin-lattice (like Ising model) systems [118], forming a small-world network.

The scale-free scaling rule is applicable in medicine, founding a new scientific approach, the "network medicine" [149]. Network medicine helps to identify, prevent, and treat diseases. This field uses network topology and dynamics to categorize diseases and develop medical drugs. A concept of disease network (diseasome) was introduced [150], focusing on the connection of diseases through shared genes, having common genetic roots, and linking the o of illness comorbidity to molecular networks [151], recognizing that the genes associated with the same disease are located in the same network neighborhood [152]. The method is a practical combination of extensive data mining [153], using as genomic database [154], and synergizing network medicine with biomedical data to optimize the clinical impact. The hubs have a central role in the connections of BA networks, but when it is damaged and cannot perform their connective functions, the network could collapse. The strong hub-connected networks have low resilience against malicious attacks. The weak links stabilize the system and reduce its vulnerability [155]. The weak ties can act as "bridge nodes" linking different network parts. They play a crucial role in shortening the paths of connection between the nodes that might not have direct connections. When a hub links in networks, it expresses relations between the nodes, which we call strong when it is an equivalence relation. The equivalence relation means that if A is mutually linked to B, and B is linked to C, then A also linked to C. The links within the network are weak if the link does not realize an equivalence relation. The equivalence relation classifies the elements in sets. The pivotal role of weak links in the strength of the network means that when the information spreads only among links that interact strongly with each other (belonging to the same equivalence subnetwork), it does not get out of the given equivalence class. The transfer may occur through fewer than six connections if the set has a single equivalence class. The weak links make the information spread broadly and transfer quickly, which was first recognized in the societies [156]. The weak links stabilize the network, which, without them, is easily broken into independent subnetworks and loses the broad information exchange. The equivalence class (strong links) is an important center, but weak links are necessary to stabilize the complete network [155]. The perturbations and information may spread effectively in the week-link stabilized complex network, which can tolerate more disturbance by perturbations in the system. The importance of the weak links in biological systems is well recognized [157]. The weak links connect hubs and may uncouple these modules when the overall homeostatic equilibrium regulates it to keep the balance [158]. The

weak links are pivotal in such complex molecular processes as protein folding [159]. The multilevel connections effectively reduce the information pathways in the networks, including the biological complexity, promoting the formation of small-worlds.

Many SW networks have robust hub-centered construction without power function in its size, forming exponential dependence from the path lengths $(N \sim e^{\mathcal{L}/\mathcal{L}_0})$. **Figure 6 (a).** These structures are not organized in fractals. They have strong hub-hub links. These attractive interactions determine the network. In another construction, the hubs are connected through non-hub nodes, forming weak links, which makes the system less compact. The hub-hub interaction is repulsive in these networks. These arrangements have fractal structure $\left(N \sim (\mathcal{L}/\mathcal{L}_0)^d\right)$.

Such networks are self-similar. Many real networks form such arrangements (metabolic and genetic networks, long-range correlated structures, etc.) **Figure 6(b)**. The weak-link networks have real fractal descriptions with solid repulsion of the highest degree nodes (hubs), arranging them dispersed [160]. The fractal architecture makes the system less vulnerable to malignant disturbances. These robust functional modules indicate evolutionary changes in their construction [160]. The deterministic scale-free networks are also self-similar and represent fractal properties [161]. Interestingly, the hardware systems are usually hub-oriented, and the software operation on this hardware has a weaklink structure, like the internet/web pair.

The biological cellular networks may contain various intracellular interaction networks [162]. The basic networks are (1) gene transcription networks [163], (2) protein-protein interaction networks (interactomes) [164] [143], (3) signaling networks [165], and (4) metabolic networks [142] [166]. Additional networks help to better understand intracellular complexity, like cytoskeletal networks, cellular organelle networks, and chromatin networks. The characteristic networks differ in their collectivity from random "democracy" through the hub-driven "rich-get-richer" to the weak-linked, which is self-similarly glued, realizing a "globality" **Figure 7**.

The position of nodes from the view of possible information transfer (possible paths through them) defines the betweenness, which measures the number of paths through a node [167].

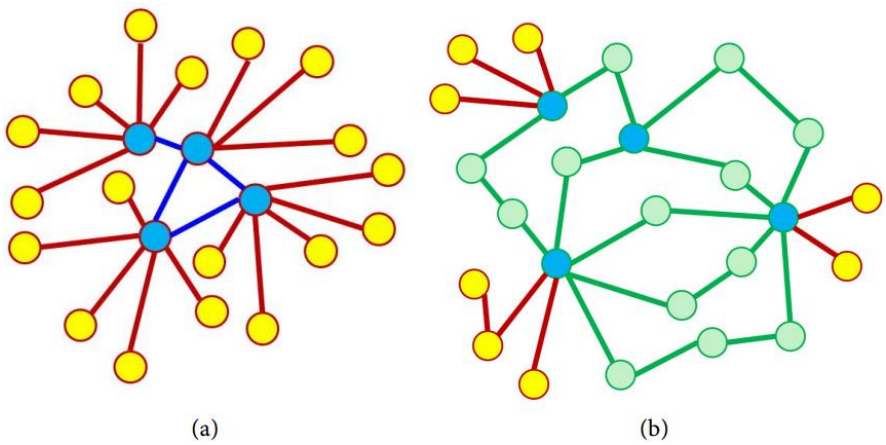


Figure 6. Two basic categories of networks. (a) Compact strong link connections, a hub-driven assortative system with strong hub-hub attraction. (b) Disortative weak-link connections, hubs are not directly connected, strong hub-hub repulsion.

The betweenness centrality measures the relative number of shortest paths through the nodes [168]. The betweenness and node degree do not necessarily correlate. Connecting to the network with low-degree weak links may form central betweenness **Figure 8**. The weak links could strengthen the network with the betweenness parameters. Network disintegration is a phase transition of complex percolated networking, which strongly depends on the breaking of betweenness of some nodes.

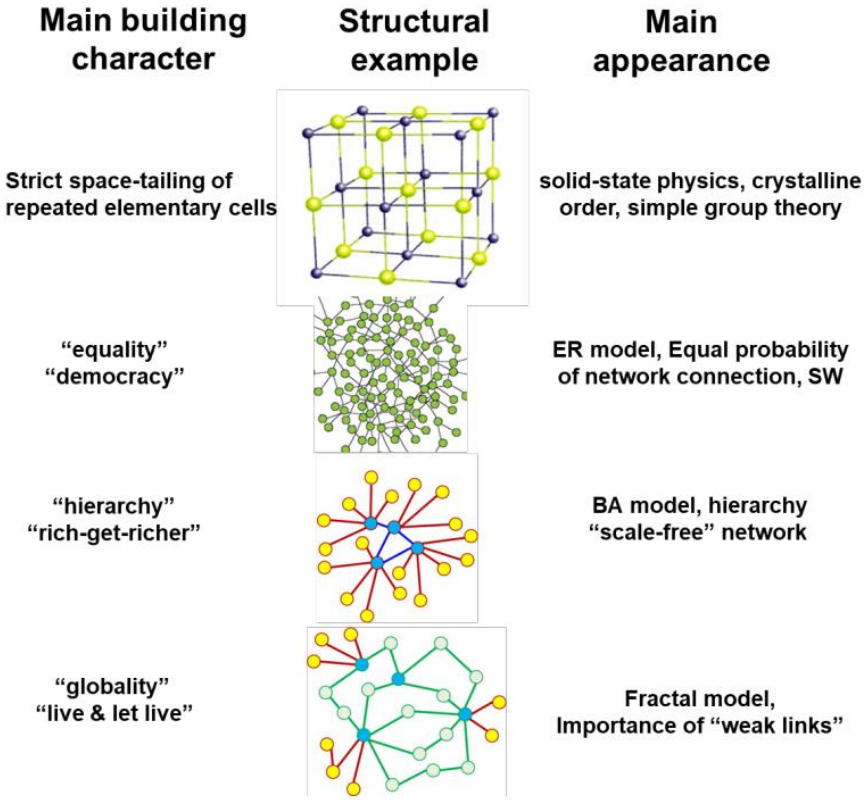


Figure 7. The main categories of the networks could be present in biology. (The crystalline structure is not biological. It is shown only for comparison.)

The biological systems may realize different network constructions, re-presented by graphs:

1) The random graph model, like the WS SW network [115], chooses links randomly and to any nodes **Figure 9**. The natural evolution processes may be described with random networks. The new connections are accidentally developed and remain when they help the system adapt to external challenges and optimize the internal structures. The genetic pool development has frequent smallworld networking [169] [170] and transcriptional networks where the nodes are the genes and the links arrange the up- or downregulation influence [125] [171]. The genome organization has naturally stochastic transcription described by the complex small-world regulatory networks [125].

2) The scale-free arrangement (BA network) [172] clearly shows the dominant content of the high interconnectivity of the molecular interactions in the complex living system **Figure 10**. The network in this model is hub-directed [126], where the links are not randomly chosen. To choose a partner, you need to know how many connections it has with other partners. The choice is optimal when this number is

significant. (The process when the rich get richer.) This hub concept is a general rule in many biological structures and processes, such as in protein-protein interactions, [173] [174]. The networks of biological functions could be functionally separated, having subnetworks (modules) describing the different slightly connected functions, introducing modular cell biology [175]. The modules may have a hierarchy by their functional connections forming hierarchical modularity [176].

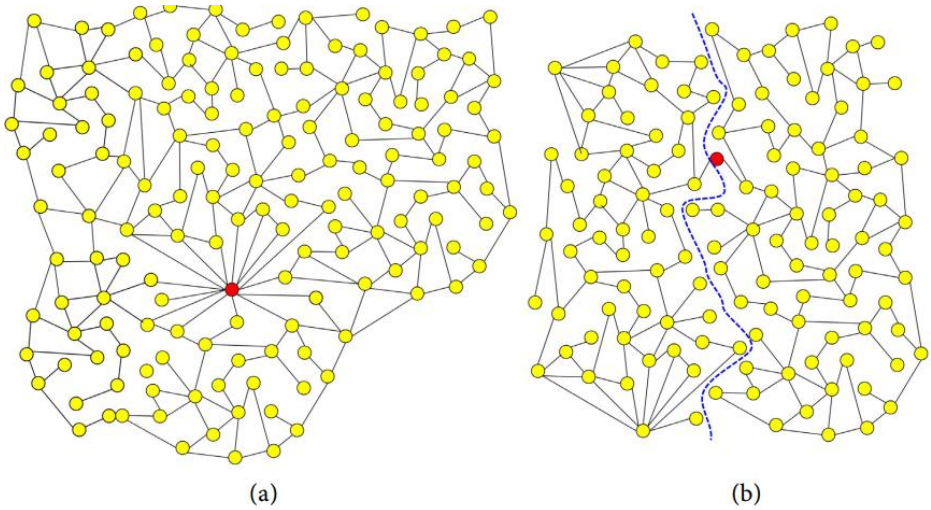


Figure 8. The central betweenness of the red nodes is shown in two different situations.
(a) Central betweenness due to hub position with high-degree node.
(b) Central betweenness of a low-degree node in weak-link position (The dashed line shows two independent network parts connected with only the weak link).

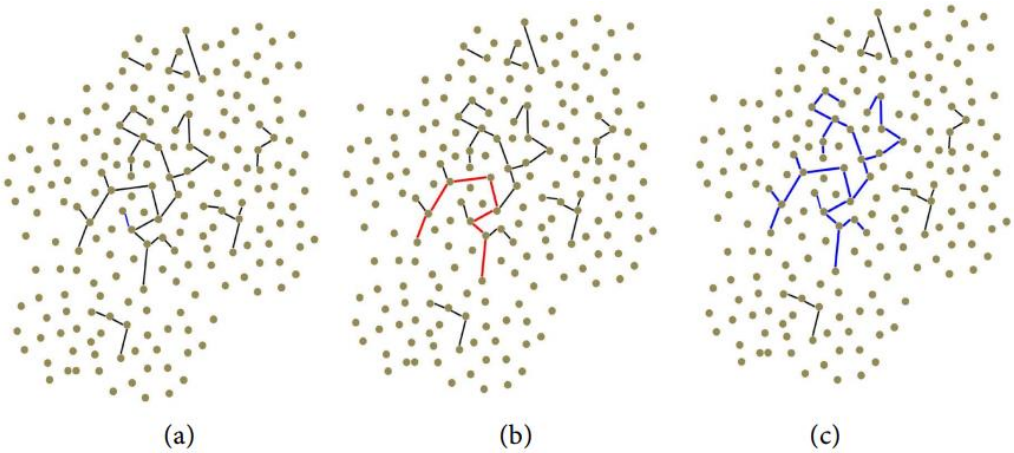


Figure 9. In a stage of a developing ER network, the nodes are randomly linked.
(a) The network in a stage.
(b) The shortest path (red links) between the two nodes. Such link-connection differs by chosen nodes.
(c) The largest domain in the network (blue links.)

3) Copying network model (growing network with redirection) [177] uses a copying mechanism by repeatedly duplicating and mutating existing nodes of the network Figure 11. Copying network models is used to model biological networks, such as protein interaction networks and genetic regulatory networks.

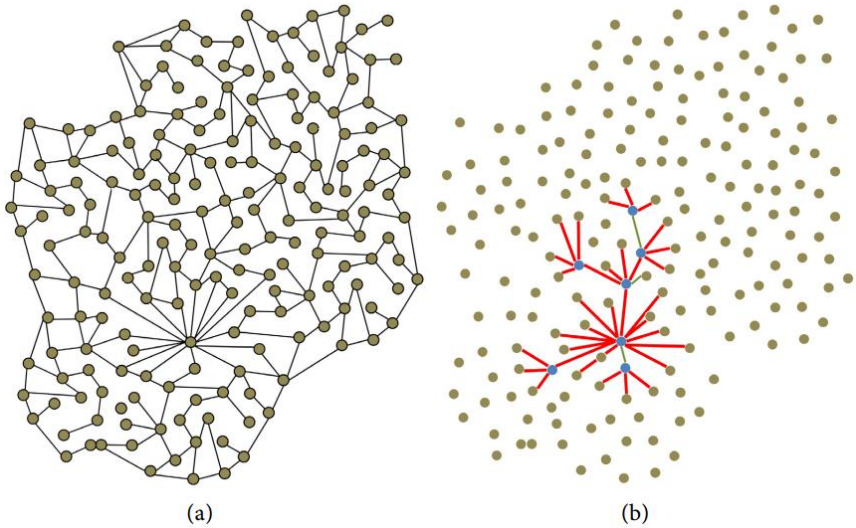


Figure 10. Dominant hub. (a) dominant hub in a complex network. (b) The initial stage of a developing hierarchic network.

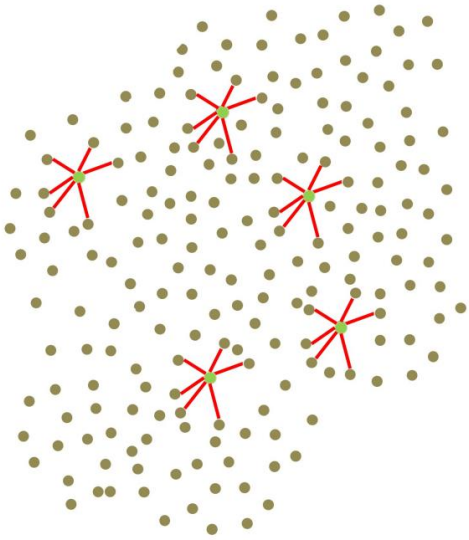


Figure 11. Copying network. The same networking structure appears (copied) in various regions of the network. Copies are the same, but their neighboring area is different, so their role could be different in the developing network.

Genes containing information about how a node in a network should interact with others tend to duplicate in evolution, thus duplicating the edges in the network. Also, preferential attachment networks can not model biological networks well, both because they are not plausible and because several biological networks have power-law degree distribution with exponent $\alpha = \frac{2-\theta}{1-\theta} < 2$ which such preferential network models do not produce where θ is the ratio of the number of the randomly added edges to the number of copied edges [178].

Duplication sometimes is a strategy of resilience. The copying may duplicate mechanisms, functions, structures, and actions [179]. The network's copying is frequently applied in the evolution

of species where the developed new generation subsequently inherits the well-adapting structures and mechanisms. The genetic networks contain many gene-sequence copies in various positions of DNA, but these coding differently because their position differs in the DNA.

4) The intrinsic fitness model develops links between nodes over time depending on the fitness of nodes [180]. Fitness is the nodes' intrinsic ability to attract links in the network, and it varies by node. The most efficient (or "fit") attracts more edges at the expense of others. In that sense, not all nodes are identical to each other. The node fits in this meaning when it ensures optimal conditions to survive the next developmental steps, and in this meaning, it is like the Darwinian selection. In simple cases, fitness optimizes the physical or chemical bonds or the bondphilic-bondphobic conditions (characteristically hydrophilic or hydrophobic, van der Waals ability, etc.) "likable" mechanisms when the nodes are molecules. Fitness is a new parameter for the competition for collecting links in the BA network. In simple cases, the Matthew effect prefers the earlier joined nodes to the network because these have a higher probability of being linked than the newcomer nodes in evolution. But the reality differs [180]. Some newcomers have better positions than others and may quickly collect more links in the developing network. These nodes are fitter than the others. The competition for links makes a difference from the simple hub preference; it creates a multiscaling situation where the fitness may modify the scaling behavior of the network. The Mathew effect, the "rich get richer," can be modified in this scale as "fitter get richer" **Figure 12**.

The Matthew rule and the minimal entropy production have similarities and potential connections. Both concepts involve positive feedback loops where advantages tend to snowball. The Matthew effect posits that those with resources or opportunities attract more, further solidifying their lead. Similarly, systems that minimize entropy production often become more efficient over time, further reducing their entropy generation. Both emphasize the optimization of processes.

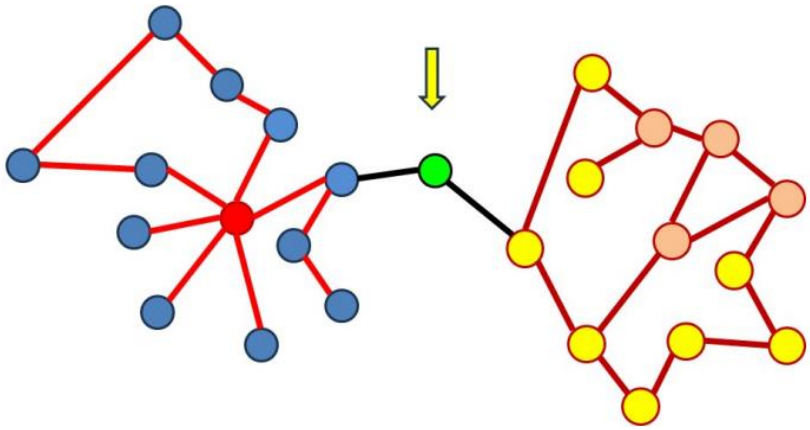


Figure 12. The newly coming node (denoted by arrow) links two independent subnetworks in one energetically preferred step during the network's evolution or two accidental lucky steps when links are created. This node has higher fitness, making it an attractive site to connect to stabilize the system with this starting weak link. These new links have high central betweenness (like **Figure 8(b)**) forming their fitness in further development.

The Matthew effect implies that systems where advantages accumulate become increasingly efficient at acquiring further benefits. Minimizing entropy production is inherently about optimizing

a system's energy usage and reducing waste. Systems that minimize entropy production might be more efficient at allocating resources, leading to situations where they acquire more resources faster than others, aligning with the Matthew effect. The value of a resource or opportunity increases with the number of users in various networks. Minimizing entropy production could lead to more efficient network formation and growth, further amplifying the Matthew effect. Systems that minimize entropy production might be more resilient and sustainable in the long run. This could give them an advantage over competitors in the long term, potentially reinforcing the Matthew effect.

However, the Matthew effect and minimal entropy production have significant differences, too. The Matthew effect primarily focuses on the distribution of advantages, while minimal entropy production focuses on a system's internal efficiency. The Matthew effect can manifest relatively quickly, while the benefits of minimizing entropy production might accrue over longer timescales. The Matthew effect often describes non-equilibrium situations where advantages keep accumulating, while minimal entropy production often refers to reaching a steady state with minimal dissipation.

The connection of interacting network parts fits into a dynamical equilibrium. The biological network development differs by its processing time, too. In the matured biosystems, the network is relatively stable by size; the development is internal, dynamically forming various nodular connections according to the energy, material, and information exchange with the internal and external environments of the system. Most of the network research focuses on the development of networks, studying how the construction of the final giant, dynamically stable network emerges and evolves in time. A network is developing if the probability of the nodes connecting links (vertex connection edges in graph representation) depends on time. Some studies are devoted to this time dependence using random or deterministic models [181]. Network development is time-dependent with the subsequent addition of connected nodes. The BA has no change in the network degree distribution over time. Small changes in fitness parameters could modify the degree distribution [182]. This variant of the BA model uses a simple modification of the "rich get richer" attractiveness, considering the second neighbors of the nodes. The influence of the second neighbors on the realized new link is one fitness parameter, increasing the attractiveness and making a link. However, the interactions with the second neighborhood development of the network deviate from BA [183] when the randomly formed BA network is unchanged underneath. At the same time, the new node builds up the second neighbor connections, rearranging the degree of nodes and modifying the network degree distribution in the region **Figure 13.**

The new node in the second neighbor attraction makes the time-step with new edges to its first and second neighbors. The probability of the choice is proportional to the availability of the first and second links [181]. This second neighbor principle appears in social networks as the connection attraction of the friends-of-friends [184]. The network's local structure with the second neighbors' connections became time dependent. The BA model does not consider the internode mechanisms, so the second neighbors of the target do not influence the newly attached node. This changes with the new model [181], when one more connection is realized than the targeted hub originally had (see **Figure 13(b)**). While the targeted hub has a large number of connections, the degree of the newcomer is nearly the same as the hub. The newcomer, in this way, has high fitness. The second neighbor links make a "gelation-like phenomenon" to the network surrounding the hub, which

modifies the linearity of BA and develops time-dependence at a higher number of the degrees of the network [181].

Some small-world networking has a surprising feature in large complex systems like societies: the "six degrees of separation" principle. It is a concept suggesting that a chain of acquaintances can connect any two people in the world with no more than six intermediate connections [185], [186] forming an ultrasmall-world (uSW). Regular small-world networks exhibit high clustering and short path lengths. uSWs take this efficiency a step further. They possess incredibly high clustering coefficients, often approaching the theoretical maximum while maintaining surprisingly short average path lengths. This extreme clustering creates tightly knit communities where information exchange is highly localized and redundant. It coexists with efficient global signal transmission thanks to "shortcuts" or long-range connections that bridge distant clusters. It was shown that the scale-free networks are uSW in large N, where $l \propto \ln(\ln(N))$, so l is de facto independent from the network size [121].

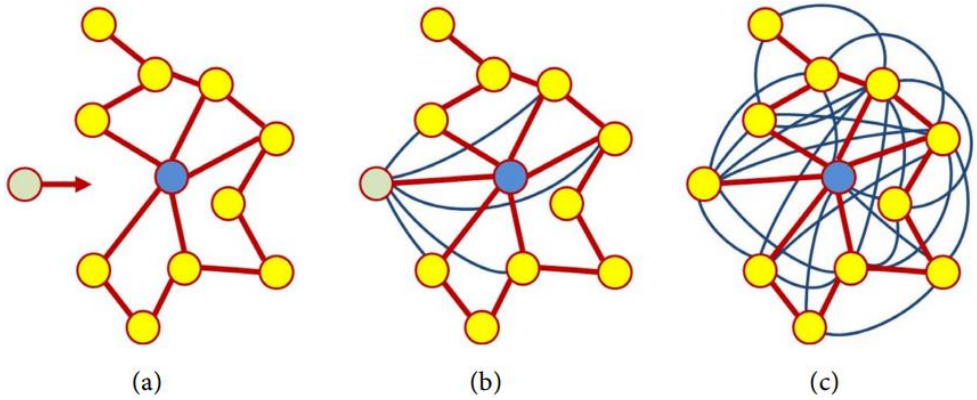


Figure 13. The modification of the BA network. (a) T arriving node to the target node in the ready network chooses the central hub. The network with the first neighbor effect where the driving force is the hub connection. (b) Considering the second neighbors (thin blue lines), make multiple links. It rearranges the degree of the second neighbor nodes. (c) Ultimately, the network may have degrees in addition to the first neighbor links.

The six degrees of separation highlight the amazing interconnectedness of elements within complex networks. It has recently been theoretically proven in social networks [187], which apply to all highly complex network systems. The six degrees of separation idea has been used to characterize the well-connectedness of elements in a complex network. It has many practical applications, ranging from social science to computer science to psychology, physiology, and marketing. The ultrasmall-world network is stable and tolerates any hostile or accidental attacks. The uSW needs a high degree of complexity, different types of connections, and extensive network size, and, of course, it needs percolated networks with no isolated subnetworks. The existing non-percolated subunits are independent, with no link between them to use the six-step connections; however, by development, they could be connected by new links.

The multilevel complexity and the interconnectedness of these levels ensure small-world networking but not uSW. The uSW is not general. It needs special conditions and high complexity with a large-size network. In some cases, the uSW with six degrees of separation appears for living networks, too [188], but usually $d > 6$. For the metabolic network, the observed SW diameter $d \approx$

8.78 [188], which in extended network consideration shows uSW diameter [166]. The calculated average degree of nodes of the substrate graph is ⟨k⟩= 4.76 in N = 275 nodes and the activity reaction graph ⟨k⟩= 9.27 with N = 311, when the most active molecule pairs (ATP-ADP, NAD-NADP, NADH-NADHP) are not included. From here the degree of separation $d_s \cong 3.6$ and $d_r \cong 2.6$ for substrate and reactions, respectively. When the active molecule pairs are included, the values are: $d_s \cong 2.8$ and $d_r \cong 1.7$. The obtained data show that the active molecules and the reactions decrease the degree of separation. The protein-protein interaction network dd has a variation of the network diameter d ≈ 1-8 , with the maximum of uSW at 3 [188].

Studies suggest that the organization of regulatory elements within genomes might resemble uSWs. Genes associated with similar functions often cluster together, forming tightly-knit communities. These clusters are then connected through long-range regulatory interactions, enabling coordinated gene expression across the entire genome. In the process of transferring genetic materials between species (horizontal gene transfer) uSW [189]. A study showed that the gene network that impacts brain wiring has a scale-free small-world topology [190], in which two features may form uSW [121].

The uSW-like architecture could potentially contribute to genetic stability. The redundancy and localized information sharing within clusters might facilitate efficient error detection and correction mechanisms. If a mutation occurs in a gene, its neighbors with similar functions can potentially signal the error and trigger repair processes. The long-range connections between clusters could be involved in propagating epigenetic modifications across the genome, ensuring consistent gene expression patterns and preventing unwanted transcriptional fluctuations. The long-range connections between clusters could be involved in propagating epigenetic modifications across the genome, ensuring consistent gene expression patterns and preventing unwanted transcriptional fluctuations. The modularity and redundancy inherent in uSWs might make genomes more resilient to environmental stresses or mutations. Damage to one cluster might be isolated and contained, preventing it from cascading into broader genomic instability. Hierarchical levels of biological networks have the same massive complexity as society. The various network levels work in tight cooperation and synchrony in a healthy system based on communication and exchange, like direct contact, chemical signaling, and electrical signaling. The primary network levels are in **Figure 14.**

- Molecular and genetic level (the ground on what life starts): Regulate the

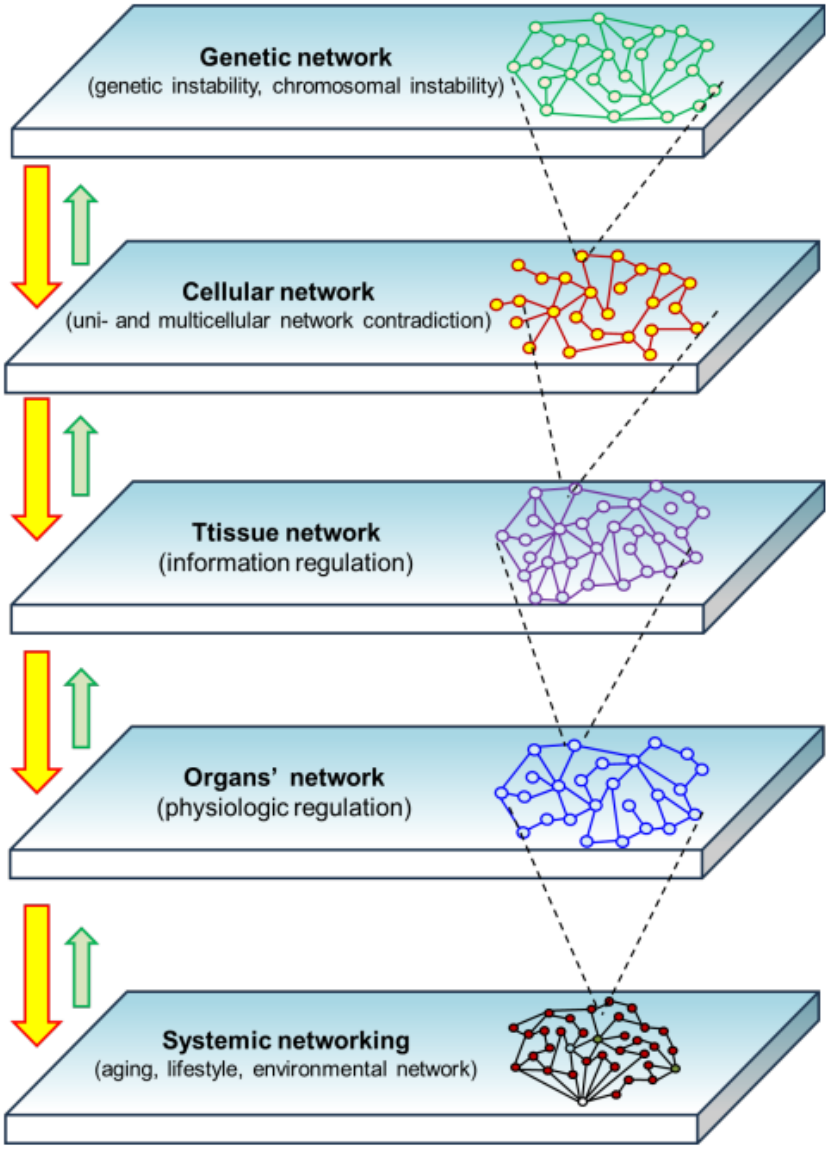


Figure 14. The interconnected networks in the developed living objects.

- Cellular processes with DNA as a blueprint for the above cellular level activities, defined as the transcription and translation processes. Gene products regulate gene expression, as proteins produced by genes can also act as transcription factors, regulating the expression of other genes. This creates feedback loops that fine-tune cellular processes and ensure appropriate responses to environmental cues. While protein-coding genes are crucial, non-coding DNA also plays a significant role in regulating gene expression, can bind to regulatory proteins, and influence the accessibility of genes to RNA polymerase. These regions can bind to regulatory proteins and affect the accessibility of genes to RNA polymerase, further shaping cellular networks. Proteins produced by genes can also act as transcription factors, regulating the expression of other genes. This creates feedback loops that fine-tune cellular processes and ensure appropriate responses to environmental cues. The scale-free networks and genetic robustness are connected [191]. The SW properties of genetic networks can vary depending on the specific network examined and the methodology used.

- Cellular level (the basic living unit): At the most fundamental level, living organisms are composed of cells, which are complex networks of organelles and macromolecules. These internal networks interact through various mechanisms like protein-protein interactions, metabolic pathways, and signal transduction. Different cell types have specific structures and functions tailored to their roles within the organ or tissue. Cells communicate with each other through a variety of mechanisms, including chemical signaling (e.g., hormones, neurotransmitters, other signaling molecules) and electrical signaling to rapidly transmit signals over long distances (e.g., electrical impulses of nerve cells); direct cell-to-cell contacts (e.g., gap junctions, cadherins, mechanical connections). Cellular networks can adjust their activities in response to internal and external stimuli. Feedback loops within cellular networks ensure homeostasis and the maintenance of a stable internal environment. At the next level, the organs function effectively due to the coordinated activities of various cell types.

- Organ level (the special functions): Groups of cells with specific functions form organs, and organ networks exchange nutrients, hormones, and electrical signals, enabling coordinated organ function. For example, the circulatory system networks with the lungs for gas exchange and the digestive system for nutrient absorption. The interaction between the cellular and organ levels in humans is a beautiful dance of microscopic machinery working in perfect harmony to achieve complex functions. Different organs are composed of specialized cell types, each with unique structures and functions tailored to the organ's overall role. Cells within an organ and between different organs communicate through a sophisticated network of chemical messengers. Endocrine glands like the thyroid or pancreas release hormones through the bloodstream to target cells in distant organs, regulating their activities. Cells can also release signaling molecules like neurotransmitters and cytokines to influence their immediate neighbors or cells in other organs. In the nervous system, cell communication happens through electrical signals carried by neurons. Nerve impulses travel along axons, triggering the release of neurotransmitters at synapses, which relay the signal to other neurons or target cells in muscles or glands, coordinating rapid responses throughout the body. The circulatory system, primarily the bloodstream, acts as a highway for essential nutrients like oxygen and glucose to reach individual cells from organs like the lungs and intestines. Conversely, waste products like carbon dioxide and metabolic byproducts are transported by the blood to organs like the lungs and kidneys for excretion. Ultimately, the interactions between cells at the cellular level orchestrate the proper functioning of organs at the organ level. The correlation of the organ's activity can be measured with various electric signals of diverse physiological organ systems [192], well-coordinated by the brain. The organ network has fractal properties, and the scaling index could be regarded as a sensor of the healthy operation of the living system [193].

- Organism level (the system): Individual organisms interact with their environment through various networks. Nervous systems facilitate communication within the organism, while sensory organs and muscles connect the organism to the external world. Additionally, interactions with other organisms form ecological networks, like food webs and symbiotic relationships. Organs constantly communicate with each other, sharing vital information through a complex web of messengers. Like the orchestra's conductor, hormones travel through the bloodstream, influencing the activity of distant organs. Additionally, nerves act

as communication cables, sending electrical signals to coordinate rapid responses. No organ operates in isolation. The digestive system breaks down food, fueling the muscles and energy for the brain. The lungs deliver oxygen to every cell, while the kidneys filter waste products from the blood. This intricate dance of give-and-take ensures the organism's overall well-being. Maintaining a stable internal environment is crucial for survival. Organ networks work together to achieve homeostasis, regulating factors like body temperature, blood sugar levels, pH balance, etc. The human body is remarkably adaptable, and organ networks play a crucial role in responding to internal and external stimuli. When exercising, the heart pumps faster, lungs increase respiration, and muscles demand more oxygen, all orchestrated by the organ network to meet the organism's needs. Communication between organs isn't one-directional. Feedback loops ensure fine-tuning and adjustments. For example, rising blood sugar levels trigger the pancreas to release insulin, which signals cells to absorb glucose, bringing blood sugar back down. The living complexity projects different networks into each other, forming a "network of networks" [194], and builds up the complex system with the interactions of these: tells are the building blocks, tissues are "communities," and organs are collaborative teams. In addition to the complexly interacting networks, the overall physiologic regulation and immune surveillance ensure the dynamic balance that characterizes a healthy organism. The projections of these to each other are not a one-way street; they are heavily modifying each other to build the final homeostatic system equilibrium. The genetic network, consisting of gene interactions, is a blueprint for cellular function. This blueprint is "read" and translated into action through gene expression. The genetic structure shows a well-organized fractal in the chaos-game representation [195]. However, the blueprint is not rigid. The nurture with random processes may modify it with mutations.

Each cell within a tissue or organism can express a unique subset of genes, forming a distinct cell type with specific functions. This diversity in gene expression patterns creates a network of cells. Therefore, the genetic network projects onto the network of cells through the selective activation and repression of genes in different cell types. Specific regulatory mechanisms, like transcription factors and signaling pathways, interpret the genetic blueprint and dictate which genes are "turned on" in each cell. Cellular signals and environmental factors can feed back and influence gene expression, impacting the overall network dynamics. Additionally, epigenetic modifications and non-coding RNAs can further finetune gene expression within specific cell types, adding another layer of complexity to the projection process. Each cell type's unique gene expression patterns define its function, impacting the overall operation of the tissue it belongs to. Different tissues within an organ work in concert through direct cell-to-cell interactions and secreted signaling molecules. This coordinated activity ensures the organ's specific function. Organs interact through various channels, like the circulatory and nervous systems. This communication allows them to coordinate their activities and maintain organismal homeostasis, the delicate balance of our internal environment. These projections are not static. Cells within tissues can adapt their gene expression in response to local signals and environmental changes, fine-tuning their functions and influencing organ behavior. The blueprint within the cell network guides the development of organs from embryonic tissues and even contributes to tissue regeneration throughout life. When cell functions or communication within the networks are disrupted, it can lead to malfunctions in tissues and organs, contributing to various diseases. The various organs interplay to maintain the stability of the human organism. Organs constantly monitor and adjust their activities with negative

feedback based on the needs of the entire organism. Many vital functions have redundant and backup systems. Organs communicate nerve impulses and signaling molecules, maintaining the physiologic regulation of the system. Many organs can adjust their operations to meet changing demands.

2.5. The Game—Fight for Resources

Resources for life are rarely unlimited. The participating organisms individually fight for resources, but in starving conditions, they cooperate to survive [34]. Both competitive and cooperative games offer valuable training grounds for individuals and groups, shaping the evolution of traits and behaviors that contribute to survival and success. The competitive games select the advantageous traits. The competition pits individuals against each other, favoring those with features that give them an edge. Over time, natural selection makes these advantageous traits more common in the population. The constant pressure to outdo competitors drives development. The skills used in play can be applied in real life, increasing survival and reproductive success. The cooperative game is a typical strength in numbers; achieving the goals in the group would be impossible alone. Cooperative behaviors that benefit the group increase the chances of survival for all participating units, indirectly promoting genes associated with those behaviors. Cooperation requires effective communication, coordination, and regulation. Some cooperative games involve sacrificing individual benefits for the good of the group. A strategic "cost" must have a bigger payoff over time. This can select genes associated with collective behavior, leading to the evolution of more cohesive and supportive organisms.

Game theory is often used to describe both competing and cooperating activities. The game theory deals with strategic exchanges, a mathematical analysis of decision-making counting the cost-benefit balance. It looks like a perfect calculation tool for the problems of competition and cooperation when the costs and payoffs are essential. The involved agents (players) try to maximize their payoff with minimal cost in a non-cooperative interaction, but the opposition's goal is contradictory due to the same strategic plan. The solution is a win-win optimization. This balancing "game" of the opposite processes may be described by the decision-making game theory, where both parties can achieve the optimum of their desired outcome without giving up their original purpose. The game evolves to reach the Nash equilibrium. It is the state in which all systems can maintain their equilibrium without disrupting the equilibrium of the other systems. In the Nash equilibrium, no further significant actions to modify the equilibrium state would produce more benefit than cost. In a Nash equilibrium, no player can improve their payoff by unilaterally changing their strategy.

They reach a Nash equilibrium, in which both parties' strategy considers the opposition's decisions and optimizes their own. Every party gets the outcome they want, so both of them win. The regulative driving force of each side seeks to assert its influence, but it is limited by the opposition, which has its desire. The negative feedback mechanisms of the complex homeostatic regulation govern the complete process [196]. Each factor wants to change the body's equilibrium in its favor, but the characteristics are also interdependent. The Nash equilibrium is when the cost of change forces one part of the process to balance the benefit that could be reached; no further actions would produce more benefit than cost [197]. The Nash equilibrium of this game is the state in which the body's equilibrium is maintained despite the changes made by the different factors. A

theoretical model describes the game with multiple "players" forming a balance with Nash equilibrium [198], which may be used for the description of homeostasis. The evolution of the network seeks Nash equilibrium, while the biological evolution fulfills the Darwinian selection. However, the Darwinian selection and Nash equilibrium differ considerably. Darwinian selection operates at the level of populations, while Nash equilibrium operates at the level of individual players. In Darwinian selection, no conscious players are making strategic choices. Instead, it is the blind forces of nature that select certain traits based on their survival and reproductive advantage. In Nash equilibrium, players are assumed to be rational and know the game's rules. However, organisms in natural selection do not act rationally or strategically. They have traits that either help them survive and reproduce or do not. In Nash equilibrium, players have a fixed set of strategies. However, in Darwinian selection, the "strategies" (i.e., traits) constantly change and evolve through mutation and natural selection.

The Matthew effect ("rich get richer") is centered on the situations, resources, or opportunities that tend to flow toward those who already have them and form "hubs" in this way in network models. This positive feedback loop can be modeled as a game where players invest in assets that offer the highest returns, further increasing the value of those assets and creating a self-reinforcing cycle. In this scenario, the "rich get richer" outcome could be a Nash equilibrium where no player has an incentive to deviate, as their best choices depend on others doing the same. The "rich" hub has strong network effects. The value of fitness increases with the number of neighboring nodes connected to the same hub. This can create a winner-takes-all dynamic where the early leader gains a significant advantage and attracts even more users, solidifying their dominant position. This outcome could also be seen as a Nash equilibrium where competing firms have no profitable alternative to following the leader's strategy. However, this Nash equilibrium involving the central hub is vulnerable to external factors disrupting the game's dynamics.

Darwinian selection and the Matthew effect are generally considered compatible, though their relationship is nuanced and not without some potential contradictions. Both concepts involve positive feedback loops where advantages tend to snowball. In Darwinian selection, individuals with advantageous traits have higher survival and reproduction, making those traits more common in the population. Similarly, the Matthew effect posits that those with resources or opportunities attract more, further solidifying their lead. Both principles emphasize that individuals or entities with specific characteristics achieve greater success than others. Darwinian selection is about survival and reproduction; in the Matthew effect, it's about accumulating resources or advantages. Both offer explanations for observed patterns in nature and society. Darwinian selection helps explain how species evolve and adapt, while the Matthew effect sheds light on phenomena like wealth inequality and the dominance of certain players in various fields. Darwinian selection and the Matthew effect are compatible in explaining how advantages can snowball and lead to differential success. Their relationship is not without complications. Darwinian selection typically operates on long time scales, while the Matthew effect can manifest more quickly. This disparity can lead to situations where short-term advantages gained through the Matthew effect might not necessarily translate into long-term evolutionary success. Darwinian selection focuses on individual traits and their impact on survival and reproduction within a population. The Matthew effect, however, often plays out at the level of groups or entities, potentially creating situations where some groups benefit at the expense of others, even if their members might not all be "fitter" in the Darwinian sense. Both concepts acknowledge the role of chance in shaping outcomes. However, the emphasis on randomness might differ. Darwinian selection often highlights the

importance of random mutations and environmental fluctuations, while the Matthew effect might focus more on initial advantages leading to self-reinforcing cycles.

The idea of life networks evolving to a Nash equilibrium intersects game theory and evolutionary biology. Living network formation as a game includes strategic processes about forming connections with others based on the relationship between potential benefits and costs. The benefits could be different aspects of the living organism, like resource sharing, mutual defense, or information exchange. The resulting network structure can be seen as an outcome of this strategic game, where each node (organism) chooses its connections (strategies) to maximize its fitness.

The network development includes strategic decision-making by the nodes, trying to maximize their payoffs Figure 15. Each intending to connect nodes is in a frustrated position between the different driving forces, which offer various benefits and costs for the link. The final joint link will be realized by the balance between the "payoff" and the "cost" of the action. The opposing driving forces are the actual (short-range in spatiotemporal arrangement) and the strategic (long-range risks) condition. Each new node in the development of the network has the same frustration upon joining. This way, the network structure evolves until it converges to the Nash equilibrium. For example, a link to a robust and high-degree hub is energetically beneficial. Still, the network's resilience with a central hub appears to be a risk in strategic network building of living systems. The cost of risk is realized by Darwinian selection. Adapting to the actual challenges could cause a fall, and the network with vulnerability is not viable in the strategic line when the central hub is damaged, and the network falls apart.

The evolution of the network by adaptation to the environment is a complex Nash equilibrium to maximize its payoff: the individual node strives to enforce its multilayered interest, which combines self-interest and local possibilities with group interests [50], harmonizing the short-range and long-range interactions in the network.

The biological network develops to ensure the energetic balance. The energetic conditions decide whether the given cell remains individual or joins the network.

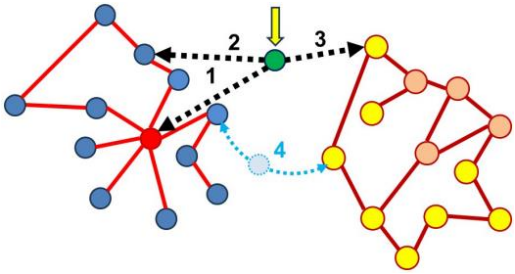


Figure 15. The network evolution game. The node (green arrow above) that intends to join the network. The just arriving node (noted by arrow) has various possibilities to link. (1) link to a vital hub. It is positive because the hub is "reach", but negative. After all, it is a vulnerable position. (2)-(3) Link to one of the independent subnetworks. It depends on which gives a higher energy payoff. Connecting (3) to the network is an energetically shallow connection, less advantageous than the option on the left, but the protection of this network is better; if any central hub (red) becomes inoperable, the network remains connected. (4) Link the two independent subsystems and connect them. The chosen position is the weak link, which stabilizes the systems. This position has high betweenness and again has a strategic role in decreasing the vulnerability of the whole structure.

The energy balance determines that the energy difference invested and received by the cell is positive, i.e., the advantages outweigh the disadvantages, and the cost is smaller than the payoffs. Cell networks, explicitly applying the concept of Nash equilibrium, have some potential scenarios. Imagine genes acting as players in a game, vying for limited resources like transcription factors to express themselves. Each gene's "strategy" could involve regulating its expression or manipulating the environment to favor its expression. Through natural selection, gene networks might evolve towards a state where no gene can significantly increase fitness by changing its strategy—a Nash equilibrium. Different metabolic pathways within a cell could compete for resources like substrates and enzymes. Their "strategies" might involve up- or down-regulating enzymes or altering substrate utilization. Over time, the network might stabilize at a stage where no pathway gains a significant advantage by deviating from its current expression levels, reaching a Nash equilibrium-like state. Signaling pathways involve complex interactions between proteins. Each protein's "strategy" could involve activating or inhibiting downstream targets. The network might evolve towards a state where no protein can significantly alter its activity for increased fitness, resembling a Nash equilibrium.

However, there are challenges to reaching equilibrium in cellular networks. Assigning fitness values to genes, metabolic pathways, or proteins within a cell network is challenging. It depends on the specific context and desired outcome (e.g., cell survival, proliferation, differentiation). Cell networks are dynamic systems with constant fluctuations and feedback loops. Predicting how natural selection will drive the network towards a specific Nash equilibrium is often tricky. Depending on the initial conditions and environmental factors, the network might reach different Nash equilibria. Identifying the relevant equilibrium for a particular biological context adds complexity. It's important to consider that cell networks might not always be in a steady-state Nash equilibrium. They might exhibit dynamic equilibria or nonequilibrium behavior in response to changing environments or internal perturbations.

The resulting network structure can be seen as an outcome of a strategic game, where each node chooses its connections (strategies) to maximize its fitness. Evolution drives selection towards equilibrium with strategies that lead to more advantageous network positions (higher fitness), which are more likely to survive and reproduce, passing on their genes and network preferences versus time. The network can evolve through natural selection towards a state where no individual node is incentivized to change its connections because deviating would lead to lower fitness. This state resembles a Nash equilibrium. Overall, the idea of life networks evolving toward Nash equilibria highlights the potential for game theory to explain the emergence of cooperative and efficient structures in biological systems. While challenges remain in modeling and verifying this concept, it continues to be an active area of research with fascinating implications for understanding the interplay between evolution and collective behavior in living organisms.

The game with two actions to cooperate or defect well approaches the biological interactions [90]. The relevance of such alternating games' strategies is sometimes more appropriate than synchronous games. [91]. The networking process in biosystems depends not only on the global degree distribution; the dynamic internal development is the primary driving force. While homeostasis macro-drives the general operations, a compensation between the cost of maintaining a connection and the obtained benefit by the chosen links explains the evolution of the biological network. Typical physiological and molecular balances have been studied by Nash equilibrium, including the regulation of the immune system and the regulation of metabolism [199].

A particular game theory (the hawk-dove game [200], chicken game [201], or snow drift [202]) is a valuable tool for understanding the complex interplay between conflict and cooperation in various biological settings. It describes the interaction between two players competing for a shared resource. Two basic strategies are conflicted: the aggressive (hawk) and the peaceful (dove) strategies. A hawk chooses to fight over the actual resource, even if it risks injury, while the dove decides to share the resource or back down to avoid conflict. The payoffs depend on the strategies in various conflict realization:

- In a hawk vs. hawk conflict, both may get injured and receive a low payoff regarding the cost of fighting.
- In a hawk vs. dove conflict, the hawk wins the entire resource and receives a high payoff, while the dove gets nothing.
- In a dove vs. dove conflict, both share the resource and receive a moderate payoff.

The critical point of the hawk-dove game is that no single best strategy exists.

While a hawk can always do better than a dove by exploiting its peaceful nature, two hawks always do worse than two doves because of the cost of fighting. This creates tension between individual gain and mutual benefit. It helps explain how cooperation can evolve and persist even when individuals might benefit from exploiting others. The hawk-dove game could be applied for physiologic responses to stress [203]; the hawk-dove game could be used for genetic development. In genetic development, we could imagine two "strategies" competing within an organism: the "hawk genes" promote rapid growth, resource acquisition, and potentially harm neighboring cells or tissues to gain an advantage, while the "dove genes" prioritize cooperation, cell-to-cell communication, and tissue development for the benefit of the whole organism. The hawk-hawk conflict in genes leads to uncontrolled growth, competition, and potentially organ dysfunction or developmental defects (low payoff); in hawk-dove conflict, the hawk genes might initially outcompete but later harm the overall development due to tissue damage (mixed payoff); and in dove-dove competition, a balanced growth, coordinated action, and healthy organ formation could be achieved (high payoff). This later payoff differed from the original game when the dove-dove conflict had given only a moderate payoff. In biological applications, the cooperative attitude has the highest benefit. The games usually need mixed strategies for stability. The opposition can easily recognize the fixed strategy and open a way for contraction and win. In biology, the random mutations at the genetic level ensure a mixed game for all, while homeostasis controls the balance. All models might be oversimplified, including the game theory and applying the hawk-dove game directly to genetic development. However, the core concept of competing strategies and the importance of cooperation offer valuable perspectives for understanding the complex interplay of genes and cellular interactions that orchestrate the development of a healthy organism.

The biological networks evolve from cell generation to cell generation inside the organism, forming an intrinsic self-time [3] while following the Darwinian selection rules on a large timescale. All changes in the biological networks tend to create local and global Nash equilibrium. The node in the network with NN nodes has to be evaluated by its positional condition, which means its links and environmental specifications (degree, betweenness, centrality, hub behavior, etc.). The network benefits from a node with a high degree of centrality. On the other hand, the growing importance of the position also means resilience, which could be lethal for the network integrity.

Under the opposite driving forces, the node will try to maximize its benefits and minimize its costs, but its environmental nodes have the same strategy, opposing the node's tendencies. The end will be a win-win position when the further cost to reach additional benefit is higher than the payoff of this action. In this state, the system is in dynamic equilibrium.

The network joining could also be studied from the system's point of view. A benefit of the network is if the newly joined node occupies a strategic position of the central betweenness [204], which measures how often a node in a network is on the shortest path between two other nodes. This state has a primary transport role. However, (as a strategic game again), this position is critical for resilience because its removal can significantly impact the network's connectivity. The lethality correlates with removing the central protein in S. cerevisiae [205]. A targeted attack on the high centrality nodes' lethality due to the damage of the hub positions was studied [206] [207]. The most common centrality metrics are degree [206] and betweenness [208] [209]. It is possible to rank the nodes (gene regulatory positions) by centrality metrics [210], which were experimentally studied in protein arrangements, testing the robustness of a network [143]. Different centrality metrics were proposed to describe the resilience of the living networks better [211] [212]. All the above considerations show the importance of the betweenness positions, which could be a risk to the lethality if that has a central betweenness position. Still, the newly joined node has a low probability of developing such a state.

The game theory is applicable for network development instead of conventional network parameters like the distributions and scaling of the distances. The ultrasmall-worlds networks can be formed by the dynamic evolution driven by a simple compensation rule. In the game approach, the nodes seek to improve their positions (connections) to maximize their payoffs in the promoter-suppressor opposition. When the invested effort exceeds the resulting advantages, a balance is formed, a win-win situation of the promoter-suppressor "fights". So, this Nash equilibrium is reached when nodes in a network consider their target to improve their centrality against the costs associated with forming and maintaining connections. The network's diameter does not depend on the network size and seeks to be six in Nash equilibrium [187]. The networks, independent of their initial structure, evolve into an ultrasmall world when nodes increase their centrality by forming connections only if the cost is smaller than the obtained benefit. Despite that, the participating individual nodes have limited information about the network structure. They form small worlds [187]. The low degrees of separation in the networks enter a new view of the complexity, considering the importance of the participating units' local and systemic connectivity and interdependence. The living objects are ultra complex, having various subnetworks on the different spatiotemporal structures, different bases of the interaction links, and very different ranges from the short (like molecular networks) to the medium (like tissues) to the large systemic (like physiological networks), but most of these networks may be renormalized. The renormalized network describes the links between the networks, which are treated as unit nodes, and their links form a new complex network in a self-organized, self-similar manner. This renormalization allows the medical approaches to use the subnetworks as independent units and so specialize the medicine on molecular specific (pathology, immunology, etc.), organ-specific (like nephrology, pneumology, etc.), physio-specific (like neurology, orthopedics, gynecology, etc.) or person-specific (like dietology, psychology, etc.) or even group specific (like sociology, ecology, etc.). Naturally, these subjects are deeply interconnected, forming the higher renormalization grouping of the investigation (like gastroenterology, cardiovascular phenomena, etc.), and the network of these significant subnetworks composes the complete system governed by a particular complex

and dynamical equilibrium, the homeostasis in living objects, and the balanced society of their groups.

3. The Cancer

Cancer is one of the most feared diseases of humans [213]. Its prevalence rapidly grows with age. Life and death are connected and assume each other. An irreparable malfunction of living processes leads to death, having the statistically expected lifetime. Cancer is one such situation when the living processes are incompatible with the energy and space requirements of developing malignant tissue. Paradoxically, cancer cells have immortality as long as their energy supply is ensured.

Various theories and hypotheses exist about the cause and origin of cancer, from ancient medicine to a long line of new explanations. The advanced search for an answer was started more than a century ago with virus concept [214] [215]; the genetic clues were later favored [216] [217], and the mutation concepts became popular [218] [219]. Recently, the immune dependences [220] and connections with wound repair have been intensively researched [221] [222], [223] [224] [225]. Despite the enormous efforts, the cause of cancer remains open [226], with groups trying "fishing" for the clue [227]. Despite even particular quantum-physical explanations [228], the recent studies do not give a final solution [229] [230]. More contemplations turn to the environmental, diet, and habit origins of malignant diseases [231] [232] [233].

Most widely, cancer is believed to be an abnormal tissue triggered by a gene mutation. However, the proto-oncogene and the oncogene appear not only in cancerous cases [234] but with pregnancy [235], with embryogenesis [236] [237], with the healing of wounds [238], and with the synthesis of growth factors [239]. Oncogenes show a great variety of anti-apoptotic functions, with the cells participating in wound healing. Cancer is a part of the evolutionary process. It is a self-organized structure [240]. A longer time scale could cause a refreshing of the genetic pool, developing a mechanism of opposing selection of mutant alleles [11] and eliminating the genome instability. Healthy homeostasis makes great efforts to avoid cancer. The first few attempts to block the proliferation start intracellularly by controlling the DNA replication. DNA replication is, of course, crucial for continuing the standard cellular replacements of the individual. The natural challenge is the exact copy of the complex DNA. The process has errors (mutations) that deviate from the standard cellular structure of the individual. The primary task of homeostasis in the first steps is to control the DNA replication and intracellular processes. The control may fail for several reasons, including primary genetic aberration [241], mitochondrial dysfunction [242], or other intracellular hallmarks of cancer [243]. An additional challenge is the extracellular factors such as permanent uncontrolled stress (chemical, mechanical, etc.) [244], unhealed wounds [245], inflammation [246], and the extracellular hallmarks of malignancy [247]. The permanent proliferation could be stopped by natural apoptosis, but this mechanism is missing, too [248].

3.1. Cancer Morphogenesis

Cancer disrupts the healthy morphogenesis [249]. The disruption appears in a drastic change of tissue architecture, the aberrant signal pathways, and activating embryonic signaling pathways to realize atavism. Malignant cells develop through massive structural and functional developments when environmental conditions make it possible. Subtle cellular and tissue behavior modifications could be an early warning sign for malignant development. Morphogenesis principles can be used to construct network models to simulate how cancer cells interact and organize. The morphogenetic variation differs in the bulk tumor and its boundary. The development of a plane lattice considered that there are structural variations governed by changes in boundary conditions [250]. In this way hypothesized, that the early stage mostly tries to drive toward normal progress, and the late stage shows a volume-minimizing fractal growth with characteristic dimensions, optimizing the maintenance of the volume constant while increasing the edge length, which allows more reactive sites for further developing [105].

The tumor development controls morphogenesis, so the ATP is the energizing factor and the regulator of morphogenetic development [251]. The construction of tumors and the malignant invasion could be regarded as losing morphogen gradient control. While morphogenesis increases the complexity of the structure, cancer could be considered as "reverse morphogenesis" when the topological complexity decreases [252]. However, the reverse effect turns again into direct morphogenesis; when the tumor is more extensive, its mechanical pressure is higher than the host's on average, and it has structural changes depending on the part of the tumor.

In morphogenetic perspective cancer is a geometrical flaw, a disease of the geometry [253], a defect pattern of a group of cells, which spatiotemporally differs from the healthy host [254]. Equivalently, cancer is a network disease, which deviates from normal networking, which is connected to the morphogenic arrangement.

Due to the self-organized self-similarity of living structures, the fractal geometry is an appropriate tool to study the geometrical [255] [256] (or temporal [72]) arrangement of the cells. The fractal geometry differs in healthy and cancerous tissues [257] [258], and even its change characterizes the tumor grade [259] and specific structures of the cancer locations [260]. Fractal dimension could also be a prognostic factor [261] and could indicate the therapeutic response [262] of a tumor, as well as be used for early diagnosis of malignant deviations [263]. The subcellular fractal dimensions appear in chromosomal abnormalities [264], cytoskeleton [265], and microtubules [266]. Fractals may be used to detect the vascular architecture of the tumor [267] [268]. The trend of fractal evolution could be the opposite in the tissue and individual cells. The cancer tissue emerges more and more segmented structure (sometimes like "cauliflower" shape [243]) and the fractal dimension grows [269] the cancer cells are structurally simplified developing a decreasing fractal dimension [270].

3.2. Cancer Networks

Network modeling could help to understand and attack the abnormal molecular and cellular processes associated with cancer [271]. The analysis of the network models yields information to describe cancer and follow their adaptation processes [272] [273] [274]. The malignancy distorts the healthy cellular network. The rules of the multicellular organization are broken in all tumorous cancers independent of their locations in the body. Disorganizing the multicellular structure is the

modified genetic activity at the active boundary between unicellular and multicellular areas, promoting primitive transcriptional programs [275]. In this sense, cancer is an organizing (networking) disease, where the cells unleashed from their networks abandon the living advantages of collectivism and individualism prevailing [86]. The change, however, is not free from new organizing processes because this unicellular autonomy brings its requirements regarding environmental conditions for survival [276]; the cancer is afforded a friendly environment by the host, which tries to "heal" the abnormality, strengthening with angiogenesis, injury current, and numerous other supports. The breaking of healthy cellular networks forming its own is a general behavior of all tumorous cancers independent of their locations in the living system, so the study of tumorous networking applies to all tumors. Contrary to the genome-wide association studies [277] [278], instead of hundreds of involved positions, the gene regulatory networks are relatively simple; a few critical transcription features can change the cellular state, as a genetic polymer model shows [125]. The model system showed [125] that the binding of the transcription factor to the transcription unit is reversible, having a role in reverse mutation. The transcription factor is a weak link that switches between the active binding site to the inactive, actually nonbinding state by a rate parameter.

We may categorize the cellular networks from rigid to plastic state [279]. Rigid networks have hub-driven hierarchy and low network entropy, usually described by the BA scale-free model. Rigid networks have only a few dominant attractors to where the network converges. It is characteristic of late-stage tumors. These networks are vulnerable to hub-distortion, so their therapy needs "network influence drug design strategy" targeting their hubs and nodes in central betweenness position [280]. Weak links dominate plastic networks, have overlapping modules with regulation loops, many attractors and high network entropy. It is characteristic of early-stage tumors.

The gene regulatory networks are relatively simple. The computer simulation of the chromosome polymer model shows the growing space correlation, allowing stochastic transcriptions and forming complex small-world networks, where one transcription affects many genes in the region [125]. Increasing transcription units in sub-saturating levels significantly simplifies the network to a small world. Small-world networks have been found to play a role in cancer development and progression [281]. Studies have shown that small-world networks exist in the tumor microenvironment and the environment surrounding a tumor tissue. The tumor microenvironment (TME) comprises a variety of cells, including cancer cells, immune cells, and stromal cells. This network structure allowed for efficient communication and coordination between the different types of cells in the TME [282]. The TME has highly correlated cellular interactions [283] and is organized as a small-world network [284], a common feature of the TME in various cancers, suggesting that small-world networks may play an essential role in cancer development and progression. The small-world network structure of the TME allows for efficient communication and coordination between the different types of cells, which can promote tumor growth and invasion. Cancer cells can use small-world networks in the lymphatic and circulatory systems to travel to other body parts and form new tumors forming metastases [285]. Cancer cells can develop resistance to cancer drugs by communicating with each other through small-world networks, making it challenging to complete the provided oncotherapy. The robustness of the cancer signaling network is also supported by small-world construction [286]. A broad spectrum of fundamental network characteristics in embedded networks exists in biological systems [287], such as transitions between scale-free to exponential degree distributions and largeworld to semi-ultrasmall-world [288] [289]. Cancer changes self-organizing and develops its rules, structure, and transport system. Cancer is a disease of the whole cellular network that supports the "renegade" conditions and allows the metastatic processes [284]. Cellular "individualism" wins and replaces collectivism, while collective healthy acceptance supports it. The cancerous part of the system parasitizes its healthy environment, using its sources for local individual survival, contradicting the systemic demands.

Molecular networks dynamically respond to inner and outer influences and tend to adapt to them. Six categories of networks based on the impacts from internal and external environments could be distinguished in **Figure 16.**

1) Genetic networks (as basic hardware at birth) are the basis of behavior, which may significantly differ between individuals and may change by mutation, which could develop cancer.
2) The genetic network primarily determines cellular network structures, but morphogenesis and other developments connect these networks to the next, the tissues. The cellular network drastically changes when cancer develops. Cells are metabolically reprogrammed with cancer, and it changes their network, too.

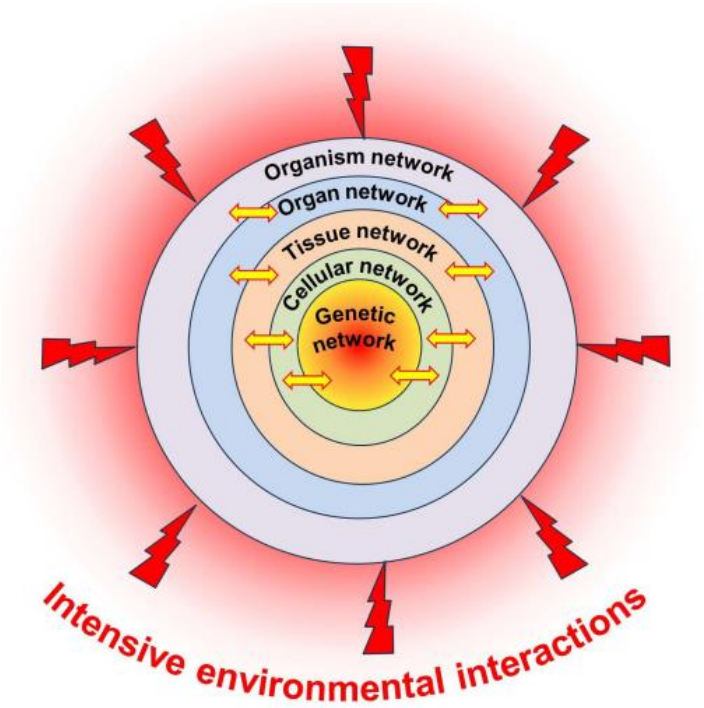


Figure 16. The various levels of networks are embedded to each other and together their crosstalk they are intensively interacting with the environment, which at the end of the day may modify the complete structure.

3) Tissue networks where the collective dynamic processes determine the links and nodes. This network is essential to understanding cancer tissue development and its support with resources by healthy tissues.
4) The organ network makes mostly physiologic interactions and regulates the internal conditions for all networks below. The physiologic transports and regulation signals are reprogrammed when cancer develops.
5) The organism's network regulates and controls the system's homeostasis. In a cancer situation, the homeostatic network is damaged and not able to perform its standard regulation role. The complete support for cancer with available resources dominates the processes.
6) External effects and signals provide nutrients and chemicals, forming general environmental conditions for the organism.

The first three (genetic, cell, and tissue) networks are mainly affected by outside resources. From the point of view of cancer, network modeling could be reduced to four network categories to follow the cancerous processes [290] and use the organ and organism networks as a stable frame of the malignant development. Even the four network categories could be reduced to three by self-organizing, regarding cancer as a disease of cell and tissue networks [291]. The complexity of the topic is well mirrored in the different models that study cancer development. Models may be centered on genetic start, on the inherited genome instabilities, on some non-genotoxic effects, or may use evolutionary biological considerations [292]. The angiogenetic network model for cancer tries to describe the cancerous process with the network of organism-regulated blood support [293], which could also be formulated by tissue-driven electric interactions [294].

The regulatory networks have many commonalities from microbes to humans [93]. The regulation of collaboration and cooperativity massively boosts the democratic character with overall genomic complexity. The complex regulatory effects tend to a partnership supporting the democratic structure, whereas others regulate primarily in isolation, in a more autocratic fashion [94]. The degree of collaboration forming autocracy in opposition to democratic behavior is a characteristic of the complexity of living systems. The game with two actions to cooperate or defect well approaches the biological interactions [90]. The relevance of the strategies of such alternating games is sometimes more appropriate than synchronous games [91].

Mutated single genes rarely cause disease (including cancer). The perturbations triggering disease affect the complex intra- and extracellular networks. Network medicine may identify the disease modules and pathways, considering molecular relationships between apparently separate phenotypes and systemically exploring the molecular network complexity of a particular disease [151]. The lethal genes are coupled to five-fold higher connectivity proteins than non-lethal ones. The results emphasize the importance of the hub-focused attack, which can disrupt 50% of the protein network integrity [295].

Various cancerous diseases have their molecular signaling network, which may statistically correlate with the survival variation of different cancer types. In the case of lung adenocarcinoma, the scale-free network is a case-specific smallworld [296]. The small-world maps describe the disordered topology of cancer in different stages of its development. The forming small-world structures are resilient to external attacks, which limits the effectiveness of pharmaceutical therapeutic interventions for lung adenocarcinoma [280].

3.3. The Aging

Aging is a normal process of living objects. The self-organizing models for aging could follow the essential functions and the crosstalk between aging and cancers [297]. The methylation is a crucial addition to aging in the self-organization model. The dysfunction of regulative and order parameters, including the immune system, is identified during aging in the self-organized model, together with the relation of aging and aging-related diseases like cancer [281]. Aging modulates the cancer progression with angiogenesis and metabolic support [298]. The transforming growth factor beta (TGFβ) is a potent inhibitor of cell proliferation and acts as a tumor suppressor; however, the aging downregulates it in the host, allowing the malignant development. The idea that cancer results from a single cell's renegade behavior [299] must be corrected. When the cell grows

individually without support from the healthy environment, no proliferation and no metastasis can occur. Cancer is a collective disease of the whole cellular network, breaking the multicellular coordination and intending to form a monocellular structure with the intensive support of the healthy host and allowing the metastatic processes [300]. The cellular "individualism" replaces collectivism, restructuring the communication network between the cells. These observations prove that the malignant processes are age-dependent, and according to the epidemiological data, they are also environment-determined [301].

A very extended study of data mining of aging and DNA methylation (DNAm) shows that DNAm can be used as an epigenetic clock, has no strong correlation with aging, but nonlinearly changes by age: it is accelerated in young ages until adulthood, and remains approximately constant later. In contrast, cancer tissues have severe age acceleration again [302]. It is essential to add that the homeostatic capacity (regulation and control) decreases with aging [303]. However, this phenomenon is also not linear; the degree and pattern of population heterogeneity may deliver new information that the statistical variance (ANOVA) evaluation does not indicate. The growth of a tumor depends on the supply of nutrients by blood flow via a vascular network. Interestingly, the new angiogenetic vessels in cancer and the healthy network do not increase the flow efficacy [285]. The seeming contradiction is similar to the traffic networks of roads described by the Braess paradox [304], describing that adding one or more routes to a road network can slow overall traffic flow. The traffic of the complete network with the added road(s) will reduce overall performance to reach the Nash equilibrium. Having linear latency, the added new edge to the transport network worsens the transport time ≤4/3 [305]. The same conditions happen when the angiogenesis adds a new blood-transport route by angiogenesis to the healthy network. However, at the same time, aging reduces the weak links [306], which means that, in the case of the vascular networks, some weak link routes disappear, working against the angiogenetic vessel addition. The weak links are gradually decreased by aging and cancer in a cellular network, too, where their disappearance increases the vulnerability of the cellular networks.

The tumor morphology changes by the random decrease of adhesion between the cancer cells [307], as it was experimentally observed in the E-cadherin/ β-catenin complexes [109] [110]. Supposing that the adhesion distribution of the tumor cells is Gaussian with a σ standard deviation The growth exponent and the surface roughness fractal dimension grow by σ having ~1.2 and ~2 saturation value, respectively [307], well corresponding to the relationship between the fractal dimension (D) and power law index (α) [308], showing a slope $s \approx \frac{5-\alpha}{2}$

This indicates that the cellular adhesion is one of the critical factors of transition to cancer cell.

3.4. Does the Tumor Have Atavistic Features, Or Is It a New Organ?

The growth of tissues is a usual process in living objects. Allometric considerations can distinguish between healthy and cancerous growth [255]. Healthy homeostasis struggles to control the malignancy. The natural apoptosis that could stop permanent proliferation is missing [248]. In this aspect, the cancerous proliferations and the growth of the bacterial colony have a lot in common [309]. At the start of developing tumors, the cancer cells gradually become autonomic, break the connections, and individually fight for survival and energy for rapid proliferation. The malignant

development commonly avoids healthy homeostatic regulation, "defrauding" the controls for their intensive, unhealthy proliferation. The cancerous lesions develop the strength to proliferate as intensively as possible, ignoring the host tissue's healthy regulations and collectivity. Cancer attacks the multicellularity, and seemingly steps back to the unicellular development, producing atavism.

Cancer development is seemingly like atavism [310] [311], but the support for its development differs. In the beginning, when the intercellular bonds weaken, the network starts to fall apart, and the quasi-independent cells try to adapt to the new condition. The uncontrolled growth of cancer has a unique behavior at the beginning, the malignant cells individually develop and refuse the healthy network connections. This denial of multicellular collectivity is like the unicellular development in the earlier development stages of life. This stage of cancer development is atavistic [310] and has a lot in common with bacteria and with the wide range of unicellular developments [309]; having self-ruled cellular behavior denies cooperativity. All malignant cells individually fight for energy in this stage. The unicellular individualism develops enormous potential for adaptability to environmental changes and makes these cells more vigorous than those in the multicellular network. However, the difference from bacterial atavism is noticeable. The bacteria, the atavistic unicellular system, has passive diffusional and mechanical availability of resources from the environment, while the starting cancer cells enjoy the available blood transport system. The fundamental similarity to atavism is its first strictly unicellular steps, where the malignant cells independently fight for their survival, the sense that the malignant cells act like self-ruled unicellular organisms. Soon, the cancer development builds up a new strategy.

The atavism-like process at the beginning of tumor growth in general, with the loss of cellular connections and the alteration of intracellular genetic structures. The unicellular individualism develops the excellent potential for adaptability to environmental changes and makes these cells more vigorously viable than those in the multicellular network. Disorganizing the multicellular structure is the modified genetic activity at the active boundary between unicellular and multicellular areas, promoting primitive transcriptional programs [275]. The healthy host supports cancer development [310], while the growth of cancer dismantles the multicellularity [312], and the cellular collectivity gradually disappears [313]. The malignancy in this general meaning is a distortion of the healthy cellular network, the multicellular organization is broken. The atavistic model could be used as a starting point, but this model does not consider all the crucial details (hallmarks) that keep the single-celled units of cancer development alive [314]. In this sense, cancer is an organizing (networking) disease, where the cells unleashed from their networks abandon the living advantages of collectivism and individualism prevailing. [86].

Cancer development is supported actively by from the surrounding host tissue. It builds up new structures in themselves [255]. Cancer cells self-organize various networks in their different development stages to survive collectively, evading homeostatic control. The rearranged cancer networks have cooperative links at first bilaterally and later generally with the host cells (reverse Warburg effect [315] [316]). The development evolves a form of new organizing because the unicellular autonomy brings its requirements regarding environmental conditions for survival [276], which needs multicellular cooperation. The cancer is afforded a friendly environment by the host, which tries to "heal the wound", strengthening the tumor with angiogenesis, injury current, and numerous other supports.

The newly developed tumor growth is angiogenesis-dependent [317] [318]. The growing tumor, within its subsequent evolution and adaptation to the changed conditions, starts to behave as an organ, having peculiar functions (the growth intensively supported by the entire body, including the cellular, the organs, and the physiologic networks. The cancer behaves as a regular organ [319] with substantial energy consumption and low efficacy. It has a unique feature that no other organ has: the metastases delivered by the lymph and blood transport, like hormones, immune cells, and other essential parts involved in circulation. The metastatic behavior is also organ-like [320], keeping the original structure of the cancer in other metastatic tissue conditions [240].

Due to the complexity of cancer, the tumor growth dynamics can have a spatio-temporal 3D computational model of the development of a cancerous tumor together with its environment [321]. The model describes the tumor as an organ having intensive and coordinated interactions with the environment of tissues and through physiologic control with other organs. A solid tumor is not a set of clones of a "renegade" cell, but it is an abnormal organ, having heterogenous cellular composition and extracellular matrix like other organs [322]. The modeling of this is not simple. Some cancer development characteristics look like a developing organ, while others are realizing tissue remodeling. Some microenvironments, particularly those associated with tissue injury, favor the progression of mutant cells, while others restrict it. Cancer cells can also instruct surrounding tissues to undergo changes that promote malignancy. Understanding the complex ways cancer cells interact with their surroundings, both locally in the tumor organ and systemically in the body, has implications for effective cancer prevention and therapy.

The increased size of the cluster of cooperating cancer cells increases the complexity of the structure, proliferates more effectively, and can share resources. Cancer cells may affect the hormone system by cancer-derived mediators (biogenic amines, neurotransmitters, neurohormones, cytokines, immune mediators, etc.), and with these can stimulate the neuroendocrine centers resetting the homeostasis [323], setting the body to favor the cancer proliferation. Numerous changes create a new homeostasis (accepting the tumor as an energy-demanding organ), which helps the tumor grow **Figure 17.4**

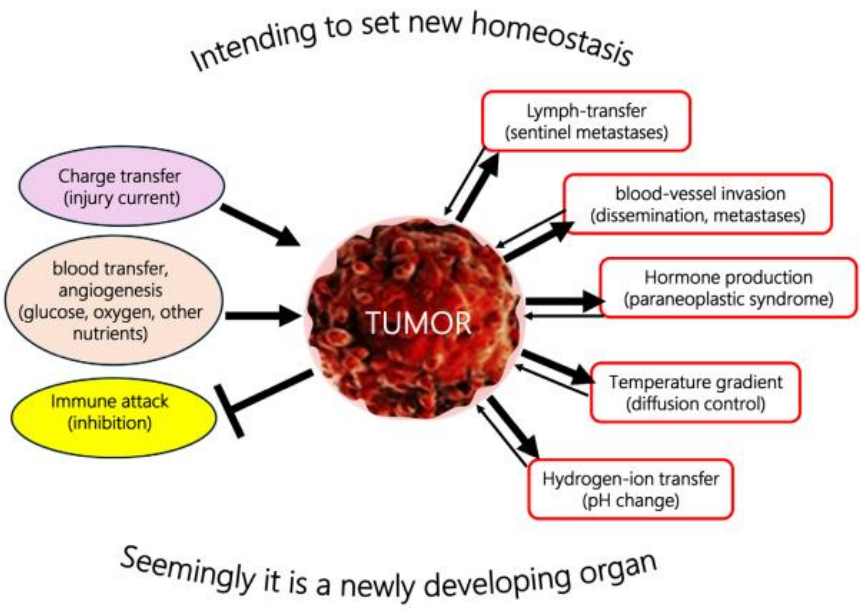
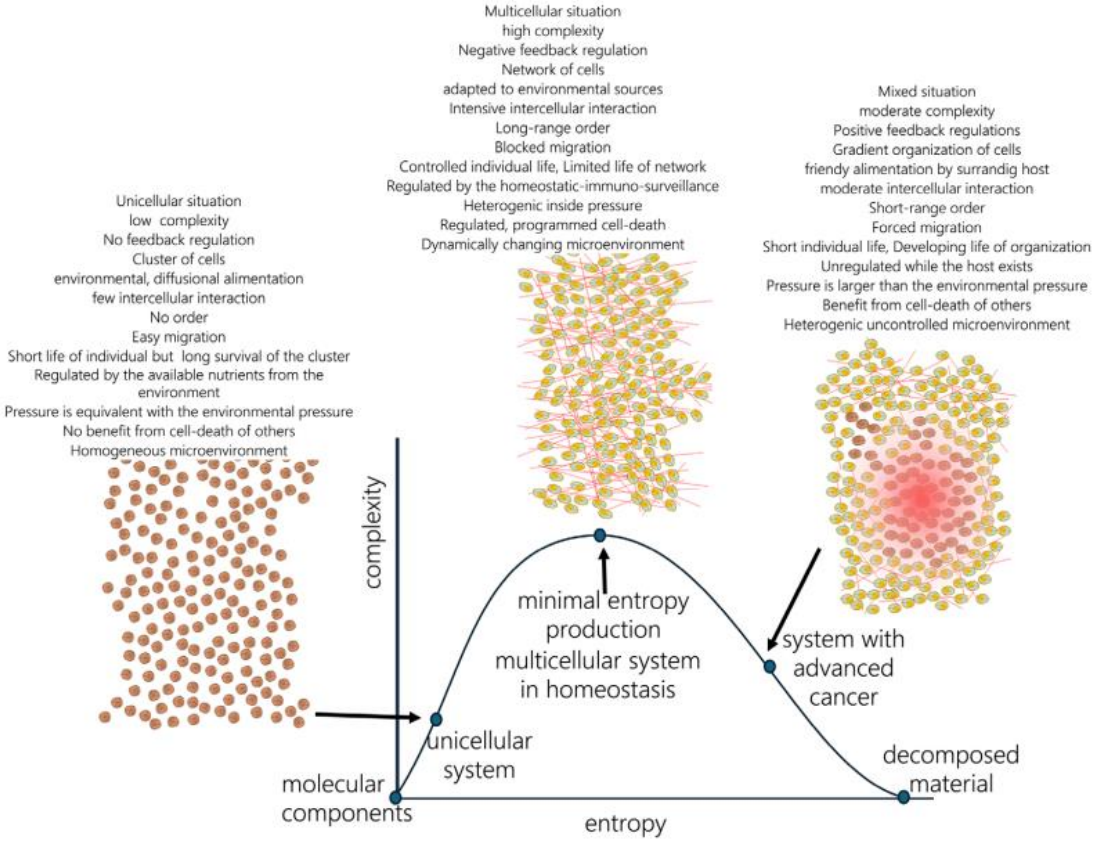


Figure 17. The physiologic changes reshape homeostatic control. The charge (injury current), liquid (blood and lymph) transport, and immune inhibition set a condition to reset homeostasis. The consequences are the dissemination of the malignant cells, a particular hormone production, increased diffusional possibilities, and lowered pH. Note that the retuning of the body equilibrium supports the tumor-organs hypothesis and does not fit the atavistic explanations.

The changes in the cellular system in the process of tumor growth have morphological differences which have crosstalk with many fundamental processes of living matter [324] Figure 18. The healthy networking is a complex multicellular network with numerous negative feedback regulations having intensive intercellular interactions in long-range order. The standard cellular network does not allow cellular migration except for those cells that are involved in immune surveillance. The transport delivers enough energy for standard dynamic equilibrium, which has high energy efficacy to use it. In the first phase of tumor development, the multicellular network falls apart in the cancer location, and the cells compete for new cell production. Here, there is no feedback regulation (except the available nutrients), no complexity, and no intercellular connections disordered, and it is easy for cells to migrate. The developed cancer has highly complex interconnected networks and extreme genetic [325] and tumor [326] cell network heterogeneity. Genetic and tumor heterogeneities are the principal reasons for the therapeutic failures and even the growing likelihood of resistance to subsequent therapies. The diverse genetic and cell populations do not equally react to the applied treatments; those may select the resistive cells on the toxic stress. So, the applied therapy selects the resistive tumor cells and blocks the possibility of successful therapies. These resistive cells have more facility to avoid apoptosis in otherwise collected random mutational states, and due to their "trained" adaptation, they form more effective distant metastases in different tissues. This critical phenomenon could be bypassed with such therapies to which all diverse cells are sensitive. For this, the synergy of thermal and nonthermal effects of the nonionizing radiation appears as an optimal candidate [327].



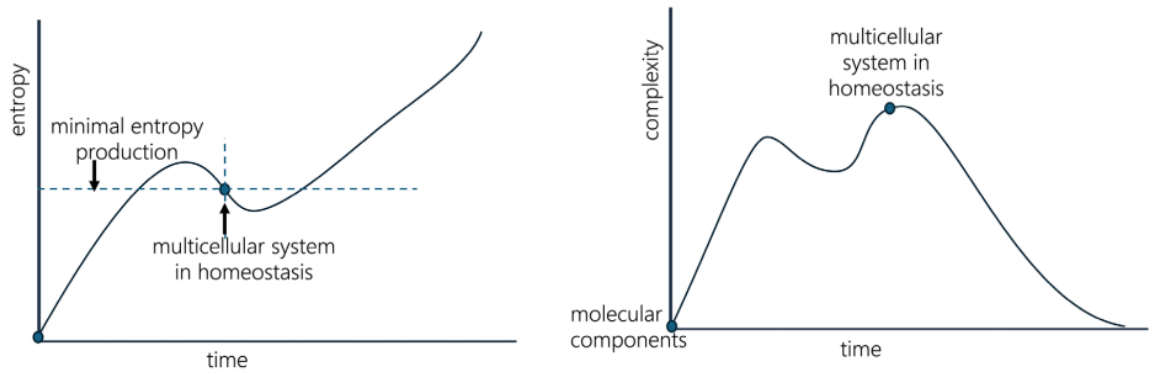


Figure 18. The differences between (a) unicellular living clusters, (b) healthy organized clusters, and (c) malignant clusters of cells. Clearly, the atavistic approach is only formal; the interactions and the organizing of the systems are different.

3.5. Cancer Prevalence

A power function of cancer incidence by the duration of exposure to the carcinogen was observed first in vivo in rodents [57]. The observed power value was 4-6, independently of the body size of mice. Human epidemiological statistics support this power law [328] [329] [330], which determines the cancer prevalence by ages:

$$(\text{prevalence}) \propto (age)^{\vartheta} \qquad (5)$$

where $\vartheta \approx 6\text{-}7$, depending on the tumor location and the environmental conditions, and looks valid between the ages of 25 and 74]. This power law means that $\vartheta \approx 6\text{-}7$ subsequent independent mutations must be collected to the clinically diagnosed cancer [331] [332]. The starting malignant cell goes through many stages with independent triggering to produce clinical observations [333]. A single "renegade" cell, as the starting point of cancer, has to be modified. Cancer development has essential complexity [334] that harmonizes with the multistep subsequent series of changes, which, in the end, manifests as a malignant tumor. Six subsequent mutations give the sixth power of age in the cancer observation. Another explanation was developed earlier [335]; oppositely to the unicellular mutations, a collection of six genetically altered cells would be a cluster, which results in a stable tumor. This clustering supposes exchange of some kind of networking information between the clustered cells, which is not the case at the beginning of cancer development; the cells follow unicellular life without a collective driving force. Even oppositely, these cells fight with each other for the available energy. The individualism and separation of the cells in starting malignancy points to the cumulative mutations that finally develop cancer, which must be intracellular at the beginning of the malignant process. The competitive evolution of the cell structure drives another possible mechanism causing the power law. The most viable cell wins. It is transformed and adapted completely to break the multicellular networking and develop individually malignantly [336].

The observed epidemiologic power function (5) practically means that a person collects a definite number of mutations for having cancer symptoms. The explanation of this observation may use network research. The complexity of biosystems is significantly more multifaceted than other

networks because the connections depend on local (like molecular, electric, structural, etc.) and global (physiologic regulation, including the material and information transports, adjustment to the permanently changing environmental conditions. All connections evaluate the interaction balance governed by the negative feedback signals.

The primary consideration for the power function of the cancer prevalence by age is the multistage cancer induction [337], where the distinct changes are heritable to the next stage, and their cumulative effect alters the normal cell to malignant. The bad luck in a single cell develops a proliferative malignant clone. The development of the subsequent steps to proliferate malignancy depends on multiple factors, including the dose of a carcinogenic load and the early history of the mutations, like ex-smokers predisposition to lung cancer [338]. Genetic instability, the single base change, or chromosomal instability may accelerate the malignant processes [339].

Note that the cancer observation, registered in the epidemiology statistics, gives information only about the diagnosed and registered tumors. This means that the last stage of the sixth degree of prevalence is the appearance of the cancer symptoms. Cancer symptoms occur in a significant portion of (~ 40%) of the lifetime of total human [340]. Still nonsymptomatic malignancy is observed in autopsies [341], and in ages 50+ probably everybody has some malignant neoplasms [342]. Mutations and genetic instability can already be present at birth [343], so cancer is a natural consequence of aging [344]. The power function may be modified in older ages when the dynamism of the cancer fission is limited. In human colorectal cancer, the power function is replaced by a linear function from the age of 60 - 65 [345], which predicts a lower incidence power. However, a single mutation could also be enough to trigger the malignancy.

A statistical model describes the power law with two independent (nonlocal) time parameters as the first manifestation of the malignant cell and the growth time of the detectable tumor, supposing their normal distribution [346]. The model described the power-law function well until the age of ~70, from where the hazard function decreases, corresponding to slower cellular development and the average human lifespan. The stochastic complexity challenges the deterministic statistical description of this model. The complexity of the dynamic interaction represents a feedback regulation of the system at every level of its structure. The complex system is not a sum of its distinct parts. The whole is more than the sum of the elements; the interactions are primarily non-linear; the system is energetically open and has adaptive exchanges with its environment. The approach to describing it must be analytic and not synthetic. Considerations regarding the complexity create considerable challenges in making the calculations. The attempted solution typically synthesizes the parts that could be calculated. However, this calculation strategy needs to be revised. The analysis must consider the complexity. Various models were elaborated for the human lifespan, and no one could be chosen as better than others to describe reality [347]. Many of these have no distinction between the development of malignant and benign tumors and do not consider the possibility of cell repair and the action of the immune system [348]. The stochastic processes in an individual and the differences between the individuals have to be considered for accurate description.

The observations prove that the malignant processes are general, and their symptom appearance is age and environment-dependent [301]. Consequently, the cancer prevalence in epidemiologic data is not equivalent to the cancer development. The collected number of steps to develop cancer differs from the epidemiologic morbidity data. The earlier statistics investigated mortality

data. Studying the age-specific mortality rates of different types of cancer [349] observed a better fit to the power-law function when the carcinogenic influences do not change during a human lifetime, while the variation of the strength of carcinogenic exposures may cause the deviation of the mortality rates from the expected function. By the time most cancers are medically manageable with various successes, modifying the mortality differing from the incidence (morbidity) of malignancy. Due to the trend variation between mortality and morbidity, the researchers narrowed their investigation scope to examine the cancer incidence rate. The six steps to cancer prevalence include the manifestation of clinical symptoms. Indeed, the transformation of the network forms and the connected interactions is a process that develops the symptoms and the clinically diagnosed form of the cancer step-by-step. The cancer development has subsequent steps that cause a power function of survival vs. age.

The biochemistry of cancer research focuses on the molecular processes of the internal driving force of cancer development [350], showing the random occurrence of malignant processes. The question appears to be whether environmental (circumstances, inherited features, aptitudes) or random ("bad luck") processes have a pivotal role in malignancy. A significant occurrence of cancer (~70%) is a consequence of random errors throughout DNA replication of healthy stem cells, which is an unpreventable "bad luck" developing malignancy [351]. The internal processes are strongly correlated with external influence. The living systems are energetically inseparable from their environment, so the synergy of the extrinsic and intrinsic factors is considered in cancer causes [352]. The inherent risk factors contribute to cancer development moderately (less than ~10% - 30% of lifetime risk), so extrinsic, environmental influences heavily affect the familiarly inherent effects [353]. According to our current knowledge, there can be many reasons for developing a malignant tumor, which in consequence changes multiple processes in the body Figure 19. These can be initially inherited by birth, can be environmental, aptitudes, or can be preventable causes by person, which are primarily connected to the lifestyle of the individual.

The standard, healthy cells are under the control of others ("social" signaling [354], a collective action). The cancer cells are different: they grow without control, their energy and material exchange are limited only by availability, and they are not affected by any regular control. Cancer has its growth factor and is not sensitive to growth inhibitors; it could avoid apoptosis and has unlimited replication potential with enhanced angiogenetic and dissemination (invasive) potential, too. They are autonomic instead of collective [completing structure]; they have a competitive driving force to survive among the shrinking sources of the diminishing availability of survival. The cancer develops through five interacting stages until became the epidemiologically observed 6th symptomatic Figure 20 [355] [356].

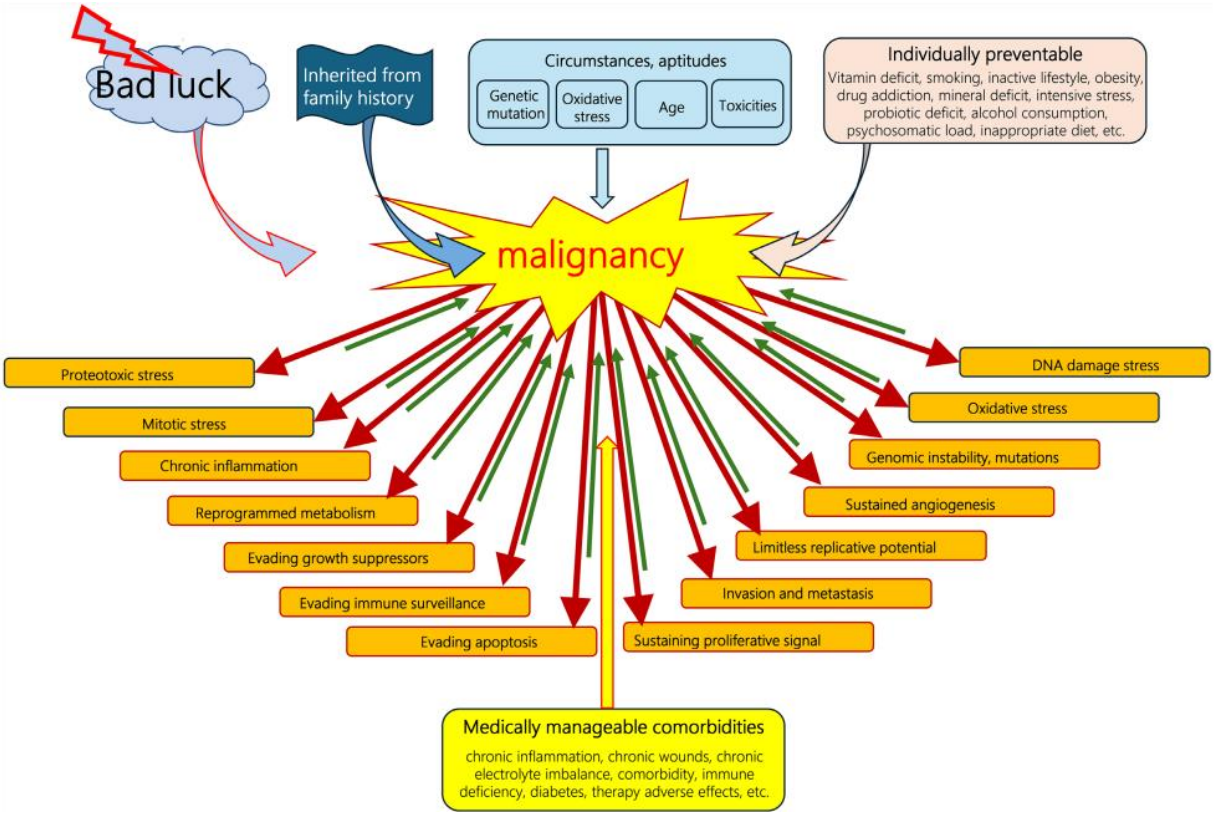


Figure 19. Some cancer-causing occurrences for humans. These are possibilities. All have a nonzero probability of cancer but are not sure to develop a malignancy. Having multiple factors rapidly increases the likelihood of cancerous diseases. The consequences modify the homeostatic control and introduce particular, only spite typical "hallmarks," which interact with the tumor and each other. The clinical symptoms of comorbidities, which can be a causing factor for cancer, are manageable, without cancerous symptoms.

3.6. The Cancer Game

Cancer is an evolutionary disease. Cells unicellularly adapt to the tissue environment; they thrive and individually fight for survival at the start of the tumor development. The Darwinian game with random mutations may describe the development of cancer.

There is a view that cancer in each population has the same role as apoptosis in the cellular structure. The part of both proceeds an altruistic suicide. Cells destroy themselves at the cellular level when damaged or pose a hazard to the network. Cancer is also a self-destruction of the individuals who carry dangerous mutations and so shows a threat to the genetic instability of the population [357]. This hypothesis argues that apoptosis is not a protection against neoplasms but a part of self-defense against genome instability. This attractive logic based on Darwinian natural selection has an evolutional contradiction. Cancer (the body's self-defensive action) massively appears in the population who are over the age, a replication of the dangerous genetic instability to the next generation. Another problem is that asymptomatic cancer development appears in most individuals during their lives, but despite its genetic instability, it does not present danger to their lives.

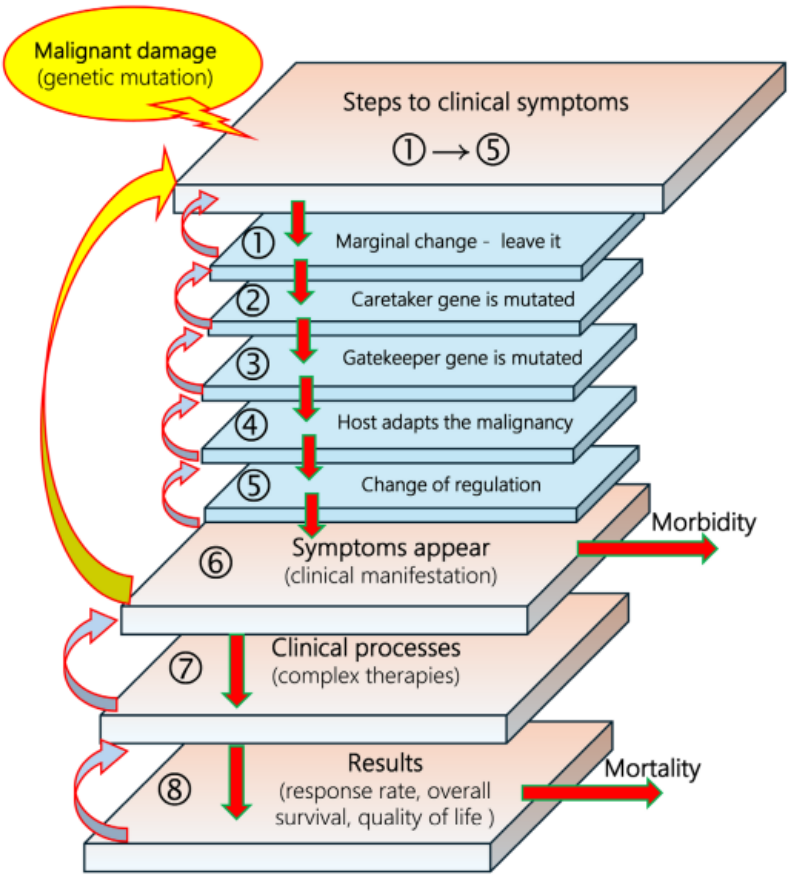


Figure 20. The steps developing cancer. All stages are interconnected with all others, the processes are driven in one direction, but they are not one directional.

The biochemical adaptation depends on the topology of the structure and the crosstalk of the nodes of the chemical reaction network. The mathematical models of evolutionary game theory could describe development and adaptation, considering non-linear interactions and newly appear traits in a population [358]. The genotypical and phenotypical extreme heterogeneity and the tumor in its elevated form significantly vary the type of cancer cell types. The interactions between the tumor cells and between the tumor and stoma cells may vary in competitive and cooperative game strategies. Tumour cells have different capabilities to cooperate, so a single cell does not have all the hallmarks of malignancy. The observed hallmarks are represented by an interacting group of cells [275], which could be used in the calculated cost of glycolysis [359] or described as predator-prey dynamics of fitness [360] generation.

The evolutional game theory (eGT) fits better for the dynamic complexity of cancer development than the classical version (c cap G cap T). G cap T centered on strategies instead of the game's players dynamically producing the payoff. While the cGT concentrates on winners in diverse conditions, static population, eGT is less varied, and the survivors with dynamic population are in the centre. The eGT examines such interactions where one's fitness depends on not only one's traits, but also the traits of others [361]. The hawk-dove game fits most to the intratumoral heterogeneity of cancer and its development, forming an evolutionarily stable strategy, a symmetric Nash equilibrium [362]. When tumors outgrow their available resources by transport from the healthy host, they reprogram their metabolic activity using energetically less efficient glycolysis (Warburg effect). The glycolysis may increase the fitness of the cancer cells due to the

advantage of their development, with quick and large ATP production and producing an acidic environment that is toxic for healthy hosts [363]. The situation is a typical classical model game called prisoner's dilemma [364], highlighting the tension between individual rationality and collective benefit. The metabolic payoffs would be higher for cells to cooperate. Still, neither the tumor nor the healthy cells prepared for unilateral change, so their metabolic strategy leads the cell population to commit evolutionary suicide. A complete understanding of cooperation among the cells of a tumor requires methods and concepts from evolutionary game theory [365]. Cancer development has distinguishable stages, which use various games by highly adaptable cancer cells for survival [356] Figure 21. All stages have the origin of Darwinian selection. In evolutionary game theory, payoff corresponds to Darwinian fitness. The players of the game, the cancer cells or stromal cells have strategies appearing in the phenotypes. Natural selection optimizes the game, which has a mixed gaming strategy over time by random mutations seeking to the highest fitness.

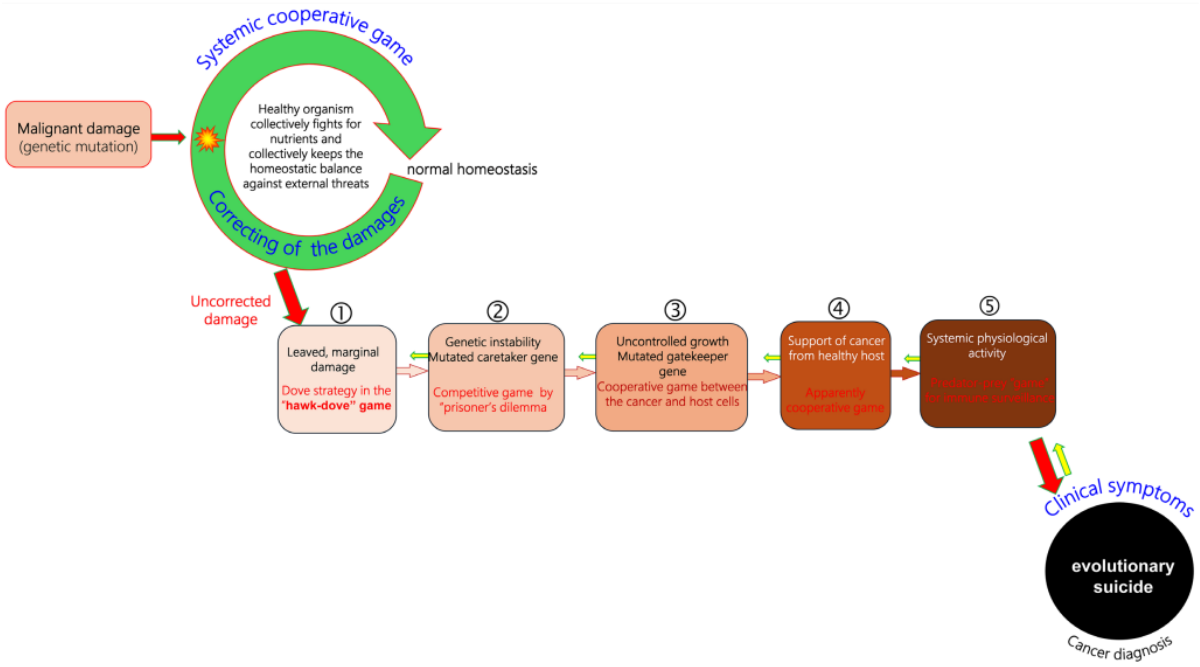


Figure 21. The five steps until the clinical appearance the sixth collected deviations. The six step to the symptomatic stage could be shorter (like the gatekeeper gene is mutated first) or longer (when the actual mutation is negligible).

The presence of clonal competition highlights the fundamental problems of neoplastic progression and problems of evolutionary biology [366]. The standard model of carcinogenesis usually applies a linear configuration of the development. The Darwinian selection model needs to consider non-linear dynamics, which studies the cellular genetic instability in the frame of the competition of genetic strategies [301]. We know that some mutations are inherited and indicate a risk of cancer connected to the mutated genes [367]. Some mutations develop de novo and are inherited in the next cellular generation. The tumor develops genetically in subsequent cell populations, not in a single cell. The cellular division replicates some epigenetic information with DNA methylation [368]. The cancer cells also have epigenetic mutations [369]. Inheritance has a crucial role in cancer development between the newborn generations and between the cells by division in a system.

The promoter-suppressor balancing effects appear in cancer development, too, having two balancing genes, the caretakers, which control the integrity of the genome, and gatekeeper genes, which regulate the functional growth rate, balancing between the proto-oncogenes, and tumor suppressor genes [370]. The mutations in caretaker genes can mutate gatekeeper genes, and the process follows the Darwinian selection [371] [372]. The environmental stress and complex interactions induce point mutations, which are believed to be adaptive, and amplification promotes genetic changes to enhance survival [373]. This interpretation does not describe the complete situation [374]. The challenge is that the random mutations can be disadvantageous with high probability and adaptively advantageous only with low likelihood. Statistically, a random mutation is an unfavorable bet. Contrary to their genetic instability, the cancer cells have a faster replication rate than the healthy cells. With simple logic, genetic instability causes a high growth rate. Nevertheless, genetic instability should be expected not only to be dangerous but also to be a part of evolution [375] [376].

Occasionally, a random mutation may modify a gatekeeper, which increases the growth rate. However, more mutations in the same cell induce cellular breakdown with a high probability. The replication of DNA is not perfect, modifying some sequences in the genome. Due to the compensatory dynamics (reversion), all stresses develop their reverse reactions, and even cancer therapies induce cancer by the reversing mechanisms [377]. Compensatory mutations benefit fitness when a deleterious mutation is present, but it does not block the vital processes. The selection pressure may favor mutants resistant to the external cytotoxic effects [378].
Genes synthesize their sequences autocatalytically, individually ("selfish" way [89]), and the cells containing them compete for resources. The cell's selection is based on its mutated gene. The cancer cells have extended adaptability to external conditions. They are not protected against environmental mutagenic attacks. Resisting and correcting errors takes time and energy, while ignoring those attacks, which are not lethal, has no cost. Consequently, errors (mutations) may be collected; the process depends on the frequency of the attacks, so the development is time dependent [301]. The accumulating mutagenic defects need increasing energy to repair, so ignoring those has an advantage when they do not affect the cell's vitality [379]. The genetic instability in mutagenic environments develops because DNA repair requests too much energy [374]. Behindhand DNA repair in normal, non mutagenic conditions also has an unbalanced payoff-cost game. The cost of DNA repair is primarily independent of the genetic location, but the cost of ignoring the error depends on its sensitivity; a slight change in the nucleotide chain has a wide range of minor to severe consequences [374]. The balance of cost/payoff preserving genetic stability is asymmetric and depends on the errors' type, occurrence frequency, and replication rate [301]. The chromosomal instability initiates the carcinogenesis [380]. In this way, carcinogenesis is based on molecular evolution in the Darwinian non-linear way. It unites the genetic and environmental influences in cancer development [379]. Carcinogenesis is based on DNA mutations. The selection of the already present mutated cells in the population of the multicellular organisms may be interpreted on the similar evolution at the population level of species, driven by the Darwinian law. The prevention of the development of mutated cells (cancer) is more complex than averting exposure to mutagens from the environment throughout the organism's lifetime. The already present mutations in the cellular population of the healthy organism can be selected by time during life when these cells have a survival advantage in the actual environmental circumstances. This interaction is non-linear, and the simple statistical variance concept does not describe the process well.

3.7. Cancer Treatment Considering Complexity

The overall surveillance of the conditions for homeostatic balance and equilibrium is the immune system. Interpreting immune activity within the framework of a predator-prey game offers a compelling and insightful perspective. The immune system acts as a predator by detecting and attacking pathogens or parasites that invade the host organism. However, the immune system and pathogens may undergo reciprocal adaptations like the coevolutionary arms race between traditional predators and prey. Pathogens evolve mechanisms to evade immune detection, while the immune system evolves to recognize and eliminate them. The immune system's actions help regulate the population of pathogens within the host. An effective immune response can control and limit the growth of pathogens, preventing them from overwhelming the host. Like the predator-prey balance in ecological systems, a well-regulated immune response contributes to the homeostasis of the host organism. Then, the fine-tuned balance of the immune system is a part of homeostasis: the overly aggressive immune response can lead to autoimmune diseases, while a weak response may allow pathogens to proliferate. A diverse immune system capable of recognizing a variety of pathogens contributes to the overall biodiversity of the host organism. The interaction between the immune system and pathogens imposes selective pressures on both parties. This process can lead to the evolution of more robust immune systems and more sophisticated evasion mechanisms in pathogens. However, investing resources in strong immunity is costly and creates a trade-off: stronger immunity might improve survival against predators but decrease resources for other life processes, impacting population dynamics.

The malignant cells may hide their behavior from immune surveillance. The malignant cells develop robust adaptability even to aggressive environmental conditions and the attack of natural immune actions. In the case of a developed malignancy, even robust natural immune procedures alone are ineffectual. The definite difficulty is that the malignant character of the tumor cells is hidden, and the immune cells cannot recognize these cells as a "disease"; the innate immune attack and the adaptive immune reaction are absent. The tumor disrupts the standard immune surveillance feedback at all points of its activity **Figure 22.**

Together with the tumor as organ concept another similar model of cancer states was developed: the tumor is a wound that has never healed [221], turning into a chronic injury [381]. The immune system does not affect the tumor as an organ (like it does not impact other healthy ones) and does not affect the wound; instead, it helps both. After an extended period, the inflammatory wound theory is emerging again [382]. The malignant tumor mimics a wound, stimulating the host tissue to support its "healing" [383], avoiding this "trick" attack by the host's Contrary the inflammatory immune cells in tumor, no immune attack destroys the developing tumor [384] because the cancer cell adapts to evade immune surveillance immune surveillance [385].

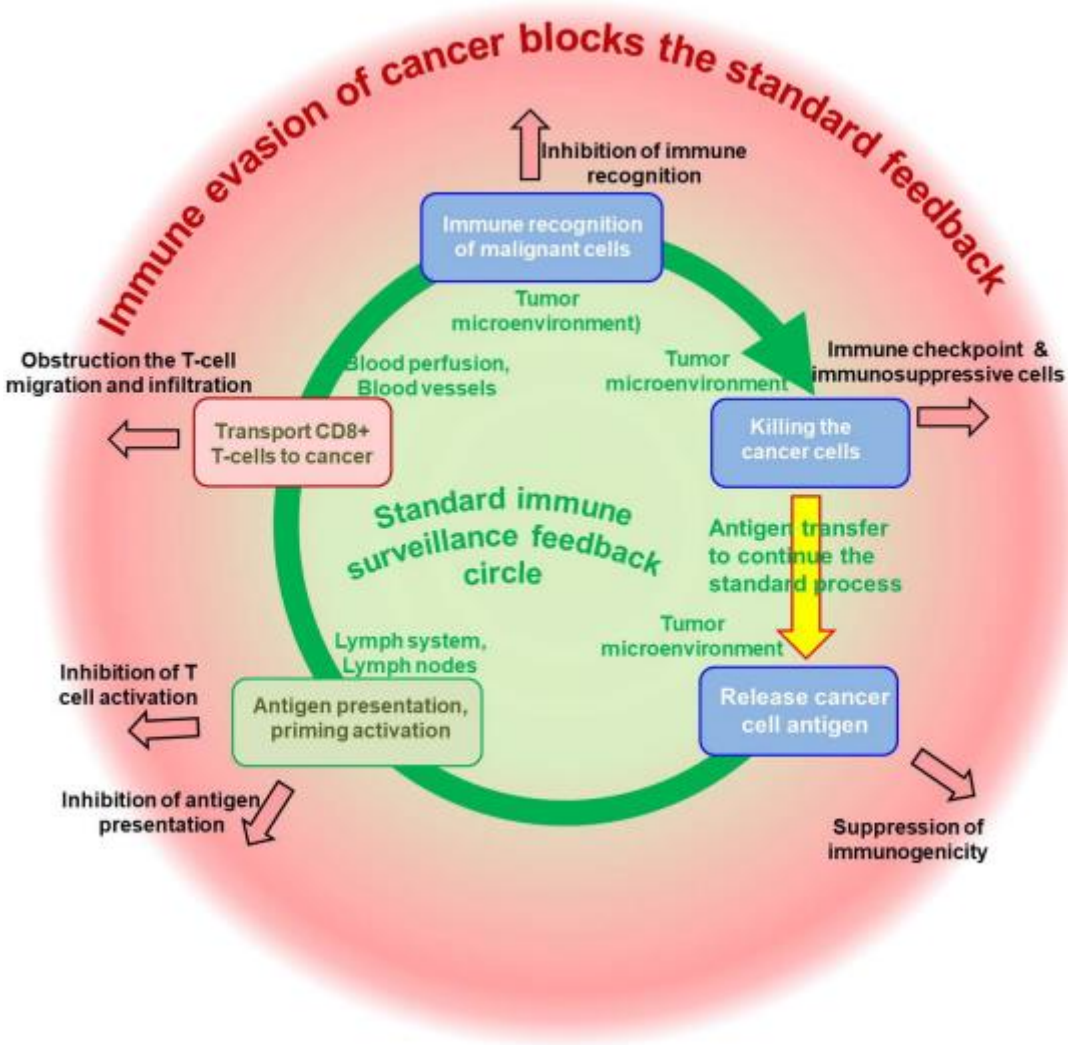


Figure 22. Malignancy evades immune surveillance. The standard immune control is diverted in all its steps, causing tumor evasion.

The malignant cells may hide their behavior from immune surveillance. The malignant cells develop robust adaptability even to aggressive environmental conditions and the attack of natural immune actions. In the case of a developed malignancy, even robust natural immune procedures alone are ineffectual. The definite difficulty is that the malignant character of the tumor cells is hidden, and the immune cells cannot recognize these cells as a "disease"; the innate immune attack and the adaptive immune reaction are absent. The supporting behavior of the host, which keeps cancer alive, forms a newer form of networking. Cancer has a strong side: its proliferation takes energy away from healthy host tissue, and the entire body will later suffer from insufficient energy. The strength of malignancy is the proliferation, and all malignant features are subordinated to this process. However, cancer has a weakness, which could be the point of attack: the cancer cells are individual (selfish). In the beginning, it destroys the healthy network around it, and in later stages, cancer also develops a network that differs from the healthy structures. The network of the malignant cells is out of systemic control; their collectivity is the common summary of the individual demands to use energy as much as possible for the cellular division, irrespective of the efficacy of the utilization. The cellular networks in cancer are deregulated; we must attack the weak side of cancer [386]; the missing or the changed networking may give crucial weaponry to the fight

against it. The fight must support the natural homeostatic balance Figure 23. The fight has to consider the interconnected networks [271] and the non-linear behavior of the processes [387]. The hybrid models that combine different modeling approaches could be the way forward in the fight against cancer.

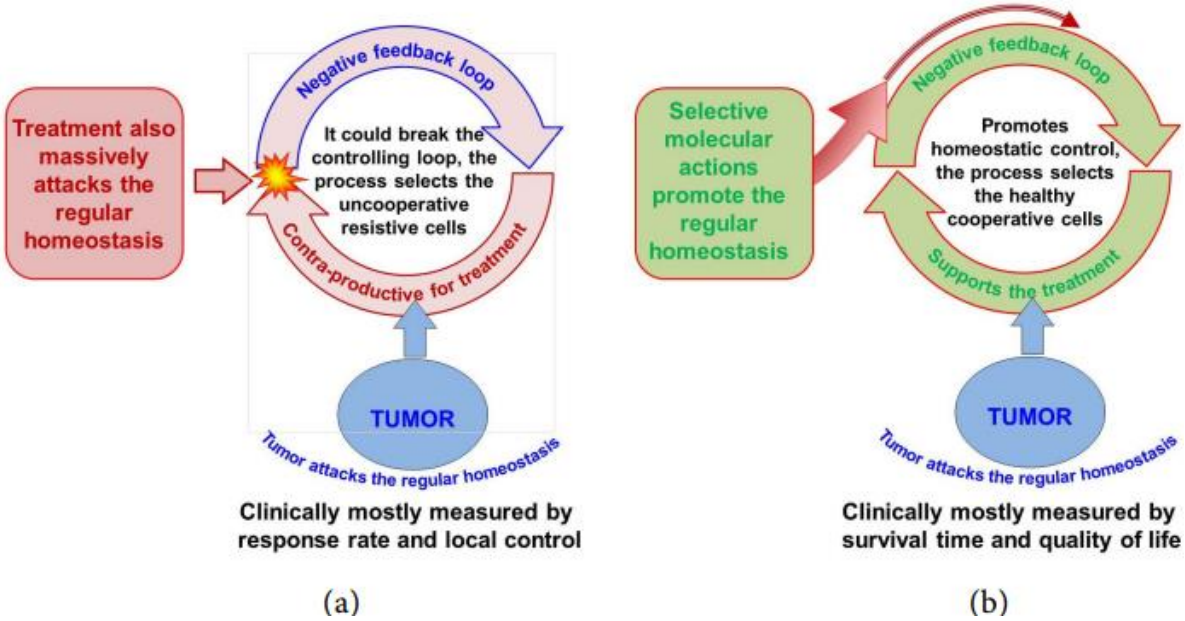


Figure 23. Treatments of clinically symptomatic tumors. (a) The therapy affects not only the tumor cells but also interacts with homeostasis, which works against the therapy and selects resistant cells to survive. (b) The efficient treatment must strengthen the natural homeostatic loops supporting the standard clearance of the malignant cells.

Based on the weakness of tumorous growth, a selective targeting of cancer cells with immuno-effective consequences could be applied. It is performed with a synergy of thermal and nonthermal effects, which are not ionizing and not chemical in origin, so it can bypass the complications associated with tumor-cell adaptation. The targeted tissue's natural electric and thermal heterogeneity is used to find the cancer cells selectively. The 13.56 MHz nonionizing electric field selects the tumor [388]. The applied 1/f modulation [389] [390] realizes a mixed game strategy with randomly appeared frequency in the distribution of the 1/f noise. Adapting this situation is possible only when the malignant structure constrained to have healthy interactions which has the same 1/f signal. Under the modulation compulsion the cellular connections could be restored [109] [110] forcing the malignant structure to follow the healthy networking strategy. The homeostatic self-similarity [59] and the dynamism with the self-time [3] repaired. The 1/f signal fluctuation characterizes the healthy homeostatic signal distribution. The deviation from it, could be a sign of unhealthy processes [193].

The amplitude-modulated radiofrequency by 1/f frequency distribution is dominantly absorbed by the transmembrane proteins of the malignant cells [391]. Exciting the TRAIL-FAS-FADD complex, the targeted cells are destroyed by immunogenic cell death [392], producing extracellular damage-associated molecular pattern (DAMP) (HSP70, HMGB1, ATP, and calreticulin). The liberated molecules help the antitumor antigen presentation and priming killer and helper T-cells, which actively attack the cancer cells in the entire body (abscopal effect) **Figure 24**. The synergy of the

thermal and nonthermal effects strengthens the immune surveillance against the malignant cells in all over the body [393].

Preclinical studies proved the selection in vitro [388] and in vivo [394] and verified the development of DAMP [395], immunogenic [396], and abscopal effect [397]. Clinical studies validate the method [327]. A Phase III study showed a significant elongation of the survival time of patients with advanced cervix cancer [398], with improved quality of life [399] [400], and abscopal effect [401]. Numerous Phase II clinical trials show the same significant improvements for pancreas, glioblastoma, and lung cancer [402]. Other studies and case reports support the success of complementary applications with immune checkpoint inhibitors [403] and supportive therapy [324] [404] and were investigated in stand-alone therapy in a palliative setting [405].

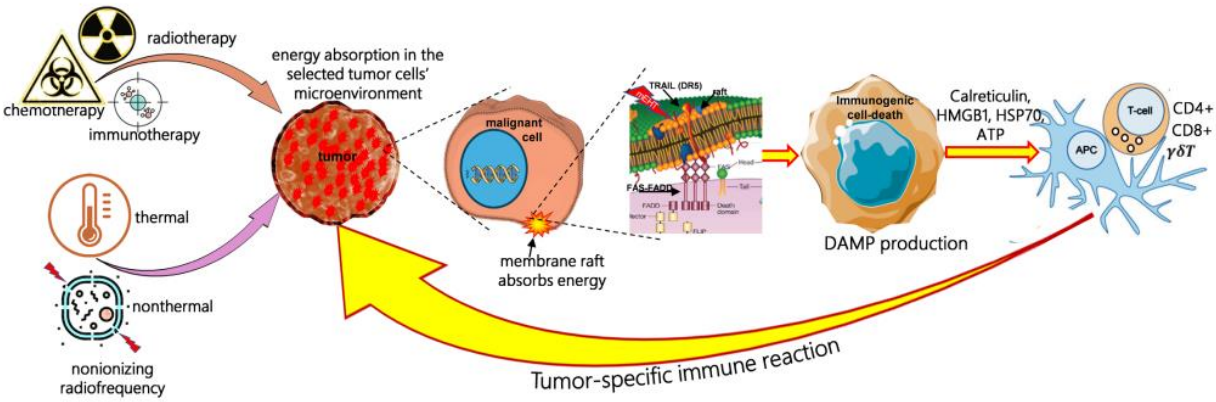


Figure 24. The applied synergy of thermal and nonthermal effects with possible (but not necessary) complementary treatments develops tumor-specific immune reactions and can kill the tumor and its metastases delivered by the systemic transport in the entire body.

4. Conclusions

Biological regulation is realized by a system of homeostasis, which regulates and controls the balance of the various processes. The system's complexity appears in its energetics, which tries the most efficient use of the available energies; for that, it organizes various well-connected networks. All processes are interconnected in networks, having decisional influence by the environmental conditions and the nurture. Homeostasis may be described as a Nash equilibrium, which ensures the distribution of the energy in a "democratic" way regarding the functions of the parts in the complete system. The game seeks to Nash equilibrium. The strategy of the game merges the self-interest (own payoff), collective interest (group payoff), and local rivalry of interest (payoff variations).

Cancer radically changes the network system in the organism, making it a network disease. Network changes appear at every level, from genetic (molecular) to cells, tissues, organs, and organisms. Aging increases the likelihood of cancer. Epidemiologic statistics show that multiple steps (collected mutations) are necessary for the prevalence of cancer. These steps could be modeled with games and network changes.

The fight against cancer must attack the weakest point of the malignant development: their missing or loose networking. Reestablishing normal homeostasis and immune surveillance appears as a reliable way to attack the weak point. One of the possibilities is to apply a synergy of thermal and nonthermal electromagnetic effects, which may modify the system but could cause minimal resistance or adaptation of the malignancy. The malignant processes can be blocked and corrected by developing a tumor-specific immune reaction; when the regular immune surveillance works again, cancer cannot evade this control.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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