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Igor Balaz
Andrew Adamatzky *Editors*

Cancer, Complexity, Computation

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Preface

Cancer is the most enigmatic health disorder humanity ever experienced. The last decade witnessed rethinking and reunderstanding of cancer. Cancer is not an evil creature. It is just a creature who wants to live, as all other living beings do. The book brings together biomedical scientists, biophysicists, mathematicians and computer scientists. They share their unorthodox views on origins, progress and treatment of cancer. J. James Frost opens the book with his chapter uncovering two key properties of cancer: symmetry-breaking and computational intelligence. Then Przemyslaw Waliszewski discusses cancer in the light of complementarity, complexity and fractal dynamics. A chapter from Thomas E. Yankeelov's laboratory analysis of how medical imaging technologies can be used to obtain patient-specific parameters for mathematical models of cancer is given. The effects of over-feeding in computational models of tumour growth are discussed by Pan Pantziarka and colleagues. Conway's Game of Life cellular automata are modified with global coupling in the chapter by Vladimir García-Morales and colleagues to model tumour growth. Oscar J. Suarez and colleagues discuss the potential of controlling genetic regulatory networks to tune cellular response to cancer. Milos Savic and colleagues present implementations of heterogeneous tumour modelling with PhyssiCell software and the implication of the heterogeneity in precision medicine. Sensitivity analysis of the cancer stem cells dynamical simulation is studied by Branislava Lalic and Igor Balaz. Marina Kovacevic presents her pioneer results on the molecular multiscale simulation of nanocarriers for cancer treatment. Michail-Antisthenis Tsompanas and colleagues present a haploid-diploid evolutionary algorithm for the Optimization of nanoparticles for cancer treatment. Perspectives of nanomedicine for cancer treatment are overviewed by Petra Gener and colleagues. A chapter from the Sabine Hauer's group outlines the future of cancer medicine based on swarms of nanorobots. The book ends with a chapter on modelling of angiogenesis with differential equations and cellular automata authored by Ioannis Karafyllidis and colleagues. Benedetta Casadei with co-authors overview strategies and mathematical models to study the complexity of drug resistance in cancer. Hector Zenil and colleagues discuss how to use computational analysis to unravel the complexity of the immune system. The book is mostly self-contained and well-illustrated, and chapters are written in a lively style. The book is accessible to readers from all walks of life and level of education, from laymen and high school students to experienced researchers.

Novi Sad, Serbia — Igor Balaz
Bristol, UK — Andrew Adamatzky
March 2022

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What Cancer Is

J. James Frost

...it seems to me that I must consider as contained in the individual concept of myself only that which is such that I should not longer be me if it were not in me: and that all that is to the contrary such that it could be or not be in me without my ceasing to be me, cannot be considered in my individual concept.
Letter from Antoine Arnauld to Gottfried Leibniz [1].

Abstract The problem of cancer is examined from the metaphysical standpoint of essence and ground. An essentialist definition of cancer is assumed that would be valid in all possible worlds in which cancer could logically exist. The grounds of cancer are then examined and elucidated. Two grounding cancer properties are identified and discussed: symmetry-breaking and computational intelligence. Each examination leads to concrete conclusions for novel therapeutic approaches and a more fundamental understanding of what cancer is at bottom. Other possible cancer grounding properties related to evolution, adaptability and stochastic features are identified for future work. This approach is novel and offers new solutions to the problem of cancer.

Keywords Cancer · Intelligence · Symmetry-breaking · Computation · Ground

1 Introduction

Identifying a solution to the unsolved problem of cancer is currently based on a program of scientific reductionism, in which each new solution attempt provides temporary patient benefit until the oncologist and the field of oncology itself reaches the end of yet another box canyon.[1] In 1990 5.7 million people died from cancer worldwide; in 2017 the number of deaths increased to 9.6 million. Each new

[1] A canyon with vertical walls and closed upstream with a similar vertical wall, that is, a dead end.

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approach, from deep DNA sequencing, to exquisitely-designed molecular targeting, to the intricacies of epigenetics follows a well-worn path of near certain scientific justification and overwhelming enthusiasm to modest gains in some cancers in select patient populations—all at a worldwide cancer research expenditure of $100 billion in 2019.

This chapter examines an alternative to the regime of scientific reductionism. It is concerned with an essentialist definition of cancer and what then grounds cancer 'at bottom'. The approach strives to strip cancer to its bare bones, and then to examine the necessary properties cancer requires to manifest the characteristics observed everyday in cancer patients. It then leads to a consideration of concrete inferences that, in turn, result in greater insight into cancer and therapeutic strategies that have not previously been considered. Two aspects of this analysis are cancer symmetry breaking and computational intelligence. Each can be derived from a fundamentality approach presented here and can be considered as two of cancer's grounds. Each additionally leads to material conclusions for novel solutions to the cancer problem.

2 Cancer's Essence and Ground

Essence is what it is for an object to be the very thing that it is. It is the fundamental definition of an object—its definition at bottom. Essence is a metaphysical concept of what it is to be that thing in all possible worlds that are logically realizable [2–4]. Essence is thus a necessary feature of an object [5–8]. It is a property an object could not lack and still be that object. An essence definition should be independent of the conceptual apparatus that observers bring to bear on it [9]. It may be singular (monadic) or plural [10, 11].

To be human is the essence of Socrates and that would be true in all possible worlds in which Socrates could exist. A possible world is an instantiation of reality in which the world's accidental or contingent properties are different than in our actual world [9], for example, a world in which I myself, giraffes, Harvard, the US Constitution, Samuel Clemens, oak trees, and Chevrolets don't exist. In their place are other objects, concepts, and relationships. For cancer, a possible world is one in which biochemistry, some physical laws, and organizational properties are different than in our actual world. For example, a world in which life is based on RNA or some other coded information, where transforming growth factor, tumour angiogenesis, or any of the cancer hallmarks [12] don't exist. A statement of essence will not include the properties of the object itself to avoid problems of self-reference and circularity [13, 14]. Essence statements may extend from coarse to fine-grained [15, 16]—fine-grained essence statements are most relevant to scientific explanations of natural phenomena.

What might be an essence statement for cancer that would be necessary in all possible worlds in which cancer could logically exist? Logically, existence means that properties cannot violate first order logical principles, such has having and simultaneously not having a certain property, or violating implication principles. We can try on the following essence statement and see if it works as we move forward: *Cancer expands physically and biochemically to overcome and destroy its host and, thereby, the cancer itself*. One could construct other essence statements in this spirit. That is, statements that do not reference the actual properties of cancer, thus avoiding circularity. Conversely, the statement could encompass other processes, like man's destruction of the environment as "a cancer on the planet" [17–19]. The cancer essence statement incorporates none of the traditional cancer hallmarks [12, 20], which can be viewed as accidental features of cancer in our world. Certainly, we have to deal with the cancer we know, including its mutable properties. But here, examination of matters of fundamentality is the goal. Again, the actual properties of cancer in our world are not features of the essence statement above. Can we learn something new about cancer by considering its essence?

Each term in this essence statement has meaning. Expansion encompasses physical extent and scope. The biochemical expansion of cancer and subversion of normal homeostatic physiology and biochemistry is a key aspect of cancer. It is as much responsible for cancer's deadly features as is physical expansion in space. Metastasis is omitted since cancer can expand in possible metaphysical scenarios without metastasizing, e.g., by the expansion of a solitary mass, as is the case in some malignant cancers. Cancer must have a host with a preexisting structure, mode of energy production, and biochemical machinery that can be co-opted for the cancer's new purpose.[2] Cancer is a progressive process that first overcomes the host's normal biochemistry by overthrowing and subverting it for a new functional purpose. It eventually destroys the host and thereby the cancer itself—how it accomplishes this is left out of the essence statement. The nature and period of time of the subversion and destruction process is variable, from months to years. Indeed, a current treatment approach is to lengthen this period in order to prolong the life of the host—the patient [21–23]. Space, energy, and information are key background features of this essence statement that require examination.

Leaving essence for now, the concept of "ground" is examined. There are a number of meanings of ground in the philosophical literature, but a useful one for scientific purposes in describing natural phenomena is: ground is a relationship between facts [15, 24–27]. A fact is grounded by grounds or ground claims. For example, that this drink is a cocktail is grounded by the drink being alcoholic and mixed [15]. Other examples include a physicalist asserting that nonphysical facts are grounded by physical processes; natural laws are grounded in patterns of local, qualitative matters of fact; and a person in pain is grounded in the firing of c-fibers [14, 15]. Thus, ground has explanatory and deterministic features that create a hierarchy of stratified facts of reality. Ground provides an explanatory or "because of" characterization of facts, creating a level structure that ends with a foundational fact in the explanatory chain. In this construct there may be ungrounded facts at bottom that are primitive or pre-rational [28]. Ground is typically a many-to-one relationship, in that many properties can jointly ground an item [29, 30]. Grounds portray

[2] Viral and other external (e.g., radiation) modifications of the host's molecular machinery that lead to cancer are a subcategory.

an antecedent-consequent relationship, in that the antecedent grounds the grounded consequent.

Grounding can be differentiated from causality on two fronts. Causality is typically diachronic whereas grounding is synchronic [31]. Second, causality is a relationship between events whereas ground is a relationship between facts [25, 31–33]. This distinction will deserve further examination for cancer. A ground may be full or partial. For example, being a mixed drink and being alcoholic are both partial grounds for being a cocktail. Partial grounds will be important for cancer. Ground obeys transitivity: if A grounds B and B grounds C, then A grounds C. The hierarchy of grounding relationships in cancer will be important to examine, as discussed below.

Ground and essence are related: when a connection of grounded facts exists, the truth of the grounded connection will be based in the essence of the constituents of the grounded fact [24, 25, 27, 34, 35]). In fact, the relationship of ground to essence, causality, and necessity is a current area of active investigation. Some argue that ground reduces to essence, and others the converse [36–39]—avoiding circularity is key here. Essence statements can be divided into *objectual, generic* and *factual* categories [11, 38–40]. Essence statements as definitions are equivalence or identity statements, such as: water is H_2O. Full essence statements are symmetric and imply necessity. The proposed essence statement for cancer above is viewed as generic essence since it refers to a process or concept, rather than a pure object, such as Socrates. Whether it is full or partial is explored subsequently.

Ground, in contrast to essence, reflects an asymmetric, irreflexive relationship between the grounded and the grounds [29, 41, 42]. In scientific analysis, in particular, ground offers an explanation between the *explanandum* and the *explanans*, the phenomenon to be explained and the sentences offered to explain that phenomenon [35, 38]. Ground is a "because of" or "makes it the case" type of statement. Ground is a *constitutive* relationship between one or more grounds for the grounded object or phenomenon that results in a *sufficiency* relationship. In the essence or definitional framework, the relationship is of *necessity* and is reflexive [36, 43, 44]. That a ball is red and round is grounded by the fact that it is red and that it is round, but not the converse direction. Another example: the laws of nature are grounded in patterns of local, qualitative matters of fact. A grounded fact is less fundamental than the fact that grounds it. Ground is a type of deterministic relationship, the strongest form of metaphysical explanation [44–46]. Hence, determination implies metaphysical sufficiency for what is grounded, and metaphysical sufficiency then suffices for necessitation [14]. For cancer, both necessary and contingent grounds exist, the former providing the explanatory role in all possible worlds and the contingent in this.[3]

Of the many varieties of grounding, "grounding explanation" is most useful for natural phenomena and scientific accounts and laws [35, 45]. An explanation has a fact that is explained, the *explanandum*, and the *explanans* fact. As addressed above,

[3] Cancer has indeterministic properties as well, for example, random mutations related to its origin and evolution, and the stochastic binding of transcription factors to their genomic sites. The overlap and interplay of deterministic grounds and non-deterministic features await further research.

the *expanandum-explanans* is a "because of" relation: the fact that the window shattered, the *explanandum*, and Suzy threw a rock at it, the *explanans*. This grounding explanation is synchronic, whereas the equivalent causal explanation is diachronic. Grounding explanations are irreflexive, asymmetric and transitive [41, 42, 47]. To clarify the overlap with causation, one considers constitutive grounding explanations. These are a hierarchy of chaining facts that constitute an object: there is a table here in virtue of there being wood arranged here in a certain 'table-like way. Lest this become too abstract for the present purposes, one can posit the question of whether cancer is explained by the arrangement of genes, proteins, signaling receptors, histones, etc. in a 'cancer-like way'. Is there something beneath the facts of cancer that provides a grounding explanation for cancer?

An important grounding category, particularly for scientific explanation, is that of *essentialist grounding mechanisms*, which link back to the essences of the objects in a hierarchical chain [32, 33, 35, 48] In this view, object essences require certain determination relations to exist. A grounding mechanism explanation then delineates how the connections run between the grounding facts and the fact they ground [49]. This can be a fine or coarse-grained description that encompasses quantum mechanics, covalent and ionic bonds, molecules, DNA, and transcription to a functioning gene. Different levels of explanation and their corresponding scientific disciplines will bottom out at different levels; molecular biologists will bottom far before quantum mechanics, for example. Here we address where cancer explanations may bottom out in the domain of necessary facts that would be true in all possible worlds.

In the case of cancer we will examine the relation of the essential definition of cancer, above, to its grounding mechanisms. This view overlaps with law-like natural phenomena and, indeed, the concept of a law itself [46]. Are there any laws of cancer that can be discovered? The Cancer Hallmarks were an early attempt at describing the recurring features or properties of cancer that might give rise to law-like explanations. The Hallmarks are, however, the "accidental" features of cancer [50]. They are, accordingly, not necessary and cannot be the basis of "cancer laws". Here, we seek laws that are not based on nor incorporate the contingent cancer facts, but rather ground these facts. The detailed relationships among grounds, laws, events, and causality is a complex area of active research [46, 49, 51, 52], but is beyond the scope of this work.

3 Cancer Hallmarks as Contingent Properties

The Hallmarks of Cancer was a seminal advance in the conceptual view of cancer [12]. The hallmarks delineate the common features or traits of cancers across organ origin and pathology. The initial list of hallmarks includes: self-sufficiency in growth signals; evasion of apoptosis; insensitivity to anti-growth signals; sustained angiogenesis; tissue invasion and metastasis; and limitless replicative potential [12].

In an updated account, two hallmarks were added: deregulating of cellular energetics, and avoiding immune destruction [20]. Two additional enabling characteristics are: tumour-promoting inflammation, and genome instability and mutation. While the hallmarks provided needed insight into common cancer traits and have been applied to new therapeutic developments, the problem of cancer has remained largely unsolved.

The centrality of the hallmarks has been questioned on several accounts. One category is the emphasis on proliferation and motility in the context of a similar importance in development and in benign tumours. Several analyses have pointed out the overlap in feature of benign and malignant tumours [53–57]. Endometriosis is example of an abnormal cell migratory process that is not cancer. Another category of critique is the reliance on the reductive regime of somatic mutation theory (SMT) [57–60]. This approach has recently given rise to the non-deterministic "bad luck" theory of cancer neogenesis based on copying mistakes proportional to the normal cellular replication rate [61, 62]. Further, the hallmark traits shift in their hierarchical importance at different times in a cancer's evolution and during treatment [20, 56]. SMT can be contrasted with the multilevel-based tissue organization field theory [54, 63]. This viewpoint avoids a purely reductionist theory and examines cancer as a multilevel process that features upward and downward causation.

The Hallmarks may also be questioned as grounds of cancer that would be necessary in all possible worlds in which cancer exists—clearly they are not. In other worlds, other Hallmarks would exist, some possibly overlapping with those in this world, some eliminated, and new ones added. The central question is: what grounds the Hallmarks at all in any possible world, including this one?

4 Cancer's Broken Symmetry

Symmetry pervades the world, from nature to human art and construction to the fundamental particles of physics [64, 65]. It is, however, uncommonly a perfect symmetry, like a sphere, but most often an imperfect or broken symmetry [66–68]. Broken symmetries appear and resolve continuously over time, for example, as water freezes and thaws again to its more symmetric liquid state. Perfect symmetry achieves little in nature nor in art or human construction. Only with a judicious level of broken symmetry does functional structure arise. Conversely, states of maximal or fully broken symmetry are chaotic and generate nothing. Symmetry and symmetry breaking is a foundational property of the universe and is grounded at bottom in space and logic itself. This can be most directly seen in the Noether theorems that demonstrate an underlying symmetry in the key conservation laws of physics, including the conservation of energy and angular momentum [69, 70]. Cancer is an interesting example: its *sine qua non* is broken symmetry from the cancer cell to the chromatin itself. A useful consequence of this fact is that all cancer is diagnosed and graded based on the degree of cellular disorganization.

The categories of cancer's broken symmetry have been examined in a previous work [71]. Three essential questions are addressed: what features or mechanisms ground the observed macroscopic broken cellular symmetries; what classes of broken symmetry exist in cancer cells; and how can improved knowledge of broken symmetry in cancer be used to advance patient treatment. The three categories of broken cancer symmetry are: combinatorial; geometric; and functional symmetry breaking [71]. One example of combinatorial symmetry breaking is the broken symmetry of the epithelial-mesenchymal hybrid cell state to the pure epithelial or mesenchymal type. Since it is the mesenchymal cell type that metastasizes, this broken symmetry is a key determinant in cancer progression. The molecular constituents underlying this symmetry change include ZEB, SLUG, TWIST, miR-200, miR-34, and many others [72–75].

The most widely-recognized feature of broken symmetry in cancer is that of the cell shape. Shape progresses from uniformity within different organs and functional cell types to an increasingly disorganized structure that correlates with malignant potential and patient prognosis. What grounds this broken symmetry? The internal cellular matrix, consisting of microtubular structural filaments, largely determines the cell shape [76–78]. These microtubules comprise a tensegrity-based supporting structure that has its own internal symmetries. Microtubules are also thought to transmit information from the environment to the internal cell structures [78–80]. Recent investigations have even shown that microtubule and actin networks can compute [81–83]. An outstanding question for future research is the degree to which broken symmetry in microtubule networks grounds intrinsic cellular computation, a topic addressed in the next section. Does cell asymmetry and coincident intracellular actin filament asymmetry confer a computational advantage for cancer cells?

In the category of functional symmetry breaking, the symmetry of gene, protein and other cellular networks is key. All networks can be classified according to the symmetry features of the connected network components [84–87]. Graph theory grounds the network symmetries and is a powerful tool for investigating cellular networks [88–91]. The automorphism group, Aut(G), is a key parameter [92–95]. The Komogorov complexity, K(G), is another that is inversely related to Aut(G) and correlated positively with information processing capacity [96–100]. Function networks must be stabilizable and controllable to store and process information required for survival of the cell or organism [101–104]. They must be resistant to disruption due to a loss of functionality at one or more points in the network [71]. Network homeostasis is closely related to network symmetry. Conversely, network vulnerability is directly related to focal network asymmetries. The vulnerability of electric power grids, for example, is related to the number of hubs where multiple connections are concentrated. The broken subgroup symmetries in cancer cell networks are related to the level of attack tolerance at the sites of reduced symmetry in cancer networks [105–111]. Identifying subgroup cancer network broken symmetries is a viable strategy to direct targeted therapeutics to these sites [84, 89, 90]. This is one of the many concrete examples of knowledge of symmetry breaking in cancer potentially leading to improved therapeutic strategies, and perhaps more importantly, the development of new, targeted drugs for these sites. In parallel, could this knowledge be used to repair cancer networks to reestablish homeostasis? Other directions for cancer symmetry-breaking research are listed elsewhere [71].

Symmetry and symmetry breaking are thus one possible ground for the essence of cancer statement above. Since symmetry exists in all possible worlds in which hosts and cancer can logically exist, it would satisfy necessity. It is, however, only a partial cancer ground, so satisfaction of the sufficiency criterion remains a question. The next section examines computational intelligence and information transfer in cancer. A question of where symmetry and symmetry breaking lie in the explanatory hierarchy with computation and information emerges: a question of fundamentality.

5 Cancer's Intelligence

Intelligent oncologists wage a valiant battle against cancer every day. They nevertheless have limited success in curing cancer or even arresting its progression in the majority of cases: there are still some 10 million cancer deaths per year worldwide. Cancer computes inventive solutions to the oncologist's various strategies, and eventually wins the game in the majority of cases. It is indeed a gameplay: the intelligence of the oncologist vs. the intelligent cancer, as has been described in a recent article [112]. This view is grounded in the definition of intelligence and what can be intelligent. The definition of intelligence for these purposes reduces to computational intelligence and excludes conscious awareness. It is most immediately concerned with the ability to learn, problem solve and adapt. Deception, bluffing, and prior computation of actions for an array of possible future events are additional features of intelligence.

Daniel Dennett has examined intelligence in terms of biological competency. He describes four levels: Darwinian, Skinnerian, Popperian and Gregorian, in order of increasing competency [113]. Each level can be linked to features of cancer, thus viewing cancer as possessing many properties of intelligence [112]. For example, does cancer learn from its earliest encounters with host defenses, store this information in memory, preemptively compute solutions to future chemotherapeutic actions by the oncologist, and at the right time implement these defense measures? Or, does cancer generate real-time intelligent strategies as new survival problems arise? The strategic balance of memory and active computation is a feature of intelligence; both are limited as a function of the computing architecture and the supply of energy. *Cancer's Intelligence* examines these and related questions [112].

What can be intelligent is broad and extends from animals to bacterial swarms [113–120] (ref from paper 9,10). In short, anything that can compute can be intelligent. It is well known that pebbles, knots on a string, a slide rule, and silicon-based computers themselves can compute. Chemical matter can compute, as well, including the Belousov-Zhabotinsky reaction, liquid crystals, carbon nanotubes and conductive foams [121–123]. Biologic matter also performs computations, including with gene networks, DNA, actin filaments and microtubules, and the famous slime mold [124–128]. In fact, biological matter can solve some of the most challenging computational problems in existence, such as the traveling salesman problem [129]. Biological computation in organisms can be classified as intrinsic computation, that is, self-computation, as opposed to external computation by the desktop computer in front of us [130–132]. Cancer, with its varied cellular composition and extended networks, eventually computes its spread throughout the body. A co-opted microenvironment and relentless evolutionary adaption presents a formidable computational adversary for the most intelligent oncologists.

The intrinsic computation of cancer can be described by its ε-machine [133–136]. The ε-machine is an inferential model of the cell's or multi-cell system's capturing and processing of information "that permits the system to read the environment's information and rate of change; store and process that information; create an internal efficient model representation of the environment; and use the model for future decisions and actions". As a function of evolutionary change, the caner ε-machine can be updated to a new computational architecture in order to better outplay the oncologist's strategies, or to develop improved resistance, such as by adopting a quiescent state. Energy, space, and other resources limit this adaptive process. Although ε-machine theory has been applied to many computational systems, it has not yet been developed for cancer. Further discussion of the ε-machine, the role of Shannon entropy-complexity descriptions, and the outlook for its application to cancer are covered elsewhere [112]. Boolean network theory provides a tractable approach to defining the cancer ε-machine(s) [137–143].

Once the caner ε-machine structure has been elucidated, the question then becomes: how can it be out-computed by the oncologist? In the concept of gameplay between the two adversaries, one can consider the most advanced types of human gameplay, including chess, go and poker. How can new artificial intelligence (AI) algorithms for human gameplay be applied to the cancer problem? One of the most exciting recent AI developments in human gameplay has been for limit and no-limit Texas hold'em poker [144–147]. Two-player poker is a vastly more complex game that chess or go, with a state space of 10^{160}. The new poker AI algorithms use counterfactual regret minimization and other techniques to make the problem solution tractable—it can now beat the best professional poker players [145, 146]. The algorithms also incorporate the bluffing plays that are central to poker and mimic the deception observed throughout nature [112, 147]. In the early development stages of game theory with imperfect information, von Neumann recognized the importance of deception in nature: "Real life consists of bluffing, of little tactics of deception, of asking yourself what is the other man going to think I mean to do. And that is what games are about in my theory." Further: "An organism that has no poker face, that communicates its state directly to all hearers, is a sitting duck, and will soon be extinct" [148]. *Cancer's Intelligence* explores the question of whether cancer bluffs and how the new poker AI algorithms can be used as future AI tools for the oncologist [112].

Limit Texas hold'em is easier to solve compared to no-limit Texas hold'em since the limit on betting places significant restraints on the number of possible game plays. The degree to which cancer gameplay is a limit or no-limit game is an interesting question for future investigation—here the limits are resource expenditures or allocations to the game by the cancer and the oncologist's time and actual monetary expenditures, or bets, for the therapy actions. Multiplayer poker is even more complex and possesses a non-computable Nash equilibrium [146]. Cancer's game against the oncologist is most certainly a multiplayer game on cancer's part since it plays multiple strategies simultaneously, and even shares cards from the hands of its multiple players within the molecular defense armamentarium it brings to game. Perhaps that is an insurmountable game for oncologist, even with improved AI tools. Only further investigation will provide the answer. Several signposts for further research are provided in *Cancer's Intelligence* [112].

Since information and information transfer grounds computation, and computation can be regarded as a partial cancer ground, we can ask what grounds information? Information theory is derived from work in the nineteenth and twentieth centuries from Gibbs, Boltzmann, Turing, Nyquist, von Neumann, Shannon, Landauer and others. Landauer showed the important relationships between information, entropy and energy and Shannon derived the measure of information as the Shannon entropy. Landuuer showed that the storage of 1 bit of information requires work equal to kTln2, k being Boltzmann's constant and T temperature [149]. Landauer also originated that concept that "all information is physical." That is, to be information it must be physically represented or encoded [150]. In other words, information is a physical entity. In fact, the universe can be regarded a having computed itself from its very beginning through the information transfer among its physical entities, essentially a self or intrinsic computation [151–154].

Further examination of these important concepts is far beyond the scope of this article, but current consideration do demonstrate the point that grounding will eventually reach its bottom at some primitive or irreducible fact that is itself ungrounded, some of which are energy and entropy, and even symmetry, as addressed above. For the purposes of understanding foundational aspects of cancer, we do not need to reach a bottom ground to achieve a useful and fundamental of explanation of cancer. Rather we only need to understand cancer at a level where we can attack and eradicate it using computation, symmetry breaking, and other foundational concepts yet to be examined. We are not concerned with what happens to the information cancer formerly possessed once it is destroyed.

6 Conclusion

This examination of the fundamental nature of cancer by employing essence and ground concepts yields new insights. Two aspects of cancer's ground have been highlighted here and in more detail previously [71, 112]. Cancer's broken symmetry is a central feature of cancer diagnosis, monitoring, and treatment employed every day in medical practice. More abstractly, the broken symmetry of the cancer gene and other regulatory networks provides guidance for directed therapies at network sites of reduced Aut(G), since these sites have greater attack vulnerability. Other practical applications of broken symmetry in cancer are presented elsewhere [71].

The approach of drilling down to cancer's fundamentality is not just a metaphysical exercise, but one that can yield new practical insights for cancer treatment. Indeed, the science we practice today is based on foundational philosophical concepts.

A second result of the cancer ground analysis is that computational intelligence is a necessary cancer property. Each cancer move in space and time is a computed decision within a vast possibility of alternatives, whether in response to innate body defenses or to the oncologist's use of lethal measures to eradicate the cancer. There are many incompletely-explored questions in this category, including: the structure of cancer's intrinsic biochemical computer, how information is stored, and how cancer's computation can be quantified in calculations per second as for external computers (such as the Summit computer, at 200 quadrillion calculations per second). Recently-developed AI algorithms for the most complex human gameplay of poker could be extended and adapted for better play against cancer once intrinsic cancer computation is better understood. Bluffing, self-aware computing, and pre-computation of future moves are other intriguing aspects of computational intelligence that merit further examination in cancer [112].

Evolution and adaptation is another ground property of cancer, but is beyond the scope of this article. It requires examination, as has been accomplished for the cases of symmetry breaking and computational intelligence. A central question will be to determine the extent to which evolution is grounded by broken symmetry and computational intelligence, or grounded by other phenomena. There is a limit to how much information can be stored by cancer cells and networks. Evolution therefore seems to be a necessary cancer property. Improved understanding of the grounds of cancer evolution could result in improved approaches to disrupting it, thereby benefiting cancer patients. This has been the approach in the analysis of symmetry breaking and computational intelligence, that is, to take the abstract analysis to concrete measures for clinical care.

The stochastic or indeterministic nature of cancer is another category requiring further ground analysis. Random fluctuations extend from gene mutations to small numbers of transcription factors stochastically binding to gene regulatory sites. How do deterministic features of ground overlay and interact with the random properties of cancer? Some signposts exist in the ground literature, but more work is needed. Use of the Langevin equation has proven helpful in examining the behavior of chromosomal system dynamics—including in VDJ recombination—and could therefore find application in systems with deterministic and stochastic features [31, 46, 155–158].

This chapter has examined the application of essence and ground analysis to cancer. Some conclusions have been reached for symmetry breaking and computational intelligence, but more work is needed, as is commonly the case in introducing new ideas to solve old problems. This must be a novel multidisciplinary effort, including the familiar cancer disciplines of molecular biology, evolution and genetics, and adding back philosophy, from which all conceptual knowledge flows.

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Complementarity, Complexity and the Fokker–Planck Equation; from the Microscale Quantum Stochastic Events to Fractal Dynamics of Cancer

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Abstract Tumourigenesis possesses no equivalent among known physical phenomena. It is initiated at the quantum level by thermodynamic fluctuations of macromolecules. Accumulation of non-lethal alterations in quasi-deterministic dynamic cellular network of genes and their regulatory protein elements facilitated by changes in microenvironment results in a weak emergence of non-complementary, malignant phenotype. The Weibull distribution of cancer incidence suggests that neuro-immuno-hormonal network modifies that process. Eucaryotic cells are supramolecular objects. They make use of quantum entanglement, quantum tunneling, coherence, and chirality in formation of novel molecular couplings with both multiple feedbacks, synergy, and hysteresis. Complementarity at each integration level and non-ergodicity are their distinguishing features. Quantum effects may contribute to the conjugated appearance of cancer mutations. Connectivity, that is, coupling between integration levels is associated with the emergence of at least three features: fractal geometry of space–time, in which growth occurs, conditional probability of events, which reduces sensitivity to the initial conditions, and entropy. The latter one determines both a capability of the supramolecular system for transfer of biologically relevant information and evolution of intercellular interactions. There is a limit for self-organization of cells into structures of higher order defined by the Fibonacci constant. A relationship between sigmoidal dynamics and the Feigenbaum diagram suggests that both growth and self-organization occur with parameters within the Mandelbrot set. The set of non-interacting, infiltrating cancer cells becomes topologically dense. It has the highest entropy. The global spatial fractal dimension approaches the integer value. Hence, the coefficient of cellular expansion is a novel quantitative measure of biological tumour aggressiveness. It is based on complexity of intercellular interactions. Neither biological complexity can be reduced to physical one, nor be fully mathematized. Computer simulations may help to elucidate details of tumourigenesis. The mathematical models should be expressed in the algebraic form of fractal sheaves and fractional equations.

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1 Introduction

Multicellular spatial transformations underlie both morphogenesis and tumourigenesis. Both proliferation and migration of cells may proceed in the similar timescale. Morphogenesis comprises teleological organization of cells into specialized tissues and organs as well as their complementary integration into one organism. Tumourigenesis results in formation of tissue with both distorted spatial organization of cells and non-teleological function. A variety of molecular aberrations modifies intra- and intercellular feed-back interactions so much that transformed cells loose polarity, cease local cooperation, evade apoptosis, and grow autonomously. They escape the neuro-immuno-hormonal surveillance owing to both damage at different levels of intraorganismic integration and immunological malfunction. Tumour progression ends up in metabolic failure in different organs and death of multicellular organism.

In response to environmental factors or physical forces, tissues can disintegrate or counterbalance the perturbation. In that latter case, molecular, cellular, or neuro-immuno-hormonal mechanisms will be activated. Organism reacts with alterations in circulation, inflammation, degeneration, or tumourigenesis [1]. Tumourigenesis is a complex, non-complementary, temporo-spatial, multistep tissue phenomenon. It seems to be initiated by alterations in cellular dynamic network of genes and their regulatory protein elements that occur in a specific kind of cells called stem cells. Those cells differentiate towards normal phenotype and renew a tissue of origin. In response to chronic perturbations, stem cells may undergo a multistep transformation towards cancer stem cells; a source of malignant phenotypes present within a malignant tumour [2, 3]. Neither cancer cells can appear as a result of de-differentiation in short living matured cells [4], nor that process is just a phase transition seen in physical systems [5]. While phenomena that resemble phase transition, such as the GTPase-controlled dynamic chain reaction of G-actin-ATP polymerization do occur in cells, both the compact and teleological organization of macromolecules excludes such simple scenario [6]. In addition, some steps of phenotype transformation are irreversible owing to both accumulation of molecular defects in cellular dynamic network and their transfer to the next cell generation. In parallel to transformation of stem cells into cancer stem cells the primary complementarity of the multilevel interactions within the organism undergoes alterations owing to aging or environmental factors, such as radiation, smoking, alcohol, carcinogens, or oncoviruses. Those changes occur at different integration levels, what results in both malfunction of neuro-immuno-hormonal system and natural selection of cell phenotypes. In consequence, malignant cells progress and form metastases eventually. Transformed cells form initially geometric patterns as normal cells do. Their growth is correlated, and temporo-spatial intercellular associations persist over some period. Pattern formation is the essence of emergence and self-organization, that is, a spontaneous formation of globally coherent pattern out of local interactions. On one hand, self-organization of cells into tissue structures of the higher order, such as glands is limited by the Fibonacci constant (see Appendix 9.5). On the other hand, diverse patterns formed by cancer cells evolve until they attain both maximal complexity and maximal entropy. At that stage, malignant cells cease intercellular interactions and metastasize spontaneously following those two principles that seem to determine the natural course of disease [7].

2 From Quantum Events to Phenotype Transformation

All macromolecules, either proteins, RNAs or DNA, undergo spontaneous deterministic chaotic oscillations at the quantum level caused by physical forces whose average value in time is zero [8]. For example, aberrant activities of various proteins including DNA polymerases, DNA methyltransferases, DNA demethylases, ATP-dependent chromatin remodelers, or histones were observed in response to the fluctuations of energy. All those alterations occur in parallel and may contribute to the phenotype transformation towards malignancy. Those thermodynamic fluctuations occur in response to a variety of energy impulses, such as heat, acoustic or electromagnetic waves, radiation with high-energy particles alpha, ultraviolet radiation, X-rays etc. It is well-known now that DNA mutations are initiated as quantum jumps [9, 10]. A hydrogen bond joins base pairs in DNA. There exists a double well potential along a hydrogen bond separated by a potential energy barrier. The double well potential is asymmetric with one well deeper than the other, so the proton normally rests in the deeper well. For a mutation to occur, the proton must have tunneled into the shallower of the two potential wells undergoing a tautomeric shift, that is, a move from one position in pyridine or pyrimidine to another one. If DNA replication takes place in that critical, instable state, the base pairing rule for DNA may be jeopardized causing a mutation [11]. In the presence of heavy metal ions, radicals, or chemical compounds, fluctuations stabilize and will be fixed in DNA structure as various gene or chromosome aberrations [12]. DNA sequence can also change owing to cell infection with some viruses with oncogenic potential, such as human papilloma virus (HPV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotrophic virus (HTLV) or human immunodeficiency virus (HIV) [13]. Some of gene mutations may already be present in germline cells and are of hereditary nature.

DNA mutations occur with frequency 10^{-6}/cell divisions (reviewed in [14]). In addition, errors in DNA synthesis during replication or repair occur at random and in parallel in different somatic stem cells [15]. Those errors lead to DNA damage and occur with a frequency of 10^4–10^6/cell/day [16]. The frequency of gene mutations can even be increased in the synergistic manner if phenotype gets growth advantage over the non-mutated cells during the process of natural selection [17]. Fortunately, only about 2% of all DNA defects occur in exons, that is, in the gene parts that are transcribed to messenger RNA to proteins. Exon sequences are rich in Alu elements, CpGs islands, and (G+C) content. They possess varied multifractality and histogram entropy as measured by the chaos-game representations of gene structure [18, 19]. Since majority of DNA defects occur in the non-coding regions of DNA with low