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Cancer's Intelligence

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Cancer is analyzed as an intelligent system of collaborating and computing cells. The limitations of the current regime of cancer research and treatment are addressed, and the resultant need for new paradigmatic thinking is presented. Features of intelligence pervade the natural world from humans to animals of all sizes and complexity to microorganisms. Yet, cancer has hitherto not been investigated as acting with intelligence as it evades the body's and the oncologist's failed attempts to eradicate it. In this analysis, concepts of computation, including self computation and the limits of computation; game playing; ε-machine analysis; self-aware systems; P and NP-hard problems; and Boolean networks are addressed and related to features of cancer that can be described as intelligent. The implications of the developed theory of cancer's intelligence are discussed, together with several signposts and recommendations for new cancer research.

Keywords: Cancer, intelligence, computation, game theory, Boolean network

1 INTRODUCTION

The grim plight of cancer continues to endure in the face of legions of targeted drugs, reams of cancer gene data, and multitudes of physicists and mathematicians on the attack (1). A pressing need for a new and foundational conceptual framework persists. The reductionist paradigm has largely failed to produce the insights needed to fully solve the cancer problem. Single-factor causal explanations and overreliance on deep sequencing of DNA and RNA, for example, are emblematic of trapped thinking within the reduction-

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ist box canyon of prevailing cancer research (1-3). In short, the plural of cancer cell is not cancer.

This article is not about "cancer intelligence", a term that refers to using human and more recently, artificial intelligence to combat cancer. A few of the many examples are the National Cancer Intelligence Network; "intelligent drug delivery"; Watson's Artificial Intelligence System for Cancer Care; artificial intelligence in image analysis; the "intelligent knife" for cancer surgery; and – last but not least – the intelligent mind of the oncologist. Rather, this article addresses the obverse problem: cancer's own intelligence. If we are to apply human-derived intelligence to battle cancer, we must understand the extent to which cancer possesses an intelligence in its own warfare against us.

The paper proceeds as follows. Section 2 lays out the framework for considering any entity as intelligent and reduces the current focus to computational intelligence. Section 3 addresses the concept of intrinsic computation and the relevance to any self-organizing, evolving, self-computing system. Section 4 lays the foundation for advanced game play computation in cancer by addressing advances in human game play, focusing on the recent AI developments in the highly complex game of poker. This section introduces deception and bluffing in poker play and its relevance to cancer. Section 5 shifts back to cancer and currently available game theoretical approaches for understanding and treating cancer, including the topic of cancer quiescence as a bluffing mechanism. Section 6 addresses signaling and information transfer mechanisms in cancer, which give essential insight into cancer game play, but require ongoing elucidation by the oncologist using different technologies. Section 7 introduces computation on Boolean networks as mechanism for measuring the computation capability of cancer and its pathways in order to identify computational solutions to cancer treatment. Section 8 ties together the concepts of Sections 2-7, identifies the remaining unknowns and offers 9 signposts and recommendations for future investigation. Supplements 1, 2, and 3 further expand the discussion of intelligence as applied to cancer; computation and its limits; and cancer computation on Boolean networks.

The current work develops a new approach to advanced personalized oncology where elucidation of the patient's intrinsic cancer computational machine and its game play strategies, coupled to recent developments in AI human gameplay, including bluffing and deception, can lead to vastly improved strategies for the oncologist to defeat the patient's cancer.

2 INTELLIGENCE

What is intelligence and what is intelligent? Broadly, features of intelligence include the ability to learn from experience; solve problems; and use knowledge to adapt to new situations. One may also consider types of intelligence,

such as analytical, creative, practical and emotional. Examples of more detailed definitions of intelligence are:

> *…a human intellectual competence must entail a set of skills of problem solving — enabling the individual to resolve genuine problems or difficulties that he or she encounters and, when appropriate, to create an effective product — and must also entail the potential for finding or creating problems — and thereby laying the groundwork for the acquisition of new knowledge (4)*

and

> *Intelligence is a force, F, that acts so as to maximize future freedom of action. It acts to maximize future freedom of action, or keep options open, with some strength T, with the diversity of possible accessible futures, S, up to some future time horizon,* τ. *In short, intelligence doesn't like to get trapped (5, 6)*

The latter definition can be related to Kaufman's account of maximization of the "adjacent possible", a foundational feature of complex adaptive biological systems (7, 8). Only a tiny fraction of all possible configurations of biological matter has even been realized in the history of the earth, but the vast possibility space available is responsible for all that we witness. Navigation of this space to survive requires the intelligence to learn, problem solve and adapt.

Understanding, comprehension and even conscious agency are features of human life that are related to intelligence, but are not necessary features of intelligence. Therefore, none of the following discussion should be conflated with aspects of human or animal conscious agency. Without comprehension, intelligence can be viewed as computational intelligence with memory, more of which will be addressed below. In this way, human intelligence and that of animals, plants and other lower life forms, including cancer, can be considered. Even the intelligence of bacterial swarms has been described, including the ability to "collectively glean information from the environment and process it, develop group identity, detect cheaters and defectors, plan for the future, learn from experience, solve problems and engage in group wide decision making" (9, 10). Thinking of cancer as an intelligent entity is a major conceptual change, which requires a detailed evaluation of intelligence and laying the predicate for a relation to cancer at each step.

Quantification and modeling of intelligence from the standpoint of information, entropy and even computational self-awareness (see *Supplement 2)* is an active area of investigation (4, 11-21). Intelligent play of computationally difficult games with asymmetric information is addressed below and linked to natural computation in biological systems. Maximization of avail-

able entropy for possible evolution pathways in non-equilibrium complex adaptive systems is a key element of intelligent systems and can be viewed a measure of the adjacent possible, that is, a way to capture the possible future histories of a dynamic evolving system (5, 15, 22). As an entropic force, its deep relationship to the human "cognitive niche" may also have relevance to cancer as a computationally intelligent system (5, 23, 24). Other aspects of intelligence relevant to cancer systems addressed below are deception, learning, memory, pre-computation of future actions and self-awareness (see *Supplement 2)*. Other aspects of contemporary theories of biological intelligence and the relationships to cancer are addressed in *Supplement 1.*

3 COMPUTATION

What is computation and what can compute? What are the limits of computation? Can something compute itself? Before computation, as we currently view the term, there was calculation, for example by moving pebbles along a line, using knotted strings, by use of an abacus, or using the addition and multiple tables that we all memorized. Calculation is a prerequisite for computation. Computation adds logical circuits, an analog-to-digital transformation and greatly increased accuracy for difficult problems. The history of calculation and computation from Babbage to Leibniz to Turing and now to the threshold of quantum computing is a remarkable aspect of human development. The first computers were humans themselves, low-paid clerks known as a *computer* or *computor*, who performed computations for the military, business and the science and engineering community (25). It is well accepted that the human brain can compute, as oncologists demonstrate every day when they strive to treat their patients with cancer.

3.1 What can compute?

Beyond pebbles, knots on a string and a slide rule, we think of computation or computers as silicon-based, that is, constructed of semiconductor transistors as the logic gates. Any material, however, that can implement a digital switch can compute. One example is chemical reaction sequence that is designed to be a reaction-diffusion system, such as the well-known Belousov-Zhabotinsky (BZ) reaction (26). Others are liquid crystals, carbon nanotubes and conductive foams (27, 28). Biological substances are another class of materials that can compute. DNA itself can be used as a computation medium for a number of functions and can even be used to provide solutions to the traveling salesman problem (29, 30). Self-propelled actin filaments or microtubules can also be harnessed for biological computation (31). At present, silicon-based computers outperform biological computers by a few orders of magnitude, but the difference is expected to narrow (32). In contrast, the

energy efficiency of biological computing radically outstrips that of conventional computers (32).

DNA in a gene regulatory circuit can also compute specific outputs from known inputs, for example a newly synthesized protein from transcription factor inputs (33-37). Computation on chromatin itself, including methylation and acetylation, has been studied as a type of epigenetic computing (38). Bacterial genetic regulatory circuits can also be used to provide solutions to the traveling salesman problem (39). The slime mold is a simple, but complete, organism that is well known for its computational abilities (40, 41). Cancer, as individual cancer cells or a cancer system consisting of many cell types over several organs, is another level up in complexity and is able to compute its own survival, similar to bacteria (10). A key question: what is the computational power of a cancer network and can cancer be outcomputed by the oncologist together with new artificial intelligence (AI) tools?

3.2 Intrinsic computation

We, as users of computational machines, that is, computers, think of an external device that is designed to perform specific operations of interest to us and with a defined purpose or usefulness. We are the agents who select the inputs, chose the computational process and observe the outputs. The outputs commonly relate to environmental factors that we seek to understand or modify for our needs.

Intrinsic computation, by contrast, refers to a dynamical entity, system or process that internally computes its own evolution over time and space, but without a defined utility (42-45). This evolution is governed by forces, particles, equations of motion and logical operations that can be viewed as a form of self or intrinsic computation. Just as for a desktop computer, memory, computational architecture and speed are key features of intrinsic computation. Defining the self-computing system defines the environment (everything else); the environment is one of the inputs to the system. The system can take information from the environment, process it and use the new information for self-modification or to modify the environment.

Key questions to understand for intrinsic computation are (46):

1) how much of the past does a process store?
2) in what architecture is that information stored?
3) how is that information used to produce new information and future behavior?

What can be intrinsically computed? Back to our example of the universe and its memory and computing potential, the universe can be viewed as a self-computing process using the laws of particles and forces to determine its own evolution since the time of big bang (47). That is, the universe computed

itself. As discussed previously, this is massive self-computation based on a maximum memory of some 10^{90} bits. Less massive entities on earth also self compute. For example, animals self compute their own formation *in utero*. The tiger's stripes and the five digits of the human hand are formed by chemical computation using a type of Besoulov-Zhabotinskyreaction (*vide supra)*. This, in turn, creates Turing waves to ultimately form the tiger's light and dark stripes or the five fingers of the hand (48-50). The actions of a single cell can also be viewed as self-computation with both internal and environmental inputs.

All purpose-built computers are limited by their computing architecture and memory—the same is the case for intrinsic computation. For intrinsic computation, capturing information about the environment and storing the information as knowledge for future actions is a key feature. How can the environmental experience be encapsulated by the agent, processed and stored? What is the upper bound for a specific system or process? What is the language for environmental sensing and for internal information processing? How does the agent self innovate its internal architecture in order to improve its computational accuracy and speed in response to new environmental? In the theory of intrinsic computation these questions are addressed by modeling an ε-machine for the agent.

The ε-machine is an inferential model of the internal information capturing and processing apparatus 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 (51-54) (Figure 1). The ε-machine is a type of hidden Markov chain model. The internal model can

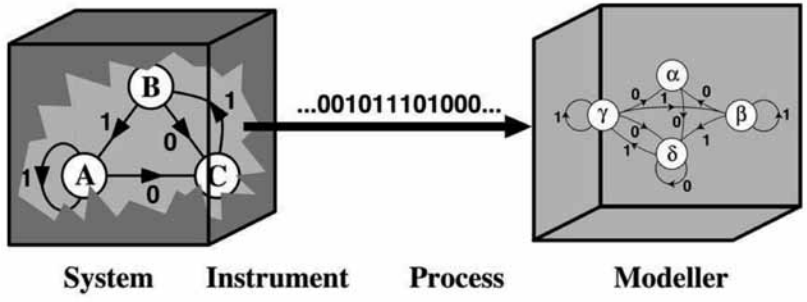


FIGURE 1
The ε-Machine.
The detailed inner mechanisms of dynamical systems, including natural systems, are hidden from direct observation. Measurement of the system's time series of outputs by external instruments, that is the communication channel, permits reconstruction of a statistical causal model of the original system.

be updated, memory permitting, to create better environment models of change and possible futures. A new computing architecture can also be created leading to a phase transition in computational capability, like going from Babbage's gear-based calculating machines to silicon-based computers or from BASIC to FORTRAN to Google's GO programing languages. An abrupt change in the system's ε-machine is emergence, where a new computational regime arises that is not predicable from the earlier state. This leads to a more powerful level of intrinsic computation with a greatly enhanced potential to alter the environment or to develop a diminished sensitivity to environmental effects by minimizing the difference between the environment's actual information and that of the agent's internal model. This process is bounded since the agent must devote resources to creating the computational architecture and to performing the computational tasks.

The ε-machine and its evolution can be described by its structural or statistical complexity (its size) and by its Shannon entropy (H) rate. Shannon entropy is information, as defined by Shannon. The difference between the agent's actual entropy rate and that of the environment determines the frequency of incorrect predictions and decisions that do not improve the state of the agent and its survival (55). A system can be characterized by the complexity-entropy diagram (56), which specifies how a system stores, organizes and processes information. The ε-machine is a causal model in that past internal state configurations of the model lead to a predictable future state with a defined probability; more that one past state configuration can lead to the same future. A major goal of current information theory is to construct a process ε-machine from minimal empirical data of past system behaviors. The full internal structure of nature is inaccessible to us; the ε-machine provides an optimal and smallest size representation of specific system behaviors of interest.

As a predictive model, ε-machine theory has been applied to the analysis of diverse complex systems, including the stock market, weather, geophysics, Monod-Wyman-Changeux molecules, and neurophysiology (57-62). In cancer, knowledge of the detailed internal computational structure of a single cancer cell or a distributed cancer network would be highly desirable. Full understanding of the internal causal state structure of cancer would improve the oncologist's ability to predict its natural evolution and more importantly, predict the response of the cancer system to therapeutic interventions, and to target the specific internal states that have the greatest weight in survival mechanisms. To our knowledge, ε-machine analysis has not yet been applied to cancer in spite of its current preeminence in information theory. Whether the cancer ε-machine(s) is a relatively constant computational cellular and network machine that computes cancer's complex self-evolution or whether the ε-machine itself is time variant will be a question for future investigation. (See Appendix 2 for additional discussion on the limits of computation and self-aware computation.)

4 COMPLEX GAMES

4.1 Magnitude of the Problem

Card, board and computer games can serve as a model for intrinsic computation in natural processes. As an agent plays a game to win against another player or players (the environment), so does a cell or cellular network in its environment in order to win its game: survival. The computational intelligence required to win in a game increases rapidly as the size of the game increases. Game complexity can be quantified as the number of decisions a player has to make in any complete game; this is the decision tree of a game. The state space complexity is the number of positions that can be theoretically reached from the initial game position.

In tic-tac-toe there are 9 squares and three states for each square (empty, X or O). The total state space is 3^9 or 19,683. When illegal moves and symmetries of board rotation and reflection are taken into account the actual state space is 765 or, for comparison purposes, approximately 10^3. The decision tree complexity is $10^5(63)$. Tic-tac-toe can be generalized to any m, n, k game played on an m by n board where the first player to get k in a row wins. Game complexity increases rapidly as m, n, and k increase. For example, in the game Connect Four the state space complexity increases to 10^{13} with a decision tree size of 10^{21} (64).

Game complexity is also determined by the rules of the game. Tic-tac-toe and its generalizations have simple rules where the complexity increase in the generalizations is driven solely by the board size increase. Games with more complex rules like checkers, backgammon, chess, and poker (limit Texas hold'em) have vastly increased state space sizes: 10^{20}, 10^{20}, 10^{47} and 10^{14}, respectively. No-limit Texas hold'em increases further to the truly astronomical size of 10^{140} with 10^{160} decision points — there are "only" 10^{80} atoms in the entire universe. Recalling the estimate of the total computational capacity of the universe since its creation of 10^{120} operations the required computational intelligence need to win at these and other complex games has become an area of intense scientific interest, particularly since many games can be generalized to problems of practical interest, which, as argued here, includes solving the problem of cancer.

4.2 Computing Game Solutions

Computational algorithms that permit AI agents to successfully play the most complex games have seen rapid improvement in the last decade. New algorithms can compete against and even predictably beat the best human players in checkers, backgammon, chess and go (65-68). Notably, these games have informational symmetry, that is, each player has perfect and identical knowledge about the state of play. This greatly simplifies the play and correspondingly, the relative ease in the creation of AI algorithms for machine players. In contrast, many card games employ asymmetric information as an attractive

aspect of games like poker, bridge and gin rummy. This greatly increases the complexity of the state space and decision tree. The individual agents have perfect information of their own hand, the public cards on the table, and often the discarded cards (i.e., the discarded strategies), but not of the other players' private cards. As a result of this feature, these games offer various ways to mislead an opponent, that is, to use deception. In poker, the main form of deception is bluffing, addressed in further detail below. The power of deception is substantial, to the extent that in bridge it is disallowed, even as a discard hesitation to mislead an opponent.

In just the past 4 years there have been exceedingly important developments in solving heads-up limit and no-limit Texas hold'em poker (69, 70). The solutions are not explicit, for that would require overcoming the insurmountable limitations of computing the vast state space of poker games. Rather, the algorithms employ approximations that are now able to beat the best human players, who themselves are, as well, unable to explicitly compute all the decision points of a game. Importantly, the recent computational advances are only for the 2-player limit and no-limit Texas-hold'em; multiplayer poker games have even greater complexity (71). Normal game play is based on the imperfect information each player has and efforts to infer an opponent's private cards based on the opponent's actions, past experience with the opponent, and subjective signs (tells). This level of recursive reasoning evolves throughout the gameplay on the part of the individual players as they strive to develop less imperfect information and process the available information to win the game.

A core aspect of the recent DeepStack algorithm is the use of counterfactual regret minimization (CFR) in order to converge on game solutions that minimize the regret or cost of making game decisions that later prove to be suboptimal (72, 73). Simulated play uses regrets of past game choices for future game play. Regret matching occurs at the Nash equilibrium in equilibrium games. Minimizing the expected regret in a game is the strategy used in the recent poker algorithms. CFR is a general approach and can, for example, be used in the game of rock-paper-scissors and many other games (73). The DeepStack strategy carries out a "deterministic computation that produces a probability distribution over the available actions" (69). It does not compute to the end of the game for each play, rather it uses a limited look-ahead strategy using the public card information. This results in a reduction from 10^{160} to 10^{17} in the number of decision points, comparable to that of other solved games (*vide supra)*. The strategy uses the deep learning approach for perfect information games, supplemented by constant resolving the look-ahead trees and maintaining assessment of the opponent's counterfactual regrets. The current analysis concerns games with discrete moves, such as playing a card or moving a chess piece, whereas in natural process and economics, the state variables may be continuous and so may the players' choices, as well (74).

Importantly, the DeepStack strategy incorporates bluffing plays. At the earliest beginnings of game theory von Neumann pointed out the reasoning difficulties in games with imperfect information: "Real life is not like that. 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." (75) In its deep learning algorithm DeepStack incorporates experience from bluffing plays, especially those at inopportune times, to exploit a player's weakness. Without this feature, DeepStack would be less able to beat the best human players who can judiciously bluff at appropriate times. Other forms of bluffing also exist in nature (*vide infra)*.

The recent experience with complex games and the features of AI needed to out-compute the most difficult games is relevant to cancer's ability to compute it own survival and spread in changing and unpredictable environments, whether from host-derived changes, cancer-engineered changes or environmental changes from externally applied treatments. What game is cancer playing and what is the state space complexity and decision tree depth? Can new computational strategies and algorithms for known board and card games be applied to cancer and if so, which games are most relevant? Are the approximate complex game solutions good enough for cancer solutions, as they are for human players? Recent results extend the two-player case to that of multi-player poker; in this case, the Nash equilibrium is non-computable, requiring simulations to estimate the multi-player outcomes (71). Since cancer is a multi-player system, simulations would also be required in AI strategies for cancer lethality. How does the cancer ε-machine(s) of intrinsic computation relate to the most effective AI game strategies and algorithms? What is the computational capacity and memory storage of a cancer cell or cancer network? Does cancer bluff or use other forms of deception? Can CFR be used in intelligent treatment strategies to minimize the oncologist's regret in cancer treatment (minimize ineffective treatment)? And finally, is cancer's game a P or NP-hard problem (see *Supplement 2)*? In human cognition and decision making, computational complexity theory (CCT) address the limits of human computation for solutions to P and NP problems encountered in real-life situations, from driving a taxi in a large city to efficiently shopping in a grocery store to inviting friends to a party so that a minimum number will know each other (the clique problem) (145, 159,160, 161) (Figure 2).

5 CANCER GAMES

The concept of cancer treatment as a game between the oncologist and the cancer itself has been intensively examined by many investigators, including mathematicians, physicists and oncologists (76-81) (82-84). Prior to treatment, cancer can also be viewed as playing a computational game with the host as it evades host immune and other defenses, plots its escape from

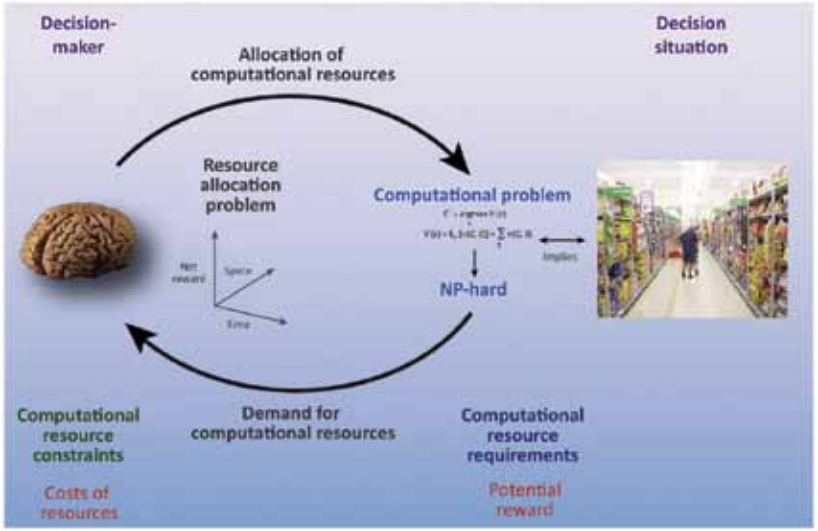


FIGURE 2
Decision as Computation
Optimal shopping in a grocery store in order to maximize the purchase utility for a given budget is an NP-hard problem. For only 100 different goods the combinatorial number of choices (configurations) is approximately 10^{30}; for 1000 goods, 10^{301} – both intractable computations for the world's fastest computers. In practice, approximate solutions using heuristics have proven adequate for basic human nutritional needs given constraints of budget, time to shop, home storage for perishable items, and many other practical factors. These decisions still require allocation of mental resources of energy, thought, and memory – in short, the resources for any computation. In cancer survival decisions, the cancer is "shopping" in its store of thousands of survival mechanisms to combat and escape from low pH, inadequate O_2, immune attack, or the oncologists' lethal interventions in order to grow, move or both. This computation also requires the cancer's ε-machine to optimally allocate resources for an adequate solution to a similar NP-hard problem. (Reprinted from (145).

low oxygen environments, and figures out the optimal balance of growth and movement, among many of the decisions cancer makes to survive. Cancer's intelligence can then lead to the formation of societies of collaborating clonal phenotypic subtypes that display synergistic cooperation, together with "free rider" or cheater clones typical of human societies (85). Similar features are also observed in bacterial populations (10). Several examples in human and experimental cancers of intelligence-based societal features of cancer cell resistance, persistence and drug tolerance are given by Tabassum and Polyak (85).

This cancer-game paradigm has led to new therapeutic approaches using adaptive therapies, including those based on evolutionary game theory (79, 81, 86). Adaptive therapies evolve following the real-time therapeutic response and other information about the tumor's status; they contrast with the conventional treatment approach using maximally tolerable drug and

radiation treatments in a progressively dose escalating regime. The knowledge gained from modeling and preclinical studies is now leading to clinical trials, including those in which the goal is "resistance management" for cases where a cure is not possible (81).

A recent highly instructive example is in prostate cancer where the assumed state space is 3: cancer cells dependent on circulating testosterone, T^+; cells dependent on testosterone produced by the cancer cells themselves, T^p; and androgen-independent cells, T^- (80). For the first two states effective treatments exist, but prostate cancer eventually progress to the androgen-independent state, for which there is no curative treatment. Even for a small state space created from 3 variables, the mathematical formulation can be formidable, but tractable. The investigators demonstrate that there is an optimal treatment scheme using abiraterone to block androgen synthesis in the self-synthesizing clone, which, in turn, reduces the emergence of the lethal androgen-independent clone. In a pilot study of 11 prostate cancer patients evaluated over 27 months the use of adaptive therapy resulted in a stable oscillating tumor burden with a reduction in the cumulative drug requirements. Additional studies in prostate and other cancers will determine the extent to which this approach will provide lasting patient benefit. The above approach treats the 3 parameters as continuous, but the formulation can always be discretized for comparison to the board and card games referenced above (87).

For some cancers, the game description may be reduced to a small parameter set, as in the above example for prostate cancer with 3 parameters, but for most cancers this will only be a rough approximation of the full game cancer plays. Single driver mutation cancers would be an exception. To the oncologist, the majority of cancer's computational framework (its ε-machine) is hidden. The analogy with no-limit Texas hold'em poker is a situation where cancer sees all the public cards, but the oncologist sees only one – it would be difficult or impossible for the oncologist to win since creating a winning hand would be largely guesswork without full knowledge of the public cards. Another analogy would be a multi-player poker game in which there are 2 or more players representing cancer and a single oncologist – the cancer team only has to have one member win (i.e., cancer only needs one effective survival mechanism). Even if the oncologist has full knowledge of the public cards it would difficult to win against multiple players, especially if the opponents share their cards and strategies, and even exchange cards, as in genetic recombination.

Game theory oncologists increasingly realize that more of cancers' cards need to be made public, that is, through repetitive measurement of circulating tumor cells, circulating DNA, and non invasive biochemical imaging, such as with PET (79, 80). Ultrasound stimulated release of intra-tumoral factors is one approach to uncovering cancers' hidden cards (88). The continued use of conventional endpoints of tumor size and burden from anatomic imaging

often plays a poor game that consists of evaluating the game's end to see that one has lost. The oncologist needs to be playing the game actively in real time, with technologies to see the result of each play, always with goal of maximizing the cancer's regret after each therapy move. FDG metabolic PET is currently used in the early stage of treatment to assess the initial tumor response (a decrease in metabolism) as a predictor of the response or nonresponse of treatment; this is an example of "real-time" tumor response monitoring during, not at the end of the treatment game (89-92). A real-time ε-machine representation of the evolving cancer state using imaging, blood markers and other inputs would provide the oncologist with the needed information. Once the minimal ε-machine representation is identified it can be more efficiently targeted for destruction. Just as in the DeepStack poker algorithms where games are simulated to minimize counterfactual regret, cancer "foreknowledge" will be important in order to permit real time treatment modification around the cancer's best response curve (81). Finally, the cancer game must be played with the view of the cancer player as a large system heterogeneous cells that communicate across a wide network encompassing the primary tumor cells, the metastatic sites and the tumor-associated cells (93-95).

5.1 Cancer's Deception

Among the properties of intelligence listed above, deception operates at the polar opposite to the more common altruistic or cooperative aspects of intelligence, but it can serve the same purpose of advancing the goals of the agent. Among the forms of deception are lies, exaggerations and understatements. The detection of deception is a component in the relationship between the deceivers' and message receivers' actions, where the receiver attempts to establish the truth of information. Bluffing a type of lie where the agent misrepresents and exaggerates its own information state and exhibits behavior or signaling consistent with the misrepresented state. The decision of an agent to bluff is dependent on its ability to learn, process information and compute the best times to bluff, for bluffing must be unpredictable (96). In poker bluffing is an essential component and has been incorporated into the DeepStack algorithm (*vide supra*). Less frequently, reverse bluffing may be employed when an agent has an advantage in temporarily understating the value of the cards it holds (97, 98). In biological systems, signaling, conflict and deception operate at the molecular sender-receiver information level (99); biomolecular signaling processes are then manifest at the microbe, cell and cellular network level for goal-directed behavior.

Deception is a constant feature of nature and an essential one for survival. An agent that accurately signals all its private information would be a "sitting duck", soon to be extinct (100). One instructive example is that seen in ground nesting birds, such as the piping plover, that lead a predator from the nest by fluttering away on the ground while feigning an injured wing, thus falsely

signaling an easy catch. After luring the predator far enough away, the bird returns to the nest. This behavior is sophisticated and has been described as dependent on a belief about an expectation: a hypothesis about the rationality of the predator; and a plan based on the hypothesis – in short, a computationally intelligent and clever move (100). The counterpart, honest signaling, is also important in nature (101-104). One example is that of gazelle stotting where the strong, young gazelles jump high and close to a predator as a show of true strength in order to signal that there are easier prey in the herd . This behavior is difficult to fake, but comes at an energetic cost—honest signaling is costly. In human behavior, altruism is a common form of honest signaling, that is also difficult to fake, but comes with a cost. Philanthropy is common type of altruism that is very costly, but with substantial benefits in society and its survival (103). Altruism in nature may help find an optimal mate and secure important food and other resources. In bacteria colonies, cooperators and cheaters have been identified, demonstrating the broad applicability of these concepts in nature (10, 105, 106).

Cancer dormancy and reemergence in primary tumor and disseminated cells, prior to and after therapy, is a foundational aspect of cancer that limits treatment effectiveness due to the greater resistance of dormant cells (77, 107-111). Similar features are observed in bacteria, fungi and higher organisms (112-114). There are a number of molecular mechanisms that mediate cell dormancy, including extracellular ERK kinase (ERK 1/2); p38 phosphorylation leading to activation of the unfolded protein response; ATF6/Rheb/mTOR signaling; and several dormancy-related transcription factors (115). Immune-mediated dormancy and dormancy reversal, and the influence of the micro-environment are also important areas of investigation (115).

Here, however, the focus is not on the detailed mechanisms of dormancy induction, but rather on the initial decision making of the cell to initiate dormancy, that is, how does the agent's ε-machine intrinsically compute the decision to initiate dormancy. The computation of dormancy and active state decisions in predator-prey relationships has recently been investigated, showing non-chaos-mediated cascades of mixed-mode oscillations are observed in the prey-predator model with dormancy prior to the onset of chaos typically observed in predator-prey systems; the introduction of dormancy stabilizes the system and avoids extinction (promotes survival) (116). Dormancy has also been evaluated from a game theoretic viewpoint as a critical system that follows power law behavior (77). These early analyses need further study and extension to dormancy decisions intrinsically computed by the cancer ε-machine. Computation on Boolean networks may offer a partial answer (*vide infra).*

Dormancy can be viewed as a type of deception since to the outside observer, for example, the oncologist, the cancer temporarily stops growing and may even shrink as a subpopulation of persistent cells remains. The oncologist who does not consider deception and bluffing on the part of the

cancer would likely stop therapy, unaware of the more lethal persister cells that will lie in wait for better external growth conditions. In poker, the bluffer has a weak hand and over-represents it to the other players (the environment). In a reverse bluff, the player has a strong hand, but represents it as weak in order to increase the betting rounds, the pot size and the reverse bluffer's eventual winnings. Cancer most often has the stronger hand, at least early in treatment, and therefore a reverse bluff would be the more preferred form of deception. A normal cancer bluff could occur in a phase of rapid growth under conditions where cellular constituents are inadequate, for example if the unfolded protein response (UPR) system is not adequately upregulated or anabolic pathway enzymes for macromolecule synthesis are too low to permit enhanced fatty acid synthesis. A rapid growth increase under these conditions would be a form of bluff, to which the oncologist would respond with a new dose escalated therapy, giving the cancer time to develop a new survival strategy. To the extent that deception strategies are coded in the cancer ε-machine (or different ε-machines in different cancers), the new computational algorithms for poker and other games with asymmetric information would offer a novel strategy for out-computing cancer. First, though, the language of cancer must be known, that it, the molecular and cellular mechanisms used by cancer to acquire, process and store (remember) information.

6 THE LANGUAGE OF CANCER

Information transfer, processing and storage requires a language. Language is a symbolic and syntactical system that permits communication for goal-oriented and other behaviors. It can be a human language, a computer language or in biology varied types of intra- and inter-cellular signal transmission and transduction mechanisms. Since all information has a physical instantiation (117, 118), information generation and transmission relies on physical encoding, whether the written symbols in human language, the state of a transistor in computing, or DNA and signaling molecules in biology. Language-based information transfer and storage requires energy, as determined by the Landauer limit to erase one bit of information: kTln2. Information is the degree of surprise compared to that of a random signal stream and is quantified by the Shannon entropy. The Shannon entropy is the number of language bits required to encode a string of N symbols, each with a probability of p_i and is given by $H = -\sum p_i \log p_i$ (119); if all the probabilities, p_i, are equal, $H = -\log N$. The cell's ε-machine is its physical information storage and processing system (*vide supra)*. Here, though, the language of cancer is addressed since knowledge of the language is a necessary, but not sufficient, prerequisite for the oncologist to effectively ablate or stabilize cancer.

The oncologist's access to cancer's language has greatly improved in the last decade. Language features including signaling molecules for quorum

sensing; circulating exosomes and free DNA; circulating tumor cells; pre-metastatic niche signaling; short and long non-coding RNA; hedgehog and notch signaling; zinc signaling and many others are increasingly well understood. The oncologist's access to the information is, however, severely limited. Non invasive imaging and liquid biopsy technologies are, however, beginning to partially address the informational needs of the oncologist. Even with greatly expanded raw information the oncologist will still be hard pressed to process and use all the information without better knowledge of cancer's computational approach to countering his or her therapeutic plays – that is, knowledge of cancer's ε-machine.

Specifically, what game is cancer playing at any given time? Human language has been described as a "language game" (Sprachspiel) by Ludwig Wittgenstein (120). That is, many different games can be played using human language since it is not a purely logical ideal language without ambiguity. It can be vague, misleading and even contradictory. As with a deck of 52 cards, many different games can be played and players must know the rules. An observer of an unknown game of even moderate complexity would find it difficult or impossible infer the complete rules of the game needed to play and win. Cancer has many survival mechanism cards it can assemble into a winning hand. The precise rules are unknown to the oncologist, who in the prevailing cancer treatment regime often holds a weak hand. Improved knowledge and access to cancer's signaling language is essential, as is the companion need to better understand the game cancer is playing in each patient – that is, each patient's individual cancer ε-machine.

The computational description of this problem is described well by Crutchfield 25 years ago (Crutchfield 1994):

> *One of the main questions in computation theory is how difficult it is to "recognize" a language - that is, to classify any given string as to whether or not it is a member of the set. "Difficulty" is made concrete by associating with a language different types of machines, or automata, that can perform the classification task. The automata themselves are distinguished by how they utilize various resources, such as memory or logic operations or even the available time, to complete the classification task. The amount and type of these resources determine the "complexity" of a language and form the basis of a computational hierarchy - a road map that delineates successively more "powerful" recognition mechanisms. Particular discrete computation problems often reduce to analyzing the descriptive capability of an automaton, or of a class of like-structured automata, in terms of the languages it can recognize. This duality, between languages as sets and automata as functions, which recognize sets, runs throughout computation theory.*

7 OUT-COMPUTING CANCER

What is the computational capacity of the cancer cell or network playing the cancer game? In complex games humans play the decision tree and state space sizes have been discussed above. No-limit Texas hold'em has 10^{160} possible decision points, which can be simplified to 10^{17} in a computational algorithm that can beat the best human players. How does that compare to a cancer cell or better conceived, a cancer cell network and how can the computational limit of cancer be itself computed? This limit will determine the oncologist's requirements to out-compute cancer.

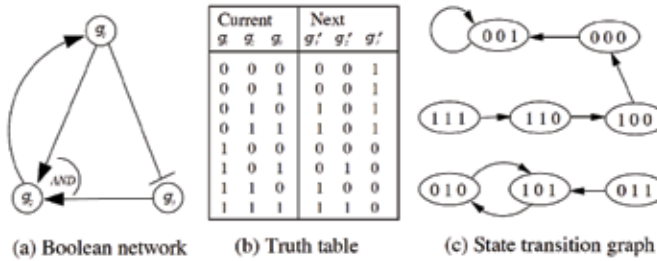
7.1 Boolean Networks

Representation of biological computational networks as Boolean networks (BN) has been extensively investigated in recent years (33, 121-128). BNs have been demonstrated to accurately represent biological behavior, to predict functional evolution and to be computationally tractable for modeling and simulations. In contrast, depiction of biological networks by concentrations, enzyme and receptor affinities, and the corresponding partial differential equations of kinetic modeling leads to greatly increased computational challenges that rapidly outstrip available computer resources (129). BNs were first intensively investigated by Kaufmann (7, 130). These early investigations characterized the BN structures that lead to ordered, chaotic and intermediate dynamic behaviors and laid the foundation for extension to biological cell networks at play in cancer.

A BN is a connected network of nodes (Figure 3). A node can be a protein, enzyme, transcription factor or any cellular constituent whose activity is determined by its connection to and regulation by other nodes in the network. In a typical BN a node can take one of two values: ON (1) or OFF (0). For example, a gene is expressed or not expressed or a molecule's concentration is above or below a certain threshold. Typically, the connections between nodes can be either activations or inhibitions, or in logic operator terms: AND or NOT, respectively. From a starting configuration of node states and the interconnection rules the future network evolution can be computed in discrete time steps according to its Boolean function, either to a ordered (e.g., cyclic), chaotic or critical state attractor (131, 132). This is a type of self or intrinsic computation, in which critical states have the greatest computational capacity (51).

BNs grow rapidly in complexity and computational potential as the number of nodes (N) and connections per node (k) increases, comparable to the complexity of card and board games. The state space of a BN is 2^N , the number of Boolean functions 2^{2^k}, and the number of possible networks is $\left(\frac{2^{2^k} N!}{(N-k)!}\right)^N$ (121). For k=2, N=10, the state space, Boolean functions, network

A



(a) Boolean network (b) Truth table (c) State transition graph

B

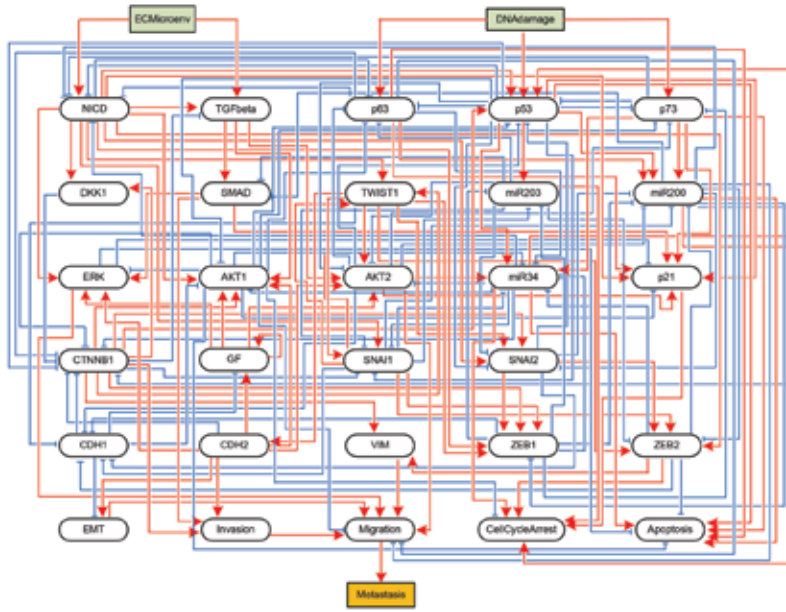


FIGURE 3
Boolean Networks.
A
A three-node Boolean network with stimulatory and inhibitory pathways. The truth table shows the transitions from the 8 possible initial conditions. The state transition graph shows how the states sequentially transition from the starting configurations. From Steggles, et al (146)
B
A metastasis BN showing inhibitions (red) and activations (blue) . From (147, 148)

number are 1,024, 16, and 5.8 x 10^{30}, respectively. For k=2, N=10, a reasonable network configuration for typical cellular functions, 1.0 x 10^{6}, 64, and 1.5 x 10^{160}, respectively. Clearly, the BN regime can support a very large functional-

ity and computational space, comparable to that required in the AI solutions to card and board games. In these examples, the mean connectivity of k=2 is used since it tends to bring a network close to a critical, highly computational state poised between order and chaos (121, 131).

7.2 Cancer Boolean Networks

Understanding the role of BNs network analysis in cancer requires understanding control; nodal sensitivity; canalizing functions; synchronous versus asynchronous BN updating; synthetic BNs; BN inference and relation to the ε-machine; BN information storage, transfer and excess entropy; BN self-perception (self-awareness); and BN control of quiescence. These topics are addressed below.

BNs have been investigated in several biological entities, including bacteria, yeasts, the single cell slime mold and the mammalian cell cycle (28, 40, 133, 134). Functional understanding of gene regulatory networks (GRN) has seen substantial progress recently by the application of BNs (121, 125, 135-138). A major aspect has been in the understanding of GRN control, optimization of control tasks, and stability; often one BN may control another (121). In general, BN control is an NP-complete problem and therefore, accurate solutions are limited to small networks unless constrained solutions can be identified (121, 139, 140). As an example, control of T helper cell differentiation toward the 3 stable cell states demonstrates how new algorithms can identify key control features in 23-node BN (121). Additional aspects of cancer Boolean networks are addressed in *Supplement 3.*

8 CONCLUSION

A novel approach to the problem of cancer is presented that treats cancer as a computationally intelligent entity. This approach brings together knowledge from diverse territories including theories of intelligence; information; cancer hallmarks; the limits of computation; intrinsic computation; complex games and game theory; Boolean networks and self-aware systems. The cancer intelligence thesis delineates the limits of current cancer research and treatment regimes, and demonstrates how cancer science can evolve and improve as the result of new paradigmatic thinking. From the standpoint of philosophy of science, current cancer theory is profoundly underdetermined as demonstrated by the woefully inadequate treatments for most cancers. This cancer construct suggests an altogether new approach to a future advanced personalized cancer medicine where knowledge of cancer's computational machine-derived strategies coupled with new human game play-based AI support for the oncologist can lead to a much more effective game against cancer.

Several signposts for future cancer investigation and application to patient care augment the analysis of the above-referenced topics. These include:

- Examine and apply the ε-machine concept to cancer cells and extended cancer networks. Since the ε-machine, by definition, is the most efficient internal causal description of a system, it could, in turn, be employed to efficiently disrupt cancer survival mechanisms with the minimal and safest interventions. This will require computational resources across the cancer types and subtypes, and empirical input information beyond that currently available.

- Expand the availability and use of biomarkers in the ε-machine model of cancer's intrinsic computation. Cancer biomarker research continues to advance in the context of personalized medicine, but the application of the biomarker information continues to reside in the reductionist regime where biomarker information simply points to a specific target for intervention. This misses how the biomarker informs the internal structure of cancer's self-computation and thus also misses an opportunity to strike at cancer's brain, not just one of its many limbs.

- Improve estimates of cancer's computational capacity. This will determine the external computation needed to fully integrate all of an individual cancer's Shannon entropy and entropy rate in order to generate lethal strategies. Capture the entire computational scope of cancer, including that for DNA, chromatin, epigenetics, and metabolic, gene regulatory and hormonal networks.

- Develop technologies to apply advanced game-solving AI algorithms (e.g., DeepStack for poker) to cancer computation and counter-computation, including the use of counterfactual regret minimization and the incorporation of deception strategies.

- Investigate the extent to which cancer's computation is self-aware. Just as self-aware computation is a cornerstone of current AI, it is likely also a feature of intrinsic computation.

- Examine the clock features and intrinsic computation of dormant or quiescent cancer cells. While quiescent cells appear completely inactive from the standpoint of growth and movement, recent analysis indicates that they self-compute their quiescence in real time and their eventual emergence from the dormant state. External control of quiescence would necessarily lead to new therapeutic measures.

- Continue to improve understanding of Boolean network-based intrinsic cancer computation and control. Determine the degree to which BN-based computation can be modified, either by targeted and efficient disruption of

BN control or by insertion of artificial BN's. Understand the symmetries in BNs and how broken symmetries alter cellular intrinsic computation and attack vulnerability (141). Correspondingly, network-based computing may offer more efficient solutions to complex problems, including NP-complete problems, than possible with conventional or DNA-based computation (32), thus permitting faster solutions of individual cancer networks and computation of lethal interventions.

- Examine how information is stored in cancer cell networks, including internally and in the microenvironment. Microenvironment targeting is a current area of cancer research, but the degree to which the targeting disrupts memory, logical operations or both has yet to be investigated. Further examine the extent to which cancer memory can be used to compute or pre-compute actions to counter the oncologist's therapy moves. Can cancer compute a future action and store the information prior to an external change in conditions, i.e., prior to the oncologist's future moves?

- Ultimately, individual genetically and phenotypically diverse cancer cells; the many types of microenvironment cells; the co-opted immune system; and the often countless metastatic sites create a information storage, transfer and processing network that is analogous to a society, like intelligent human societies, with bottom-up and top-down causal effects and central monitoring components that control the system at large (142). Artificial society research is relevant in this regard, including the theory showing that intelligent societies are not computable by a deterministic Turing machine, thus placing limits on the oncologist's ability, even together with AI, to out-compute cancer (143, 144). Where does cancer lie on the P to NP-hard computational spectrum? That is the most fundamental question, as it is for all computation.

The concepts summarized in this article squarely juxtapose the current cancer paradigm and the conditions for progress to a foundational level of understanding cancer and its intelligence. This new knowledge would necessarily lead to the development of novel measures to disrupt or reverse the cancer process. The road will be long and broad, requiring many disciplines to seamlessly stream together. It cannot be bypassed. The stakes are too high

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none

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SUPPLEMENT 1

Biologic Competency and Cancer

Four levels of biologic competency have been described: Darwinian, Skinnerian, Popperian and Gregorian (100). Darwinian organisms start with hardwired competencies and then develop more or less random variations that are then tested against Nature – the winners are copied in larger numbers. Skinnerian competence adds judicious reinforcement and entropic pathways with an operant conditioning component, but still with no inkling of comprehension or internal review of possible decisions.

Next come the *Popperian creatures*, as Dennett calls them, after the philosopher Karl Popper, who is revered among scientists for his view of empirical falsification as a foundational truth criterion in science. These creatures "extract information from the cruel world and keep it handy, so they can use it to pretest hypothetical behaviors offline, letting their hypotheses die in their stead", as Popper put it. The judgment and decision making required in these organisms represents a significant elevation from the prior two and involves much more computation to track all the possible outcome scenarios. Last are the Gregorian creatures, named for the psychologist, Richard Gregory, who formulated the idea of "thinking tools" that in the entropic pathway theory help bootstrap the possible pathways analysis, ruling in or ruling out large pathway territories. These tools encompass things like arithmetic, democracy, PET scanners, computers, maps and satellite imagery (100).

Cancer certainly has features of the Darwinian competency, its *sine qua non*. The ability of cancer to seek reinforcement by facile switching between oxidative, glycolytic, or amino acid metabolism or an optimal combination depending on the environmental conditions is an example of a Skinnerian competency. The intermediate Popperian realm is a compelling one for cancer operations where many complex factors are involved in decisions for the future to move or grow in place; to divide or wait in a quiescence state for optimal environmental conditions to prevail; or devise a plan to escape the effects of a lethal cancer drug.

The Gregorian competency may seem too far for cancer even though, as will be further elaborated, cancer itself does compute, i.e., possesses its own biological non silicon-based computer. It has stored informational and spatial maps of its extended system of newly prepared provisional metastatic niches, sites of active metastases, coopted immune cells, and tumor stromal cells. Could it also be an example of computation self-awareness? A map tool does not have to be a physical folding map printed on paper, but could simply be the stored information. The dividing line between competency and intelligence is not sharp, but the two latter competency domains are in accord with many of the previously described definitions of intelligence.

What do we value as intelligence and in an intelligent system? Dennett examines this question by asking what's desirable in an intelligent chess

playing computer: it keeps track of all the pieces; notices opportunities; recognizes and makes gambits; expects the opponent to make intelligent moves; values the pieces soundly; and looks out for traps (100). An addition to Dennett's list is the ability to use deception and set traps.

Dense signaling, for example quorum signaling and signaling to cells at metastatic sites, permits the cancer network to keep track (communicate with) of all its cellular constituents, including cancer and tumor-associated cells. Cancer notices opportunities for growth or movement in response to variable energy sources and their locations and it can even decide to adopt a quiescent state of neither growth nor movement in the face of inhospitable conditions (i.e., a reduced possibility space).

The other features of game-playing intelligence raise additional questions for cancer. Can cancer make gambits in its game of survival as it first moves and grow to overcome the adverse host environment, sacrificing certain cell types as it advances the survival of the global system? Later in the cancer game, cancer's opponent is the medical oncologist. Whether or not cancer "expects" and pre-computes intelligent moves by the oncologist, it certainly has a vast armamentarium of plays available and the computational intelligence to make many different survival plays. Does cancer first learn from the experience of overcoming the body's own defenses and later on, from the experience of external lethal drug moves to then expect and plan for the oncologist's future moves? Theories of computational self-awareness may offer a partial answer (*Supplement 2)*.

Finally, does cancer have the capacity of deception to set traps or bluff when faced with the oncologist's therapy moves? Is cancer bluffing (often times, a reverse bluff) when a tumor initially shrinks after therapy only to grow more virulently after therapy ceases? Is growth arrest simply the result of the lethal drug or a planned strategy to adopt a more resistant state, e.g., dormancy. Adaptive therapies seek to play a stronger game against cancer as they strategically dose, starting and stopping treatment with an idea to better outplay cancer (86, 149-151). Adaptive therapies have shown better outcomes in some cancers, but while cancer plays multidimensional chess, the oncologist currently moves on a flat surface following tumor volume and possibly a blood marker – a weak game, with a common and not unexpected poor outcome.

SUPPLEMENT 2

Computation and Its Limits

At the most basic level, computation transforms an input into an output. A computation is information processing. This happens daily as we find an optimal route on Google maps, send a rocket to Mars, play chess on a laptop, use Siri for voice recognition or in a myriad of other scientific or engineering aspects of daily living. The limit of computation also plays a key role in daily living: the intractable problem of factoring very large integer numbers, which serves an essential role in banking and other areas of information encryption; the difficulty and inaccuracy of forecasting the weather over short time periods; predicting the stock market and many others.

A famous example of a difficult problem is that of the traveling salesman: the problem of determining the shortest route to visit a given number of cities only once and returning to the starting point. For N cities, the problem's difficulty increases as N! or N-factorial, which can quickly outstrip the computational capacity of the world's most powerful computers. Importantly, there is no exact "shortcut" algorithm for the calculation as the number of cities increases; the length of each path must be individually computed for an exact answer. For only 35 cities, 35! » $1x10^{40}$. As the world's most powerful computers approach a quintillion (10^{18}) operations per second (OPS), the computation would still take about $3x10^{14}$ years: longer than the age of the universe (about 10^{10} years). Approximate heuristic algorithms can provide estimations within 2-3% for up to a million cities (152, 153), which may be adequate for some practical problems of this type, including for accurate cancer solutions sufficient for treatment (*vide infra*). The traveling salesman permutation problem is related to others: computer wiring; wallpaper cutting; hole punching; job sequencing; and even the design of a dartboard (154).

What is the maximum computational potential of any device? An iPhone 6 operates at about $3x10^{9}$ OPS and the fastest mainframes are approaching 10^{18} OPS. Quantum computers will increase the speeds by orders of magnitude. At the far extreme, one can ask what the computational limit is for the entire universe. This question was first addressed by Seth Lloyd (155-157). Briefly, the calculation views the universe (the visible universe) as divisible into the smallest Planck lengths (from the Heisenberg uncertainty principle) of 10^{-34} cm. Each Planck length can then be treated as an on-off logic switch for computational purposes. The size (volume) of the visible universe gives the total number of 0-1 switches and the age of the universe gives the total number of operations that could have ever been performed: 10^{120} operations. Therefore, any computational problem that requires more that 10^{120} operations is not only intractable, but impossible. Boolean networks in cells or cellular networks with similar 0-1 or OFF-ON switches also permit computation (*vide supra).*

Computation complexity can be divided into classes of computational time requirement as the size of the problem increases. Problems that increase in polynomial time, using a deterministic Turing machine, as a function of size are termed P. They require increased computational time, t, as the size (N) raised to some power, a: $t \sim N^a$. Answers can also be checked in polynomial time. Examples of P problems are determining whether a number is prime; calculating the greatest common divisor; determining whether a cell in Conway's Game of Life is alive after N steps; and linear optimization problems that have application in economics and logistics (https://en.wikipedia.org/wiki/P_versus_NP_problem) (158, 159). P complexity problems are not necessarily easy problems, but they are often tractable with available computing technologies.

NP-hard problems are in a fundamentally different complexity class. They require an exponential increase in the computational time as a function of the problem size: $t \sim e^N$. NP-hard problems require a non-deterministic Turing machine, that is, they require an initial guess of the problem solution and then verification by a deterministic Turing machine approach. They require a quasi trial-and-error approach in which every possible solution must be tried and then verified as a solution. The traveling salesman problem is NP-hard. Other examples are factoring very large numbers; the clique problem; coloring problems and many others. Many computer games are also classified as NP-hard, including Super Mario and related Nintendo games; Minesweeper; and Battleship. For a list of NP-hard problems see https://en.wikipedia.org/wiki/List_of_NP-complete_problems.

NP-hard problems are exceedingly difficult to solve, but can be much more easily verified in polynomial time, such as the factors of very large numbers, verifiable by multiplication. NP-complete problems are the class of NP-hard problems where a solution of one in P-time would solve all the remaining in the NP-complete class. A major research area of computational science is to answer the question of whether P=NP, that is whether there are P solutions to NP-hard problems. In human cognition and decision making, computational complexity theory (CCT) address the limits of human computation for solutions to P and NP problems encountered in real-life situations, from driving a taxi in a large city to efficiently shopping in a grocery store to inviting friends to a party so that a minimum number will know each other (the clique problem) (145, 159, 160, 161) (Figure 2).

To summarize, the NP computational class includes all P problems and NP-complete problems. If P=NP, then NP, P, and NP-complete problems would all reduce to a single class. There could still be other NP-hard problems, such as the Turing machine halting problem, where $NP \neq P$ (158). Some P-complex problems can still outstrip current computational capacities, including the Advanced Encryption Standard (162).

Computational Self-Awareness

As intelligent beings, humans possess self-awareness. Self-awareness is defined as: the capacity for introspection and the ability to recognize oneself as an individual separate from the environment and other individuals (Merriam-Webster Dictionary). Humans also have awareness of their own self-awareness, that is meta self-awareness. Since a salient feature of intelligence is computation, one can examine the extent to which other computational systems or processes demonstrate self-awareness.

Computational self-awareness is indeed an active area of investigation in the computing sciences and in engineering. It is a prominent aspect of AI. A self-aware computing system can:

> *1. learn models capturing knowledge about themselves and their environment (such as their structure, design, state, possible actions, and runtime behavior) on an ongoing basis and*
> *2. reason using the models (e.g., predict, analyze, consider, and plan) enabling them to act based on their knowledge and reasoning (e.g., explore, explain, report, suggest, self-adapt, or impact their environment)in accordance with higher-level goals, which may also be subject to change. (163)*

In human-built computational systems, self-aware learning and reasoning is directed to the purpose for which the computing system is designed and constructed, either for the entity who built the system or for the end user. The learning process relates to the system processes, to the environment and to their relationship and interactions.

As in the case of human intelligence and computation, other natural or organic computational processes, by the above definition, can be or become self-aware at a sufficient level of complexity. Indeed, it has been stated that self-awareness is necessary for a complex system to have adaptive behavior (164). Natural computing and self-awareness could take place at the level of an individual cell, a distributed cellular network or at the organism level. Self-awareness can also be decentralized as in ant colonies, flocks of birds, and schools of fish (163). These are self-organizing systems that can adapt to changing internal and external circumstances.

In the ε-machine regime, self-learning, self-awareness and reasoning could result in increased resources for memory storage of past histories, increased energy allocation to computational requirements, or a change in the computing architecture. In the case of cancer, it would be extremely valuable to have better information and understanding of how the cancer system (individual cancer cells, tumor-associated cells, metastatic sites, etc.) monitors itself, computes decisions and then executes adaptions to survive in novel adverse environments, from that of outstripping its oxygen supply to externally applied toxic agents. Attacking the central internal monitoring system

of cancer – that is, at the heart of its computational intelligence or self-awareness – could be effective in degrading or destroying cancer's ability to adapt and hence its ability to survival.

Cancer displays periods of rapid growth and times of quiescence when growth and movement ceases (77, 107-111). What are the computational features of this behavior? Does computation continue in quiescence and what is computed when quiescent cells start to rapidly divide and eventually lead to death of the patient? What is the ε-machine of a quiescent group of cancer cells and how can elucidation of the ε-machine structure permit the oncologist to maintain the quiescent state and prevent active cellular growth? This dimension of the problem is related to "off line learning", that is, learning conducted by an information processing system using simulation analysis of possible future events (163, 165, 166). The new knowledge from simulation and internal modeling can be stored and subsequently used for planning the response to actual future events. This is the mode of the Popperian intelligence (*vide supra)*. Improved understanding of computational self-awareness in cancer could help the oncologist play a better game against cancer. In short, can cancer be out-computed?

SUPPLEMENT 3

Boolean Networks in Cancer Computation

In cancer Boolean networks, the goal is to understand how certain nodes are maintained in the ON state and others in the OFF state. For example, BN analysis of castrate-resistant prostate cancer pathways identified the key controlling nodes and connections in maintaining the treatment resistant state and correspondingly, the minimal target perturbations that could disrupt the cancer state and lead to treatment responsiveness (167). Efficient detection of nodes in BNs that are sensitive to functional perturbations is a complex theoretical task that is under active investigation (129). BN analysis has permitted detection of the key network components initiating quiescence, apoptosis and proliferation in a cancer network of 96 nodes and 249 connections or edges (127). Thirty-two million initial micro environmental states were shown to flow into 36 fixed states and 26 limit cycles. Network control sensitivity to nodal mutations was also measured. Altered environmental conditions of nutrient and oxygen supply could then be evaluated and the outcome following different therapeutic interventions could be predicted.

A related BN problem is the detection of canalizing functions, that is the critical nodes and connections that drive a network to a desired state independently of all the other nodal states, and how the canalizing functions can be efficiently identified (168-172). This concept is critical in cancer since the oncologist desires to therapeutically target cancer in an efficient manner, avoiding targets that play a minor role in maintaining the cancer network. As in the example of no-limit Texas hold'em poker, reduction of the problem size is highly advantageous in finding winning solutions. Automatic screening for network perturbations that result in long-term user-specified functional changes is another area of investigation (173). Rapid canalizing function identification as applied to prevention of the immune response after DNA damage in cancer is one example of this approach (173, 174).

Another important aspect of dynamic BNs is whether the network is updated synchronously or asynchronously in time (175), that is, from a starting configuration and a single nodal perturbation, do the connected nodes update asynchronously in a series or do all nodes update synchronously (the more realistic *in vivo* situation)? This has been investigated in a bladder carcinogenesis network to identify therapeutic targets (175). A similar approach has been used in colon cancer (176). Together, these recent theoretical developments and results in cancer models are beginning to identify the key computational features of cancer and how they can be disrupted or even reversed (177-179). The idea of transfecting new synthetic BN control circuits in to cancer cell networks is especially intriguing (36, 180, 181).

A major challenge is inferring a BN from indirect and incomplete empirical measurements, particularly when some measurements may be correlated and noisy. New approaches are advancing solutions to the BN inference prob-

lem, as exemplified by the Partially-Observed Boolean Dynamical System (POBDS) model (135). The key is progressive pruning of the hypothesis tree space – similar to the case of poker previously addressed – in order to keep the solution space tractable. BN inference is directly analogous to the problem of determining the system ε-machine of intrinsic computation, if not identical when the ε-machine is depicted as a BN. Yet, ε-machine concepts of excess entropy and statistical complexity have been inadequately addressed for the cellular BN regime, thus limiting elucidation of the causal structure in biological networks. A recent exception in the BN regime uses the concept of integrated information to identify macro level network structures possessing emergent features of control beyond that of the composite microstructures (182). The identification of non-reducible control features of a cancer network could be exceedingly useful for disruptive targeting by the oncologist. Bringing together and reconciling the BN "black box" and ε-machine approaches is an important future goal for understanding cancer and destroying its ability to self-compute its future. In this regard, the theory cascading failure avoidance within large networks (183, 184) could be employed in order to promote, rather than prevent, cascading failures in cancer. In cancer, the network solutions are typically the inverse of the more common goals of retaining and strengthening biological networks. Since cancer can be viewed as a phase transition from a critical control state (185), reversing the cancer phase transition, possibly by transfection of artificial BNs circuits, is an exciting concept.

Information transfer and modification within the network is another important aspect of biologic systems and a foundational component of intrinsic computation (51, 186-188). Information storage (system memory) dictates responses to novel environmental conditions and determines the cell's future based on its past (51, 134). Excess entropy is the total amount of information from that past that can be used to predict the future (186) (55) (187). A cell can store information in its neighbors and even in its environment for later retrieval and processing (186). Systems at criticality have the greatest capacity for information storage and information flow (51, 189), thus understanding the basis of cancer's criticality is a goal for disruption.

Self-perception of an agent's influence over its environment is another feature of intrinsic computation relevant to cancer, as it both reacts to its environment and modifies its microenvironment and its distant environment (e.g., the metastatic niche) to advance its survival (184, 190). Information storage and information processing (modification) are central; cancer cells may learn and remember how to fight the oncologist's lethal measures from their very early experiences of developing measures to survive in low oxygen, low pH and nutrient-starved environments. Cell memory of DNA damage and hypoxia has been measured cell preparations and been shown to determine future environmental responses (36). Additional examples of cell memory circuits are given in Purcell and Lu (36), including the integration of memory

and logical information processing. Disrupting cancer memory circuits could be as therapeutically useful as interference with cancer's intrinsic computation and information processing.

Finally, cell quiescence or dormancy appears to also manifest a computational state; lack of division or movement does not imply complete inactivity. Since quiescent cells sequestered in specialized niches commonly and unpredictably begin to divide to levels lethal for the host, it is important to understand how to preserve the quiescent state or to carefully reverse quiescence in order to increase susceptibility to chemotherapeutic drugs. Quiescent cells, including hair follicles, appear to have a running clock and the ability to compute emergence from the quiescent state (133, 191-193). Improved understanding computational quiescence would have a profound influence on cancer treatment, including for prostate cancer where the emergence of quiescent cancer cells in bone is the major cause of death.