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TOPICAL REVIEW

Cancer as a disorder of patterning information: computational and biophysical perspectives on the cancer problem

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Abstract

The current paradigm views cancer as arising clonally from a degradation of genetic information in single cells. A complementary perspective, originating at the dawn of modern developmental biology, is that cancer is the result of a system disorder of algorithms that normally orchestrate individual cell activities toward specific anatomical structures and away from tumorigenesis. A view of cancer as a disease of geometry focuses on the pathways that allow cells to cooperate to build and maintain large-scale anatomical patterning. Cancer may result when cells stop maintaining higher-order structures and reduce the boundary of their computational selves to a single-cell level, reverting to a unicellular lifestyle in which the rest of the organism is merely part of the environment at the expense of which all living things survive. While this view has been widely discussed, little progress has been made in providing a quantitative, mechanistic framework within which this perspective's specific and unique implications for treatment strategies can be tested and biomedically exploited. Here, we highlight two recent areas of progress which may facilitate much-needed progress on the cancer problem. First, we review the roles that endogenous bioelectrical networks, operating across many tissues *in vivo*, play as a medium of information processing in tumor suppression, progression, and reprogramming. Second, we provide a primer to the development of computational theory and tools for quantifying the information and causal control structures in cancer and other complex biological systems. Rigorous mathematical formalisms now exist to measure and analyze the extent to which 'a whole is more than the sum of its parts', applications of which could lead to new strategies for cancer reprogramming. Here, we review the basic landscape of these related subfields, and sketch specific ways in which a synthesis of novel integrative biophysics and mathematical analysis may contribute to novel ways to understand and address cancer *in vivo*.

1. Introduction

Cancer is well-recognized not only as an extremely pernicious medical problem, but also as a group of phenomena deeply connected to the fundamental questions of evolution, multicellularity, pattern (disregulation, and the interplay between the genome and the environment [1, 2]. Two fundamental paradigms currently divide the field. One is that cancer results from disorders of genetics: cancer cells are fundamentally broken due to genomic mutation or instability, and their clonal progeny form tumors and metastases. This view is sometimes called the SMT, *somatic mutation theory* [3–5]. A competing perspective is that of cancer as a circuit disease—a disorder of the complex biophysical, transcriptional, and epigenetic dynamics that regulate cellular state and the ability of cells to cooperate *in vivo* [6–8]. Under this view (sometimes called the tissue organization field theory or TOFT, [9, 10]), cancer is akin to a traffic jam [11]—the problem is not a permanent discrete alteration within a founder cell and all of its clonal descendants, but an undesirable stable attractor in the complex network of controls that normally guides anatomical homeostasis [12].

The relative merits of the two models have been discussed extensively [10, 13–17]. We do not rehash the arguments here, nor do we claim that cancer is a

monolithic phenomenon that is entirely explained by either model in all cases. Nevertheless, there is widespread agreement that fundamental advances in the basic understanding of cancer are necessary to break the stalemate in cancer medicine. Here, we focus on the under-appreciated developmental perspective because it hold potential to generate such fundamental advances. We review the classical and recent data suggesting a complementary top-down strategy for control of the cancer process, and outline an emerging set of quantitative approaches that we believe are an ideal formalism from which to functionally address this conceptualization of the cancer problem at the bench.

This view places the locus of cancer at a multicellular level—specifically, a failure of the mechanisms that orchestrate individual cell behaviors toward large-scale anatomical outcomes: the organism's target morphology [18]. This is important, because this view makes unique predictions that could overcome the increasingly acknowledged gap between the amount of effort spent on molecular biology and the modest gains in cancer medicine to date [19]. For example, the SMT model implies that cancer cells are irrevocably damaged and must be killed to address cancer outcomes. In contrast, TOFT suggests rebooting/reprogramming strategies that could avoid toxic chemotherapy and compensatory proliferation by shifting control networks back into the regime that normally instructs their morphogenetic functions within a complex organism. In the SMT model, each cancer cell must be addressed individually, lest it initiate relapse. TOFT suggests that diagnostics and intervention may include a non-local, tissue-scale component involving long-range integration of cell states and communication into global (dis)order. Finally, SMT and TOFT make opposing predictions about the relationship between induction of regenerative repair and carcinogenic susceptibility (discussed below).

Indeed, an anatomical framework is what is used to diagnose cancer clinically, and is the context in which SMT-derived or other therapies are evaluated. Nevertheless, the developmental perspective receives less attention because the successes of mechanistic molecular genetics (genomics, high throughput sequencing) make it easy to amass increasingly high-resolution subcellular data comparing cells within and across tumors, making it tempting to search for the source of transformation within the massive volumes of genomic data. The alternative requires a much more difficult journey to understanding how the default program of unicellular life is normally harnessed in the context of morphogenesis, regeneration, and tumor suppression towards creation and maintenance of a complex body. Below, we first review some little-known data that support a top-down perspective and functional importance of anatomical homeostasis [20] for the cancer problem. We then discuss two essential aspects of a new approach: mathematical theory applicable to higher-order biological function, and an emerging set of biophysical control mechanisms that can be effectively targeted by interventions motivated by the theoretical work.

Crucially, a full understanding of the cancer problem will involve not only the mechanisms of cellular control, but also the algorithms that guide their communication and other activities at a population level. We propose a research program that includes investigating how cell networks operate as well as the development of new quantitative theory that describes the control policies and information-processing executed by multicellular tissues. This latter point is essential if the field is to move beyond the qualitative idea of target morphology as the missing control factor when cells go rogue, toward specific models that make testable, quantitative predictions to identify novel intervention strategies for biomedicine. In the next section, we introduce the unacquainted reader to basic concepts of information theory as applied to biological systems. How do cell networks process information, and how can cancer biologists acquire data that can be analyzed using these methods? We then go on to review how endogenous bioelectric circuits help regulate large-scale growth and form (section 3), and how information theory may yield insights into their control processes (section 4). We conclude with a discussion of cancer as a disease of global physiological dynamics (section 5), and how this may be viewed from the perspective of information theory as a breakdown or reduction of information integration (section 6).

2. Information in biological systems

The cancer problem has been considered from many different modeling perspectives ranging from the standard mechanistic models [21–25], to applications of population dynamics [26–29], evolutionary game theory [30–32], and models of swarm dynamics [33, 34]. However, these methods generally only consider one or two levels of organization in describing the dynamics of the systems they consider, and almost exclusively view the lowest level as giving rise to the higher levels. This ultimately endows the lowest level of organization with the most causal power, and rejects the possibility that, as complex systems, cells and collectives exhibit behavior and function that cannot necessarily be better described or deduced based solely on the dynamics of smaller and smaller components [35]. Moreover, the above approaches largely do not address the loss of patterning or the goal-seeking behavior of cancer systems, which we argue in are its defining characteristics and offer tractable points for intervention.

An alternative approach is to take a more wholistic perspective, treating the system as composed of many levels of organization and inquiring about the interaction and information flow between them. We propose an '*information-theoretic toolkit*' which may

be utilized to refine and quantify how the various levels of organization of a system interact and ultimately exert influence upon one another. Such a quantitative approach will be essential in the coming decades to begin to understand the measurements that cells and tissues make *in vivo*, which include measurements of distant cells' properties and likely measurements of properties that do not exist at the level of single cells or molecules (e.g. organ size, topology, or position).

Information theory has gained widespread application in the biological sciences, from understanding the information content of genomes [36–38], to identifying individuality [39], and patterns of information processing in brain tissue [40–42]. It has even been suggested by Smith that without drawing on informational analogies, the discoveries made in molecular biology over the last 60 years would have been accomplished at a slower pace, or perhaps not even at all [43]. However, information theory has so far seen less application to the problem of cancer (see e.g. [44, 45] for exceptions) than other areas of biological research despite the fact that information is a way to quantify patterning and structure, precisely the features that we argue break down during oncogenesis making it a disease of pattern dysregulation.

Modern formulations of information theory began with the seminal work of Claude Shannon in 1948 who defined a quantity now termed *Shannon entropy* (H),

$$H(X) = -\sum_{i=1}^{N} p(x_i) \log p(x_i), \qquad (1)$$

where X is a finite random variable, which can take on one of N different states, $\{x_1, x_2, \ldots, x_N\}$ each with probability $p(x_i)$. Shannon entropy is often informally described as the expected degree of surprise at learning the outcome of an event: the more unlikely the event, the more surprised you feel at learning that it happened. Equation (1) forms the core of information theory. To quantify shared information due to communication, Shannon introduced the concepts of sender and receiver, described by two random variables X and Y, respectively. The idea is to determine how strongly events drawn from each are correlated as, upon communication, the state of sender and receiver should become correlated. This can be thought of as inquiring as to how much information variable X carries about variable Y, and vice versa. One can then ask, by making observations of X, how much can be learned about Y? To quantify this notion of information, Shannon defined *mutual information* as

$$I(X, Y) = \sum_{i=1}^{N_X} \sum_{j=1}^{N_Y} p(x_i, y_j) \log \frac{p(x_i, y_j)}{p(x_i)p(y_j)}, \qquad (2)$$

where $p(x, y)$ denotes the probability of observing X and Y in the states x and y, respectively. Intuitively, mutual information precisely measures how much the distribution of X and Y jointly differs from the distribution of each independently. That is, equation (2) can be thought of as the entropy shared between X and Y.

As a conceptual example of the role mutual information plays in biological systems, consider two cells communicating via cell potentials and inter- and intracellular ion concentrations. The expectation is that the internal state of a cell is in some way correlated with the pumping of ions in and out of the cell and thereby with the cell's membrane potential. They should therefore have non-zero mutual information. When neighboring cells observe changes in intercellular ion concentrations, via changes in their membrane potentials, they respond mechanistically. Other examples of the application of mutual information in biological modeling include quantifying the correlation between the information content of the genomes and their environment [46], between molecules within the cell [47] and between early life replicators [48] and their environment.

It should be noted that mutual information is not directional: it is not concerned with which event *preceded* the other and therefore is not a measure of causation. In biomedical research, we are often interested in the idea of *intervention* rather than correlation. For example, in cancer therapy a small molecule drug might be used to block a cell surface receptor, or a key point in a chemical pathway within the cell, inactivating some downstream process, such as the production of cellular growth factors [49, 50]. Two cellular growth factors could be the output of some of the same series of steps and therefore would be correlated even if they do not causally interact. The goal of an information-based approach is to uncover the structure of integrated healthy tissue and how this structure breaks down because of cancer progression. While correlations do not directly imply causation, they nonetheless resolve features of the non-linear causal structure of a complex system. We discuss below under what circumstances this could also be useful to identifying targets for therapy. The next section reviews the biological foundation for such an information-based approach.

3. Cancer as a disorder of pattern regulation

3.1. Dynamic pattern control as anatomical homeostasis: the healthy state

The existence of multicellular organisms requires that individual cells abandon their normal unicellular behavior patterns; they must specialize morphologically and behaviorally, reduce or abandon their own proliferative tendencies, and cooperate to build and continuously repair complex large-scale anatomical structures (as occurs in embryogenesis and regenerative repair/remodeling, respectively). A process that subjugates individual agents' needs towards group-level goals will inevitably suffer occasional breakdowns; cancer is in a sense, the cost of doing business as a metazoan [51]. A related issue

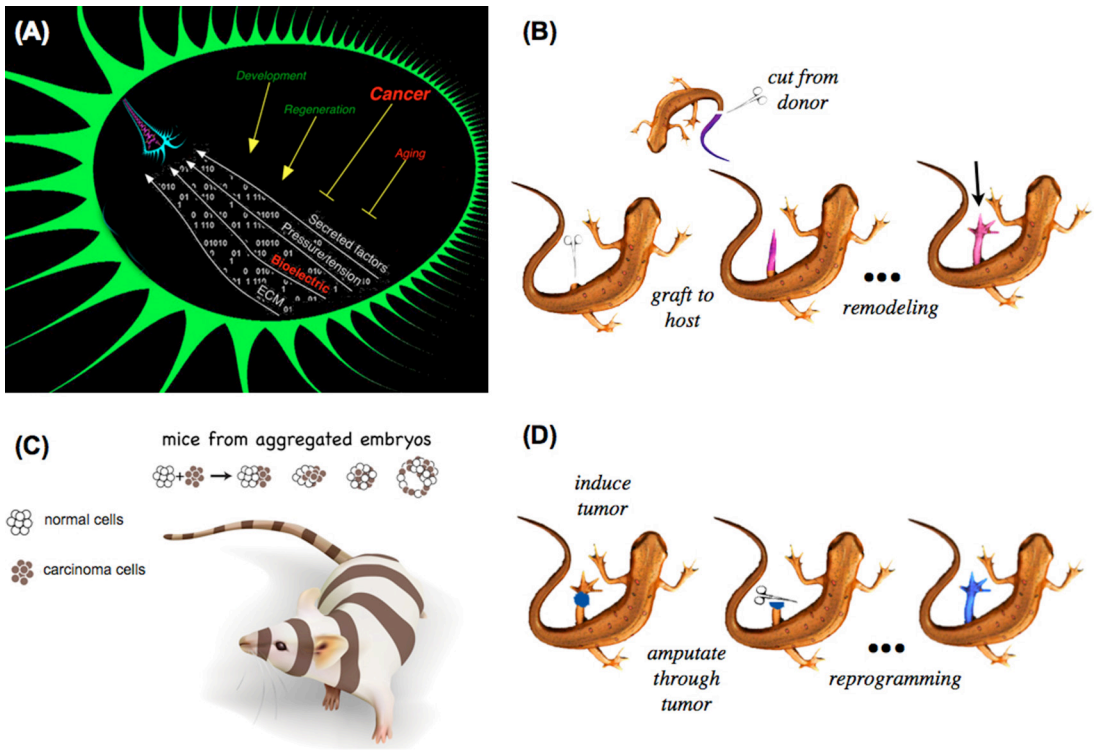

Figure 1. Morphogenetic field underlies large-scale pattern control and remodeling. (A) Substructures and cells in an organism *in vivo* continuously receive information from the entire body; this information makes up the morphogenetic field (mediated by gradients of secreted factors, physical forces (stresses and strains), bioelectric states, and extracellular matrix components). The morphogenetic field is what allows the coordination of cell activities toward correct patterning during embryogenesis and regeneration, and what allows structures to resist dysmorphologies such as cancer and aging. (B) Amphibian models reveal large-scale (non-local) aspects of the morphogenetic field: tails transplanted to the flank slowly remodel into limbs—structures more appropriate to that anatomical location. Importantly, even the tail tip cells (whose local environment, a tail, is correct) remodel into fingers, illustrating the integrated large-scale anatomical surveillance and remodeling of pattern homeostasis. (C) The view of cancer as a disease of geometry is supported by data showing that when provided with strong patterning cues (in this case, when implanted into a developing embryo), the cells contribute to normal morphogenesis, not tumors. (D) The same is true in regeneration, where initiation of regenerative patterning of a new limb is able to reprogram limb tumors in that region. Artwork in panels (B)–(D) produced by Jeremy Guay of Peregrine Creative. Panel (A) used with permission from [478] John Wiley & Sons. © 2013 Wiley Periodicals, Inc. Panel (B) reproduced from [182] with permission of The Royal Society of Chemistry.

for future investigation is: what does a unicellular organism's cancer look like? Is it possible for a paramecium to enter a cancer state? The SMT model might predict novel phenotypes (increased proliferation rate? increased motility?) after DNA damage to typical tumor suppressor genes. The TOFT model would instead predict that default unicellular behavior *is* the cancer phenotype, and that further cancerization of a unicellular animal might be impossible (although it might predict interesting effects of TOFT-inspired cancer therapies upon normal unicellular organisms).

The antithesis of cancer is the remarkable fidelity of pattern homeostasis observed in biological organisms—maintenance of the same body over hundreds of years in some long-lived species. How embryos, which begin as one stem cell (the fertilized egg), reliably build a complex stereotypic anatomy is a major unanswered puzzle, but it is clear that a complex morphogenetic field of chemical, biomechanical, and bioelectrical signals impinges on cells and provides instructive influence *in vivo* (figure 1(A)). However, development is just the first manifestation of a more fundamental property of living things: pattern homeostasis [18, 52]. The problem of reliably generating a specific anatomy is difficult enough, but at least the feed-forward development of a zygote into a predictable outcome gives some hope that complexity theory will explain the eventual emergence of a specific structural endpoint. However, beyond forming a single well-defined structure, many biological systems have the ability to *repair* their complex shape if it is damaged in unpredictable ways [53], and remodel themselves to fit specific anatomical criteria (figure 1(B)). Many early embryos, when cut in half, or combined, will reorganize, and give rise to normal organisms [54–56]. Even in adulthood, some organisms (such as salamanders) can regenerate amputated limbs, jaws, hearts, tails, and portions of the brain [57, 58]. Masters of regeneration, such as planaria [59, 60], have also solved the aging problem - achieving body-wide immortality through continuous regeneration (while individual cells senesce and die). Importantly, planaria reproduce by fission, bypassing the Weissmann barrier [61] and accumulating mutation at a high rate [62], despite a remarkably rock-solid developmental and regenerative morphology.

The problem before us is that of closed loop morphostasis: maintaining a complex shape despite deformations that cannot be known in advance [63]. How do systems detect when their correct shape has been altered by injury or disease, compute what steps to take to restore their correct target morphology, and decide when to stop growing (after their anatomical goal has been reached)? Regenerating animals rebuild precisely what is missing—no more, no less—in the face of external injuries they could not have anticipated. When half of a planarian's head is removed, a perfect match is restored, of the right size and orientation, and then growth stops. Such systems process information about their current state and its deviation from the target morphology, perform computations about what should be done next, and make decisions about what to grow and when to stop [64, 65]. Importantly, these decisions are global. When planaria are bisected, the two blastemas form a head and tail, respectively, even though the cells on either side of the cut were adjacent neighbors. A tail grafted to the flank of a salamander slowly remodels to a structure more appropriate to its new location [66], illustrating shape homeostasis towards a normal amphibian body plan (figure 1(B)). Even the tail tip cells (which are in their expected location, at the tip of a tail) slowly become fingers. Similarly, planarian tumors disappear when regeneration is induced even at the opposite end of the animal [67]. This all shows that the remodeling is driven, at least in part, by non-local information.

The common feature in these examples is that individual cell behaviors are guided toward *large-scale anatomical setpoints*—goal states of system-level homeostatic processes that harness cell activity toward a specific morphological outcome. This requires long-range coordination among cells, and significant amounts of signaling that enables sensing of local and long-rage states, whether this takes place through a series of neighbor interactions or via a long-range signaling modality. It is easy to see that cells that cannot perceive the morphogenetic field of organizing cues [18, 68–70], or that end up in locales with a local low-point in the morphogenetic field, would be unable to coordinate with others and revert to single-cell behavior. In such a case, cells would proliferate, consume resources, migrate, and evolve, without regard for the whole of the organism, as observed in cancer.

The distinction between cell-level mechanisms and global patterning needs is clearly observed in an old experiment showing a kind of 'implementation independence' of morphogenesis. Kidney tubules in the newt possess a constant size, while cell size can vary drastically with ploidy [71]. The tubule pattern (a macroscopic goal state) can be implemented by diverse underlying molecular mechanisms such as cell-to-cell interactions (when there are many small cells) or cytoskeletal bending that curls one cell around itself, to make a tubule (when cells are very large). Such discordance between macroscopic pattern and underlying molecular mechanisms is one way to conceptualize the often-bewildering lack of one-to-one match between molecular marker states and cancer outcomes. A key puzzle for future research is to clarify how cells can sense metrics not defined at the individual cell level (e.g. size, position, orientation, and symmetry of a given organ), and how these macroscopic states can serve functional determinants of phenotype. A quantitative view of systems in which global states have causal power and dominate the functional roles of molecular states is discussed below in 5.

3.2. Cancer as a disease of anatomical homeostasis

Importantly, cancer is not an imposition of runaway growth—instead, it is a lifting of normal constraints and order provided by the host. 'No cancer exhibits any trait which cannot be found in some normal tissue as the expression of normal genomic activity; no cancer grows faster than an embryo nor is any cancer cell more invasive than a macrophage nor are cancer cell lines more immortal than are germ lines' [72, 73]. Indeed, because growth and disorder is the default condition, continuous input from the host is required to keep tissue organization. One mechanism used to coordinate cell activity away from cancer is communication via the nervous system. Tumors are readily induced by denervation in salivary organ and alimentary canal in cockroach [74, 75] and in mammalian skin [76]. Similarly, tumors are chemically induced more easily in denervated rabbit ears as compared with contralateral controls bearing normal innervation [76]; the same has been observed in sarcomas implanted into normal or denervated frog limbs [77]. The ability of the host to regulate local cell activity in accordance to global patterning needs can be generalized as the influence of a '*morphogenetic field*'—the sum total of signaling cues impinging upon all cells *in vivo*.

Cancerous failure of morphostasis can occur because a morphogenetic field is missing, altered, or not successfully perceived (all three of which can occur due to genetic or physiological state change). Cells in dispersed monolayer culture are several orders of magnitude more sensitive to chemical carcinogenesis than are organized tissues within an intact organism [78], and placing normal primary mammalian cells in culture results in the appearance of cells with malignant potential [78–81]. Chick embryos infected with the v-Src virus exhibit no malignant phenotype, but the same cells in culture undergo massive transformation [82]. A number of recent papers stress the suppressive nature of signals from neighboring tissues [83–86]. Consistently, re-establishing appropriate interactions of human cancer cells with the microenvironment and normal neighbors underlies the observed reversion of malignant phenotype in a number of cell lines [87–89].

Consistent with the need for cell-to-cell interactions in suppressing cancer are data showing that tumorigenesis is promoted when cells are isolated from

their neighbors (and thus from the morphogenetic guidance they would otherwise receive) by physical barriers. Implanting into connective tissue of the rat rectangles of inert plastic, metal foil, or glass coverslips induces sarcomas when the material is $>1\,cm^2$. If the material is perforated, the incidence is reduced, and the effect does not occur with powders of the same material (which actually increases surface area, ruling out chemical induction or genetic damage mechanisms) [90–93]. These kind of data clearly underscore the importance of environment [94], not only intrinsic state.

More recent data have focused attention on interruption of cell-to-cell communication via ions and other small molecules through electrical synapses known as gap junctions (GJs)—aqueous channels made of connexin proteins that allow physiological signaling directly between the cytoplasmic interiors of docking adjacent cells [95–100]. For example, Connexin32-deficient mice have a 25-fold increased incidence of spontaneous liver tumors [101]. Gap junctional isolation is known to be a tumor-promoting agent [100, 102–107], although there are counterexamples [108]. Active GJ communication allows cells to make sophisticated decisions comparing relative levels of specific compounds between themselves and their neighbors [109] and thus can underlie the transmission of physiological patterning signals [110–120].

Anticipating recent discoveries of the importance of gap-junction cell-to-cell communication for planarian regenerative patterning [119, 121], in 1965 Seilern-Aspang described planarian experiments in which a carcinogen led to formation of many head teratomas with irregular nerves and un-oriented eyes, concluding that 'the *cell-isolating* action of the carcinogen prevents formation of a single morphogenetic field and leads to the establishment of several separated fields of reduced dimensions' [67]. Thus, tumors could also represent establishment of a local 'subfield'—a fragmentation of the host's morphogenetic field such that integration with the host body plan is lost. Unlike normal somatic tissues, which remodel when transplanted into foreign locations [66, 122, 123], the histopathological structure of metastasis reflects the tissue of origin, not of their destination [16], confirming an inability to respond to neighboring signals such as positional information and remodeling cues.

One of the key predictions of a view of cancer as a disease of geometry is that it should be reversible. If it results from the lack of morphogenetic influences upon cells, then contexts in which very strong patterning cues are being imposed should have the power to reverse or reprogram neoplasm. The morphogenetic field ought to be the most active and accessible during embryogenesis. It is thus not surprising that despite considerable malignancy and aneuploidy, tumor cells introduced into wild-type embryos become integrated (figure 1(C)) as normal tissue [124–134]. Human metastatic melanoma cells injected into zebrafish embryos acquire a non-neoplastic phenotype, but form tumors when injected into zebrafish *after* organogenesis [135, 136]. Likewise, implanted sarcoma progressed in 80% of adult rats but only in 6.4% of rat embryos. Similar data have been recently shown for chick and other kinds of embryos that are able to tame aggressive cancer cells when these are implanted [136–139]. Cancer normalization can occur cell-autonomously [140], or induced by communication from other cells, such as the mammary stroma [124, 141–146]. Indeed the embryonic field present in the blastocyst can normalize several types of cancer cells including those isolated from embryonic carcinoma, leukemia and neuroblastoma [134], although the limits of this normalization process (with respect to large-scale chromosome aberrations found in some tumors) remain to be probed fully. Thus, active patterning signals can normalize cancer (over-ride genetic defects and reboot cell behavior programs); this is a finding that is not predicted by the cell-level view of cancer as embryos have high levels of many growth factors that could be expected to potentiate tumor growth (and do, in experimental contexts such as cell culture which is devoid of large-scale patterning structure).

It has been long known that regeneration and cancer are closely related [147–152]. Highly-regenerative organisms are resistant to carcinogenesis and indeed activating regenerative response (figure 1(D)) can normalize existing tumors [147–150, 152–156], although this does not always occur [157]. The inverse relationship between regeneration and cancer susceptibility [72, 158] is more compatible with the importance of morphogenetic field guidance than with cancer risk associated with the presence of highly-active, undifferentiated cells [68]. Mammalian liver regeneration can overcome cancer—early nodules initiated by carcinogens are remodeled to normal-appearing liver [159, 160], hepatocarcinoma cells can be normalized by injection into wild-type liver [161, 162], and over 95% of nascent tumor sites remodel into normal tissue by the highly-regenerative liver [163–165]. Clinically however, this capability is tempered by the fact that many patients have a damaged liver (Hepatitis C or other burden which induces cirrhosis and may prevent regenerative response). In zebrafish brain regeneration, a remarkable degree of aneuploidy does not lead to cancer, while amphibian limb regeneration can likewise normalize tumors [6, 151, 166], showing that in some cases, an active patterning program can trump chromosomal damage [167].

What kind of data are conveyed by the morphogenetic field? Information conveyed by the morphogenetic field includes positional coordinates. It has long been known that mismatches in positional identity, in grafting experiments, causes supernumerary structures to form [168–170]—the so-called 'rule of normal neighbors', in which tissues grow as needed to intercalate new structures to keep continuous positional information gradients. In the cancer field, this

is observed in differences of anterior-posterior axial positions to cancer susceptibility, and in the ability of tumors to form from the juxtaposition of normal but ectopic tissues. Tumors grow on posterior regions of *Triturus* less readily than they do on anterior regions [67], and numerous such differences are observed in human tumors as well [171–176]. Despite lack of DNA damage or cytotoxic chemical stressor, transplantation of rat testis to the spleen induces formation of interstitial cell tumors [177], while normal rat ovary tissue put into normal rat spleen results in malignant neoplasm [178]. Implantation of early embryos (which organize their own field of signals) under the kidney capsule of an adult makes transplantable malignant teratomas despite a lack of any infective, chemical, or radiation initiator to cause genetic damage [16], while normal adult *Xenopus* kidney implanted in the non-amputated forelimbs of recently-metamorphosed larvae will make lymphosarcomas as well as accessory limb structures [179]. Implantation of mouse embryos into adults causes teratocarcinomas [180], possibly due to an interference between the host and implanted embryo's morphogenetic field signals.

The morphogenetic field is mediated by a number of physical modalities, including the well-known gradients of chemical morphogens (secreted factors), extracellular matrix, physical forces (tension and compression), and bioelectric cell states. Addressing cancer from the perspective of large-scale coordination cues requires familiarity with the properties of mechanisms that underlie long-range pattern control. Non-neural bioelectricity is precisely such a set of mechanisms, and is increasingly implicated in cancer by molecular studies [181]. Most importantly, the known ability of bioelectric networks to process global information and implement networks with multiple causal layers (e.g. goal-directed activity mediated by brain bioelectric circuits) make it an ideal nexus from which to understand and manipulate cancer as an error of global organization [20, 182]. Thus, in prelude to the discussion of mathematical theory germane to top-down approaches to cancer, we first review a set of important emerging mechanisms that provide plentiful fodder—both quantitative and conceptual data—for computational analyses to the control of cancer as a defection from normal developmental cues.

3.3. Bioelectric regulators of growth and form: a new locus of intervention in cancer

As in the brain, somatic endogenous ion currents, plasma membrane resting potentials (V_{mem}), and electric fields are produced by the activity of ion channel and pump proteins across cell membranes. One difference from action potentials is their temporal dynamics, which are slower and continuous (not discrete millisecond spiking activity as in the CNS). The tissue-wide gradients thus produced, and the networks of endogenous bioelectric states present across many cell types (figure 2) serve as instructive determinants of cell behavior [183, 184], and—more importantly, of collective dynamics during pattern regulation. Due to length limitations, here we omit discussion of other biophysical phenomena including transepithelial electric fields [185, 186], ultraweak photon emission [187, 188], and coherent AC electromagnetic fields [189, 190], all of which also have considerable relevance for the cancer problem. Likewise, the many interesting studies of applied field effects in the cancer context are discussed in several excellent recent reviews [191–194]. Here we focus on distributions of V_{mem} or membrane potential [195], as a mediator of information processing in cellular networks. Due to their central role in pattern homeostasis, these bioelectric patterns are both an important target for neoplastic disregulation and biomedical strategies seeking to restore appropriate dynamics between cells and body-wide patterning fields.

3.4. Bioelectric states control cell behavior

Bioelectric properties of cells and the electrical states of cells in the microenvironment control several key behaviors of relevance to cancer (reviewed in [186, 196–202]). For example, electric fields generated by ion pumping across epithelia serve as migration cues for cellular galvanotaxis [203–207]—an important guidance modality for cell movement within the host. Cell shape changes, such as increased arborization, are also driven by endogenous electric fields and changes in V_{mem} [208–212]. Together, migration and shape properties are key elements of successful metastasis [213, 214].

Resting potentials determine differentiation state and proliferation; generally, a depolarized state is indicative of plastic, undifferentiated cells (e.g. stem cells), while differentiation is caused by increase of negative V_{mem} [215]. Functional control of cell state by changes in V_{mem} has been observed in many kinds of stem and progenitor cells [216–226], including adult human mesenchymal stem cells [222, 227], which can be kept stem-like despite the presence of chemical differentiation factors by forced depolarization, and in induced pluripotent stem cells [228]. Even mature CNS neurons can be made to re-enter mitosis by sustained depolarization [229, 230], revealing the power of transmembrane potential to regulate proliferative potential in adult somatic cells.

Changes in V_{mem} of cells, such as cancer-associated depolarization, can trigger transcriptional changes by (1) regulating the movement of morphogens such as serotonin, calcium, and inositol triphosphate through gap junctions [116, 117, 231–235], (2) controlling the import/export of small signaling molecules such as butyrate across membrane exchangers [208, 235–238], and (3) modulating the activity level of phosphatases such as PTEN [239–242]. Together, these transduction mechanisms convert an essentially biophysical state change into secondary messenger events that impact on transcriptional and epigenetic regulation of loci

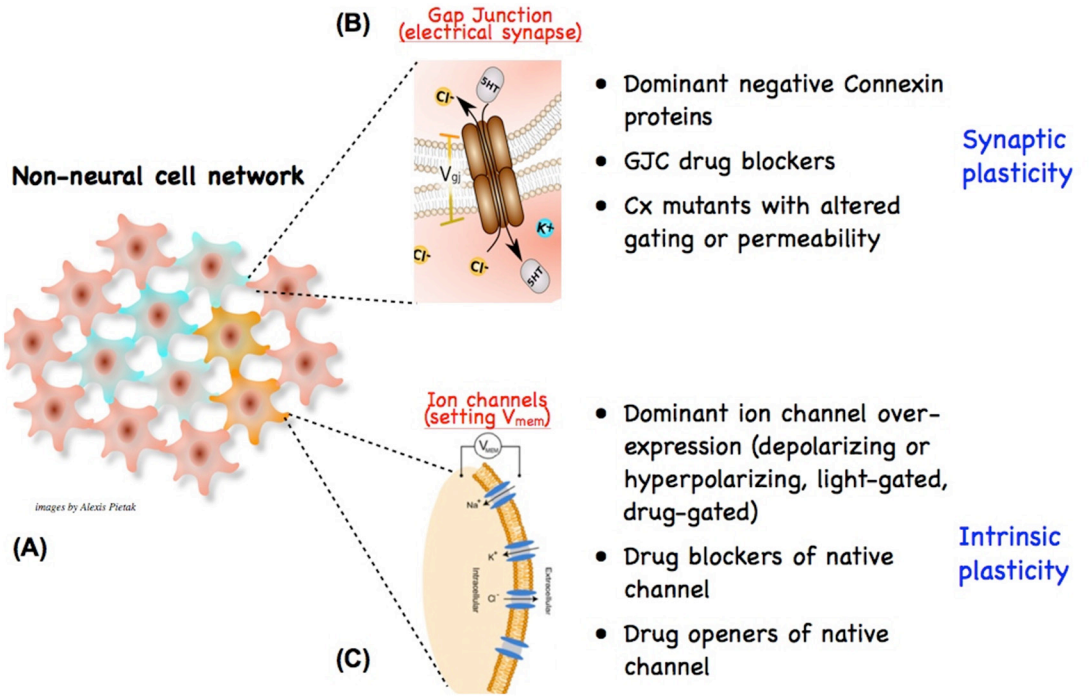

Figure 2. Bioelectric networks and their manipulation. Developmental bioelectricity concerns the dynamics of ion-mediated, slowly-changing voltage gradients in many types of tissues (not necessarily neurons). Cells form networks (A) connected by electrical synapses known as gap junctions (B), which pass current and other small signaling molecules. The connectivity among cells can be modified using pharmacological blockers, and expression of mutant connexins/innexins with altered gating properties or sensitivity to factors such as trans-junctional voltage and pH. Modulating the network topology, either experimentally or via endogenous physiological signals, is analogous to synaptic plasticity in the CNS. The bioelectric state of individual cells (which is communicated across tissues via the gap junctions) is set by the activity of ion channels and pumps (C) in cell membranes. The resting potential (V_{mem}) of individual cells can be modified, as in neural intrinsic plasticity, by endogenous regulators or experimental strategies using dominant-negative or wild-type ion channel misexpression (including sophisticated ligand-gated channels or optogenetics), or pharmacological reagents that will open or close existing channels to alter resting potential dynamics. Graphics by Alexis Pietak; Reproduced from [438]. CC BY-NC 3.0.

such as NODAL or SLUG which are important intermediate effectors for the cancer phenotype [238, 243].

3.5. Spatio-temporal gradients of V_{mem} are instructive cues maintaining healthy anatomy

Importantly, relatively recent development of state-of-the-art tools for the detection and experimental manipulation of biophysical signals in multicellular patterning contexts [244–247] has revealed how distributions of voltage gradients mediate positional information, organ identity of large cell groups, and initiation signals for complex developmental modules such as tail or limb regeneration. Using a combination of fluorescent voltage-reporter dyes to characterize spatial V_{mem} distributions and functional studies using targeted misexpression of well-characterized ion transporters to specifically modify those gradients *in vivo*, instructive signaling roles of transmembrane voltage gradients have been identified in embryogenesis and regeneration, adding to the list of such roles identified in classical work that utilized functional physiology [248, 249]. A number of recent molecular studies using unbiased approaches in human syndromes and non-human model systems have identified a range of ion channels, gap junctions, and ion pumps in developmental and regenerative morphogenesis of the face, brain, heart, appendages, growth of the cerebellum [250–258] and many other structures [259–271]. These physiological states are ideal inputs for the computational analysis delineated in the next section.

During early frog development, the redistribution of maternal potassium channels and proton pumps in early blastomeres results in a V_{mem} gradient that determines asymmetric expression of key transcription factors [243, 272, 273]. Later, during craniofacial patterning, the positions of the eyes [274] and other elements of the face [275] are determined by a regionalization of naïve ectoderm into distinct domains of hyperpolarized cells—a bioelectric pre-pattern or scaffold for the nascent structures. These voltage gradients regulate the expression of genes like *Frizzled*, and artificially altering this pattern by misexpression of specific ion channels and pumps is sufficient to perturb normal craniofacial anatomy and to reprogram tissues far away from the head to form properly-patterned eyes [274]. Importantly, in such cases, as in the cancer phenotypes discussed below, it is really the V_{mem} that is the necessary and sufficient factor for inducing specific shape change—it does not matter which ion translocator protein is involved, or what ion species is used: a given voltage change, no matter how it is produced, activates specific downstream events.

During regeneration of flatworms, the patterning activity of adult stem cells (neoblasts) is regulated by gap junctional connectivity and a set of proton and potassium flows [119, 121, 276]. By regulation of apoptotic remodeling and downstream activity of genes such as *Wnt11* [277], the physiological gradient determines the anatomy of the organs built after injury. In vertebrates, where electric fields were long ago implicated in limb regeneration [278–285], recent experiments showed that driving proton and sodium fluxes can force complete tail [286, 287] or limb [288] regeneration in a range of non-regenerative conditions. The mechanisms involve guidance of innervation into the stump, activation of blastema genes such as MSX1, Notch, Delta, BMP2, and BMP4, and induction of cell proliferation in the wound mesenchyme.

With respect to wound healing, inhibition is known to be a tumor promoting agent [289–291], elegant molecular genetic experiments have now revealed some of the elements underlying endogenous electric field-mediated cell migrations. Epithelial wound closure involves Integrin Beta-4 (ITGB4), Cyclic AMP, betaphosphatidylinositol-3-OH kinase-γ (PI(3) Kγ) and phosphatase and tensin homolog (PTEN) [197, 292–295]. Having seen that endogenous electric fields and V_{mem} gradients play an instructive role in normal patterning, what is the evidence that dysregulation of bioelectrical communication can underlie the cancer phenotype?

3.6. Ion channels are oncogenes and important drug targets

The view that cancer is a developmental disorder predicts that molecular mechanisms known to be important mediators of the morphogenetic field would be involved in tumorigenesis. Indeed, there is mounting evidence that the bioelectric cues that establish normal pattern can go awry and result in cancerous growth (reviewed in [199, 296, 297]). The function of ion channels is involved in the self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis [200]. Ion channels, pumps, and gap junctions are now recognized as oncogenes [199], predictive markers [200], and an important set of targets for new cancer drugs that seek to modulate cell behavior by tweaking electrical controls of proliferation or metastatic behavior [298]. Importantly however, onco-channel misregulation occurs not only through mutations in channel genes but also by changes in the rich network of events that implement post-translational gating of wild-type ion channels.

Tumor cells differ from untransformed cells in terms of the type of ion channels and pumps they express and in the resulting membrane potential of the cells [299–308]. Some channel levels are thus used as markers, such as the K2P channel TREK-1 and the sodium channel NaV in prostate cancer [309, 310], and the TRPM1 channel in melanoma [311, 312]. Tumor cells' membrane voltage is often determined by a different transporter than that of normal cells and it has been suggested that this gives the cells a selective advantage [303].

The function of ion translocators, such as voltage-gated K^+ channels [313, 314] and Cl^- channels [315], controls the proliferation rate of a number of cells that often form tumors [316–327] or leukemia [328]. ERG is particularly involved in cell growth signals [303, 329–333], and is implicated in transformation of prostate epithelium [334]. Also implicated are 2-pore channels such as KCNK9 [335, 336], and voltage-gated sodium channels, being definitive oncogenes—necessary and sufficient for a transformed phenotype [337]. Metastatic potential correlates with voltage-gated inward sodium current and it has been suggested that some sodium channels may be oncofetal genes, encoding signals that are active during the rapid and autonomous growth of tumors and embryos [310, 338–341].

Migration of cells including B-16 melanoma is dependent on K^+ channels [342]. The voltage-gated sodium channels (VGSCs) potentiate breast cancer metastasis [341], and indeed the involvement of NaV in the galvanotaxis that allows prostate and breast cancer cells to move across vessel lumens [213, 337, 343–349] is one of the leading stories on ion channels in cancer. Highly up-regulated activities of NaV confers on cancer cells directional motility and invasive characteristics via Ca^{2+} and pH-sensitive cytoskeletal remodeling processes which facilitate metastasis [337, 341]. Certain channelopathies result in syndromes associated with cancer such as the lung cancer seen in Lambert–Eaton syndrome [350], and the tumors present in Beckwith–Wiedemann syndrome, which is caused by abnormal imprinting of a voltage-gated potassium channel [351–353].

The involvement of ion channels in transformation, growth control, and metastasis has led to efforts to develop potassium, chloride, and sodium channel and pump modulators as clinical agents for ovarian [354], breast [355], and prostate [356] cancer [298, 357]. Unbiased drug screens for inhibitors of cancer stem cells have implicated potassium ionophores such as salinomycin [358], and tetraethylammonium (TEA, a potassium channel blocker), was found to suppress colony formation in endometrial cancer cells while withdrawal of TEA resulted in a significant enhancement of tumorigenesis [359]. Known cancer-fighting agents are now beginning to be recognized as ion channel modulators, for example resveratrol [360–362]. Indeed, drugs that target membrane voltage-generating transporters have already shown clinical promise in cancer [363].

Which ion channels should be targeted by therapeutic drugs? In an important sense, focusing on the channel gene or protein may be missing the bigger picture. In the current literature, ion translocators are

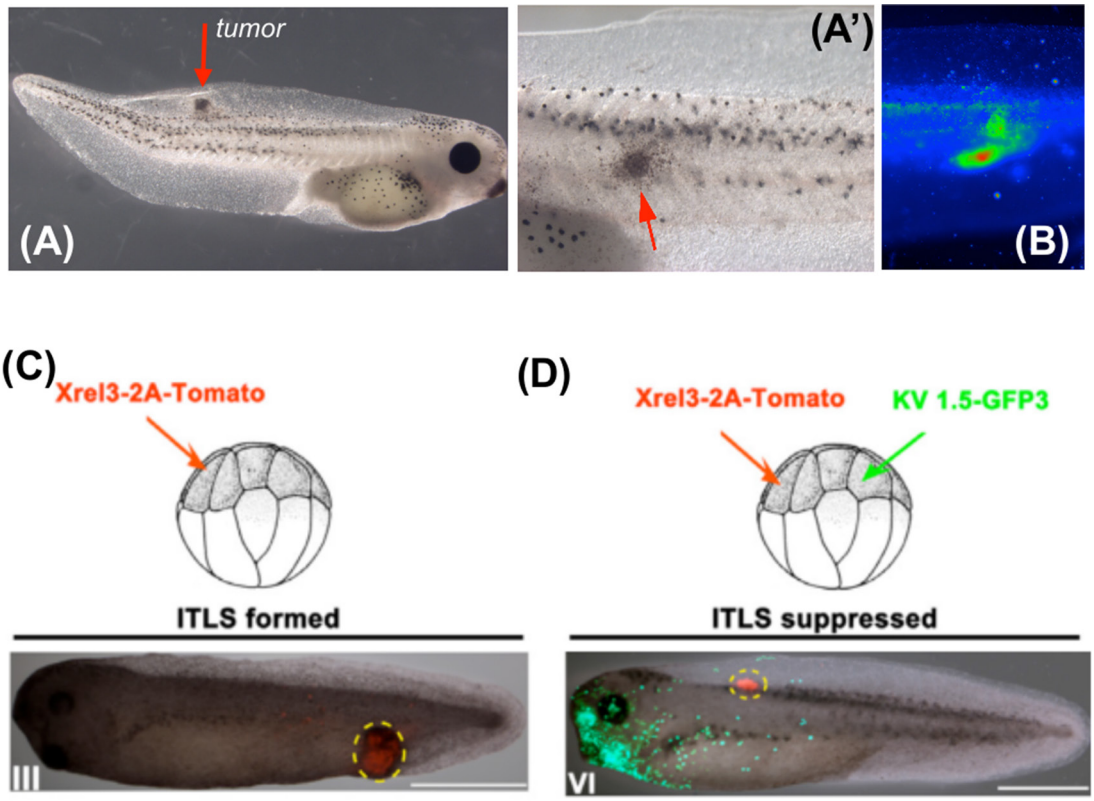

Figure 3. Cancer: detecting its bioelectric signature and suppressing tumors by managing bioelectric state. Microinjection of human oncogene mRNA (A) induces tumor-like structures (ITLS) in Xenopus embryos (A′). Soaking in voltage-reporting fluorescent dye reveals the voltage depolarization that occurs at the earliest stages of tumorigenesis (B). Remarkably, tumors normally induced by Xrel3 fused to a fluorescent red protein (C) can be suppressed by misexpression of hyperpolarizing channels such as Kv1.5, even when the hyperpolarizing region is at a considerable distance from the oncogene (visualized by its red fluorescence). Panels C and D reproduced from [398]. CC BY-NC 3.0.

usually treated as single genes or proteins responsible for a specific cell behavior (metastasis, hyperproliferation, etc)—a cell-level view that neglects the fact that numerous channels and pumps contribute to the V_{mem} gradients that mediate large-scale patterning cues [202, 364]. The true impact of bioelectricity in cancer will only occur when we understand and target the storage of patterning information in *physiological* networks that is misprocessed in cancer [365, 366]; such networks are dynamical systems with complex feedback between the post-translational gating of many different channel and pump proteins.

3.7. A unique bioelectric signature reveals incipient cancer

A variety of bioelectric properties have been used as detection modalities for tumors; these capitalize on cancer cells' distinct electrical impedance [367–381] or ion content [382, 383]. Zeta potential is also associated with cancer; for example asbestos fibers and sheets of positively-charged materials (but not powders of the same material) induce tumors, probably by acting as a capacitor for bioelectric potential, the positive side corresponding to the electron sink existing at a wound (reviewed in [384]). In this section, we focus on depolarized V_{mem}, which has been suggested to correspond to the cancer state [215, 385–387].

One way to probe the physiology of the effects of canonical mammalian oncogenes (Gli1, Xrel3 and KRASG12D) and a mutant tumor suppressors ($p53^{Trp248}$) *in vivo* is to misexpress them in Xenopus and zebrafish embryos [388–391], which induces the formation of tumor like structures (ITLS). ITLS's thus form as a result of genetic interference with signaling pathways altered in several cancer types including basal cell carcinoma, lung cancer, leukemia, melanoma, and rhabdomysarcoma [392–395]. Examination of injected animals using fluorescence reporters of V_{mem} [396] revealed unique depolarization of tumors (and increased sodium content) (figures 3(A) and (B)) compared to healthy surrounding tissues [237, 397]. Moreover, depolarization foci are present in oncogene-expressing, pre-neoplastic cells that are yet to undergo transformation or show any morphological phenotype. Such depolarized foci, while present in only 19–30% of oncogene-injected embryos (depending on oncogene used), predict tumor formation with 50–56% success rate (15–21% false negatives). For comparison, prostate specific antigen (PSA) level in the serum, when used as a biomarker for prostate cancer, has ~29% predictive value [399, 400].

The existing data reveal local bioelectric disruptions that correlate with incipient cancer and could be exploited as a diagnostic modality for prediction of

tumor sites and margins. In addition, it is imperative to establish molecular models in which to investigate the fact that transplanted or chemically-induced tumors can be detected by aberrant voltmeter readings taken at locations far away from the tumor [8, 401–406]. In the meantime, work has progressed to show that voltage states are not merely a marker that correlates with cancer, but are a functional driver of the process. These bioelectric readings, together with the information analyses discussed in sections 4 and 6, may enable both, highly predictive new cancer biomarkers, and a unique description of the functional aspects of biophysical regulators of cancer progression.

3.8. Bioelectric modulation can induce global metastatic phenotype

Can bioelectric disruption alone, in the absence of classic carcinogens or mutagenic compounds, induce a cancer phenotype? Genetic or pharmacological targeting of a specific cell population (sparse but ubiquitous cells expressing the GlyR channel) in an amphibian model revealed a remarkable phenotype: over-proliferation, increased migration, and drastic arborization of melanocytes (pigment cells). By transiently depolarizing GlyR-expressing cells *in vivo*, an entirely different cell type (melanocytes) underwent a metastatic-like conversion, turning on expression of genes such as Sox10 and SLUG [209]. The melanocytes acquired a dendritic morphology, upregulated mitotic activity, and invaded blood vessels and soft tissues like the neural tube lumen and brain. In addition to melanocytes, disorganization and ectopic growth of blood vessels was also observed [397], but otherwise the tadpoles were remarkably normal in terms of overall growth and development. Importantly, the same exact effect was induced by *any* method of depolarization, including by the movement of chloride, sodium, potassium, or hydrogen ions—truly an effect initiated by V_{mem} depolarization, not any specific gene product or chemical ion species, and a metastatic phenotype induced by a purely physiological perturbation.

Most interesting was the non-cell-autonomous nature of the effect: the cells that acquired a melanoma-like phenotype were not the cells whose resting potential was changed (the GlyR-bearing cells were thus called 'instructor cells') [208, 209]. Indeed, only a small number of instructor cells had to be depolarized in order to induce the hyperpigmentation phenotype (which is all-or-none within any individual animal). How was the communication between these two cell types mediated? A suppression screen testing the several known methods of transducing voltage change into transcriptional cascades revealed that the serotonin transporter SERT, which powers uptake or efflux of serotonin depending on resting potential, was involved (much like in the bioelectric regulation of left-right patterning); blockade of SERT could rescue the hyperpigmentation effect, and direct application of serotonin could trigger a similar phenotype. This pathway, comprising bioelectric dynamics and downstream neurotransmitter responses (all outside the nervous system) has now been extensively analyzed by machine-learning approaches to assist human scientists in rationally modifying its complex dynamics *in vivo* [397, 407, 408].

3.9. Hyperpolarization inhibits oncogene-induced tumorigenesis

The above data show that depolarization of V_{mem} can, itself, activate a metastatic-like phenotype. What role could V_{mem} play in carcinogenesis induced by genetic perturbation? Well-characterized channels such as inward rectifying potassium channel (Kir 4.1) and constitutively open glycine-gated chloride channel mutant (GlyRF99A) can be used to generate strong hyperpolarizing currents [409, 410]. When GlyRF99A was co-injected with the Xrel3 oncogene in Xenopus larvae [237], it significantly suppressed the incidence of ITLS formation induced by oncogene alone (figures 3(C) and (D)). Florescent tags on the oncogene protein revealed that hyperpolarization could prevent the formation of tumor-like structures despite very robust expression of oncogene in cells. The use of several different hyperpolarizing channels based on Cl^- and K^+ confirmed that suppression of neoplastic transformation was due to V_{mem} hyperpolarization, as opposed to ion-specific or scaffolding functions of the ion channel proteins. Consistent with this, data in rats showed that the ion channel modulator drug ivermectin can likewise modulate the effectiveness of carcinogenic compounds [411].

More recent work has used light to trigger optogenetic ion channels in prevention and normalization of human oncogene-induced tumors [412]. Crucially, a dissection of the spatial relationship between the cells expressing the oncogene and the cells expressing hyperpolarizing channels revealed *long-range* signaling mediated by electrical synapses known as gap junctions, and bacterial-derived butyrate [413]. Thus, whether or not a tumor formed on one side of the animal depended on whether or not cells on the opposite sides were connected electrically, demonstrating the importance of distributed decision-making in the appearance of tumors at a given site and the importance of not restricting attention to the tumor site itself.

These results must be translated into mammalian models, and tested in a variety of different types of cancer in order to determine in what cases mutational burden has to be addressed before cure, and in which cases patterning signals might be sufficient to permanently solve the problem regardless of the DNA state. A crucial component of this effort is to understand the information-bearing signals that keep cells, both normal and mutant, under control [7, 414]. Study of these signals must take place both at the bench (unraveling the biochemical and biophysical mediators of pattern

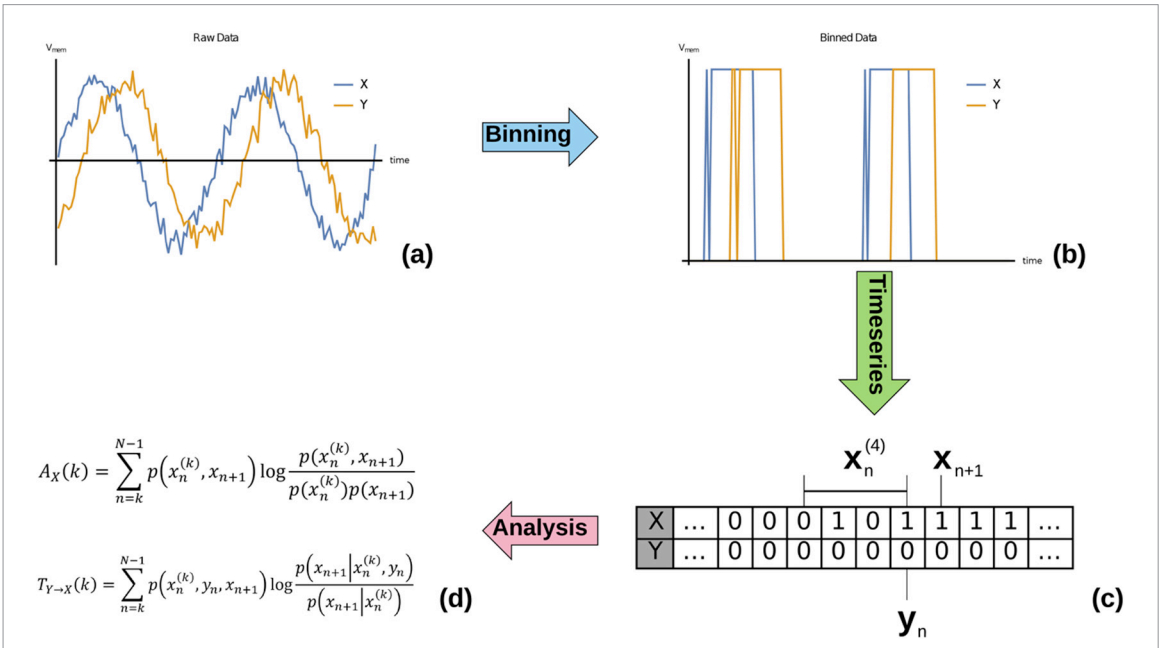

Figure 4. A toy example of how to apply active information or transfer entropy. (a) V_{mem} time series data for two cells X and Y. (b) The time series is binned per some specification. While continuous time series can be handled in principle, binning is more common. (c) The binned time series is broken up into histories, $x_n^{(k)}$ and y_n, and futures, x_{n+1}, and used to estimate probabilities, e.g. $p(x_n^{(k)}, x_{n+1})$, $p(x_n^{(k)}, y_n, x_{n+1})$, etc… (d) The active information and transfer entropy are then computed based on the probabilities.

control mechanisms) and *in silico* (establishing rigorous analytical frameworks for quantifying and decoding specific control policies operating in cell collectives). Advances in this area will also help identify key tipping points in physiological and genetic state space that reveal when a system can and cannot be brought back to normal by specific interventions. Having seen the relevance of patterned bioelectric states for both normal development and cancer, we next describe the information dynamics approach to information theory as a quantitative toolset for understanding information processing in development and cancer.

4. Information dynamics

Information dynamics is an extension of information theory that permits quantifying the component operations of computation within dynamical systems by analyzing their time series data [415]. It has utility in decoding the 'logic of life' [416] as one can make direct analogy with the more intuitive computational concepts of information storage and processing. In information dynamics, these concepts are quantified by active information (AI) and transfer entropy (TE), respectively. Figure 4 provides a schematic description of how to apply AI and TE to time series data, e.g. V_{mem} for two cell membranes.

4.1. Information storage

In an isolated mechanical system with no noise, past states are good predictors of future states. However, in the messy and noisy cellular environment, the past states of a process within a cellular network, or an individual cell within a tissue, will in general be inadequate for guiding prediction of future states due to strong nonlinear coupling between cellular components. Local active information storage (LAIS) quantifies the degree to which uncertainty about the future of an agent X is reduced by knowledge of its own past states [417]. Formally, local active information storage for an agent X is the local (unaveraged) mutual information between its semi-infinite past $x_n^{(k)}$ (as $k \to \infty$) and its next state x_{n+1} at time $t+1$:

$$a_X(n+1) = \lim_{k\to\infty} \log \frac{p(x_n^{(k)},\ x_{n+1})}{p(x_{\text{n}}^{(k)})p(x_{n+1})}, \qquad (3)$$

where $x_n^{(k)} = \left\{x_{n-k+1}, x_{n-k+2}, \ldots, x_n\right\}$ is a vector of k previous states of X. For real-world data, time series are finite, and local active information is often approximated by defining a history length k shorter than the dynamical time scales of interest. Averaging equation (3) gives the *active information* for a dynamical process [417]:

$$A_X(k) = \sum_{n=k}^{N-1} p(x_n^{(k)}, x_{n+1}) \log \frac{p(x_n^{(k)}, x_{n+1})}{p(x_n^{(k)})p(x_{n+1})}. \qquad (4)$$

Average and local active information have been used been used to understand information storage in biological systems as diverse as swarm behavior [418–420], gene regulatory networks [421], neural information processing [40, 41], and to evolve artificial information processing systems [415]. Application to neural information processing is particularly relevant to the cancer problem since the measurements of voltage potential tracking V_{mem} across populations of cells is similar in data content to that acquired by fMRI of brain tissue. In particular, LAIS has been applied to

voltage sensitive dye imaging from brain tissue from area 18 of the cat visual cortex [40]. LAIS was shown to reflect functional properties, such as the response to stimulus, and the surprise on change of stimulus (despite the locally random nature of the stimulus).

As discussed in section 3.4, tumor cells' V_{mem} is typically determined by different transporters than normal cells [303] and no single channel dominates the global dynamics of large-scale patterning. Applied to physiological networks of cell cultures containing cancer, LAIS might separate cells with the cancer phenotype from healthy cells. It could be used to identify functional interfaces of the intra and inter-cellular interactions of cancer and normal cells, given that functional control of cell state changes is known to be driven by changes in V_{mem} [215]. Since healthy cells are expected to act 'more collectively' within a tissue we might expect LAIS to be, on average, lower for healthy cells than for cancerous cells that have gone rogue and act independently. For cancer, an interesting question is whether this information-theoretic approach would pick out behavior that was largely uncorrelated (e.g. random behavior of the cancer phenotype) or if cancer cells are predictable based on their own local past history.

4.2. Information processing

Information processing in information dynamics is quantified using Schreiber's transfer entropy (TE) [422], a directional measure of information transfer between random variables. The information transferred from a source node Y to a target node X may be defined as the reduction in uncertainty provided by the source about the next state of the target, above the reduction in uncertainty due to knowledge of the past of the target. Formally, TE from Y to X is the mutual information between the previous state of the source y_n, and the next state of the target x_{n+1}, conditioned on k previous states of target, $x_n^{(k)}$:

$$T_{Y\to X}(k) = \sum_{n=k}^{N-1} p(x_n^{(k)}, y_n, x_{n+1}) \log \frac{p(x_{n+1}|x_n^{(k)}, y_n)}{p(x_{n+1}|x_n^{(k)})}. \quad (5)$$

TE naturally exhibits an asymmetry between the source and target nodes. This asymmetry lends a directionality to the measure, and as such TE can be utilized to measure 'information flows', which cannot be captured by symmetric measures such as mutual information [422]. One can view the transfer entropy as conditional mutual information between a target and source, conditioned on the past states of the target. The basic idea is that the prediction of the next value for a given variable at step n, given knowledge of its past k states, could be improved by taking account of the state of other variables at step n. If that is the case, then in some sense information has been transferred between the two variables since there is a directed correlation. If the correlation is high, it implies that knowledge of the other source variable leads to better prediction of the state of the destination variable at step n.

In neuroscience, transfer entropy is used to uncover effective connectivity [423, 424]. It has been used to evaluate information transfer between auditory cortical neurons [42], and on simulated data for cortical interactions [425], electroencephalogram (EEG) data [426], and fMRI data [427]. In the case of cancer, TE could be used to determine effective connectivity of cancer and healthy tissue, and infer if these represent distinct patterns in information flow, related to whether the behavior of cancer cells is somehow coordinated (non-zero TE) within the population of cancer cells, or if instead behavior of cancer cells is coordinated with the surrounding healthy tissue. Multivariate analysis can be implemented to infer additional structure by assuming that X and Y in equation (5) no longer represent individual elements in a system, but instead are collections of sets of elements. For example, one could measure the directional information transfer between a tumor and surrounding tissue, or between cell types with different phenotypes. Inter-regional information transfer has, for example, been measured in neural fMRI data [428] to infer the informational structure of visuo-motor tracking in the brain. Importantly, metrics from computational neuroscience have begun to be applied to the problem of developmental/regenerative patterning [65, 182, 429], and the emerging field of primitive cognition suggests a research program to understand the information processing/computational capacity of tumor cells versus normal cells, and tumors versus normal organs.

4.3. Information processing, storage and drug targets in gene regulatory networks

Recently, information dynamics analysis was utilized to study the informational structure of gene regulatory networks using Boolean models [421, 430, 431]. Both active information and transfer entropy were applied to study cell cycle regulation of the fission yeast *Schizosaccharomyces Pombe* [421]. In a Boolean network model, genes are represented by nodes (or equivalently in this abstract representation, their protein product) and can take on a value of '1' or '0' corresponding to whether the gene is expressed or not, respectively [432]. In the case of the fission yeast cell cycle Boolean model, the network consists of nine nodes, shown in figure 5(A). The biologically functional attractor, corresponding to the stationary **G1** resting phase of the cell, dominates the attractor landscape: for this network 73% of all states will eventually converge to this single state [433]. The four nodes highlighted in figure 5(A) are identified as a 'control kernel' that regulates the function of the entire network. Pinning the state of control nodes to their value in the primary attractor corresponding to the **G1** resting phase increases this to 100% convergence, such that *every* possible trajectory terminates on the primary attractor. Control kernels were also discovered in a number of other Boolean network models for gene regulatory networks [434]. A survey of the control

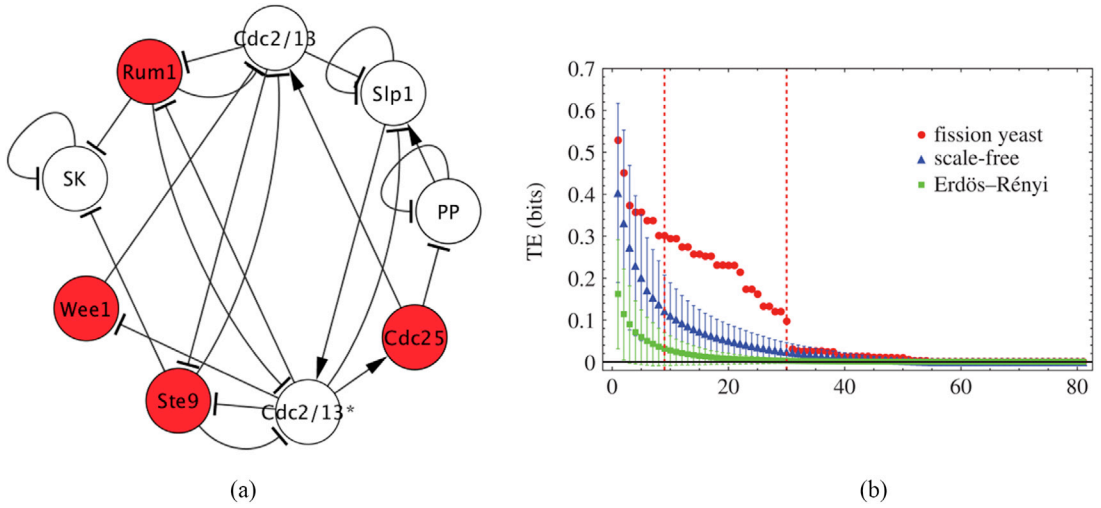

Figure 5. (A) The Boolean network model of the gene regulatory network of the fission yeast *S. Pombe* cell cycle. Nodes and edges represent regulatory proteins and their causal interactions, respectively. Red nodes are components of the control kernel (see text). (B) Scaling of transfer entropy between pairs of nodes for history length $k = 2$ for the Boolean network model of the fission yeast cell cycle regulatory network (red), and ensembles of scale-free random networks (blue) and Erdös–Rényi random networks (green). Ensemble statistics are taken over a sample of 1000 networks. The *y*-axis and *x*-axis are the TE between a pair of nodes and its relative rank, respectively, over all network pairs. Red dashed lines indicate the region where the real fission yeast model differs by $> 2\sigma$ from either random ensemble. Figures adopted from [421], by permission of the Royal Society.

nodes of these regulatory networks reveals that drug targets are statistically overrepresented [434].

Interestingly, the active information and transfer entropy also indicate a special role for control nodes in the correlational structure of the fission yeast cell cycle network. A scaling relation for TE between pairs of nodes was compared to the TE scaling of Erdös–Rényi random networks and scale-free random networks by Kim *et al* [421], shown in figure 5(B). The analysis shows that the biological network is quite distinct from random in terms of amount of 'information processed' as quantified by TE. Important for discussion here is that the most distinctive regime for the real fission yeast model ($> 2\sigma$ deviation from either the Erdös–Rényi or scale-free random networks, highlighted between red dashed lines in figure 5(B).) is dominated by information transfer either to control nodes from the rest of the network, or from the rest of the network to control nodes (see [421], figure 5). That is, the control nodes act as hubs for information processing in the network. They additionally play a dominant role in information storage, with higher values of active information than the majority of other nodes in the network [430]. While this provides only one case study, it opens the possibility that informational analyses of time series data of gene expression might provide a non-interventionist approach to identifying drug targets that regulate cellular behavior. Much work remains must be done to detail how information is organized through the pattern of gene-expression states in both healthy and cancerous cells, and in turn whether this kind of approach can indeed provide a novel platform for identifying targets for therapy.

Cancer involves processes guided by changes in gradients of membrane potential (V_{mem}) and also by gene regulatory networks within cells. Part of the power of information-based approaches is that they are agnostic to the details of the problem to which they are applied. Thus, information-based approaches could provide a unified framework for addressing the onset of and progression of cancer as it occurs both within a cell through changes to the attractor landscapes of the gene regulatory networks of cancer cells [435] and to the neural-like pattern memories encoded as attractors in the state space of bioelectric networks. Analyzing multiple levels of information dynamics in tandem could provide greater insights into the complexity of the cancer disease.

5. Global physiological dynamics underlie cancer: information, not molecules

'For those who believe in the simplification and rationalization of the cancer process, the actual course of research on the molecular basis of cancer has been largely disappointing. Rather than revealing a small number of genetic and biochemical determinants operating within cancer cells, molecular analyses of human cancers have revealed a bewilderingly complex array of such factors' [436]. It is now appreciated that the essence of cancer may not be in specific driver genes but in the dynamics of cells traversing state spaces and shifting between different attractors [12, 437]. While these state spaces are commonly thought of in terms of transcription (gene-regulatory networks), the data on bioelectricity in cancer suggests that another important concept may be the physiological state space [438].

The existing data in developmental bioelectrics reveal that the decision of any given region to develop

a tumor or not depends on the bioelectric state of far-off regions of the body, and the combined activity of many ion translocators that interact with, and partially compensate for, each other to establish a specific spatio-temporal voltage profile. Thus, predicting and normalizing cancer may be best achieved not by local, gene-focused approaches, but rather a focus on information (which bioelectrical networks are superbly suited for processing). What do cells measure, remember, and use for decision-making as they shift between normal and neoplastic state?

One way to think about cancer is as a shift of the border between self and environment [439, 440]—a contraction of the functional integration of the self-organizing system [441, 442]. In contrast to normal cells, which work for the good of a macroscopic host (the combined 'self'), cancer cells have reduced their computational boundary to their own surface: to each cancer cell, the whole body is just 'the environment', at the expense of which all living things reproduce and survive. Cancer may be not be an increase of selfishness, but rather an unchanged self-interest coupled to a shift (reduction) of the internal self-model [65, 443–445]. This view challenges us to explore models that rely not on selfishness-based evolutionary dynamics but rather on the computational aspects of what cells and cell collectives measure and how they form internal models of self and environment [445–447].

It is also possible that the right level of description for some tumors is not the single cancer cell but the tumor, which may embody not only a *loss* of normal organ patterning dominating individual cell dynamics, but also a coherent, goal-seeking subsystem that exists outside the morphospace of healthy somatic organs. Tumors may not be just aggregates of replicating selfish neoplastic cells but complex living entities composed of numerous cell types that work together to acquire nutrients, survive, and evade the efforts of an environment that is trying to kill them [448, 449]. Perhaps, a tumor is, in some practical sense, an independent colonial organism [450] with its own (primitive) morphogenetic field, and a self-boundary that is more than unicellular but reduced from the whole body to that of a much smaller structure. Such a view is suggested by a number of findings. First, histological analysis indicates that tumors can indeed be regarded as complex tissues with a distinct internal organization [79, 451]. Tumors reproduce themselves via metastasis, and execute many adaptive strategies (such as up-regulating multi-drug resistance proteins in the face of chemotherapy) to preserve their homeostasis and existence—just as organisms within an ecological niche do [452–454]. Much like organisms maintaining morphostasis, tumors maintain their identity during massive cell turnover during selection for founder cells resistant to chemotherapy drugs [455]. Recent work describes the highly malignant brain tumor as an 'opportunistic, self-organizing, and adaptive complex dynamic biosystem' [456], which is also a great description of an embryo; proper characterization of the essential principles predictive of the properties of tumor invasion makes uses of concepts such as least resistance, most permission, and highest attraction—these are systems-level, goal-directed elements that are very compatible with the conceptual modeling techniques suggested for understanding embryogenesis and regeneration of whole organisms [20, 182]. Much analysis and experimentation will be needed to reveal whether a tumor and its activity in the body is best modeled as the activity of unicellular organisms, emergent swarm dynamics of the tumor 'colony', or a cognitive structure embodied in a kind of group cognition of the tumor 'organoid' [457–460].

Next, we consider computational strategies that can be applied to sharpen, quantify, and make rigorous the above-mentioned qualitative arguments about the most effective (causally potent) level of organization at which to attack the cancer problem and the information flow that exists in normal and abnormal morphogenetic field scenarios.

6. Integration and information

We argue in the previous section that cancer may be the result of a retracted notion of 'self', a contraction of the functional integration of a self-organizing system of cells [441, 442]. One important aspect is whether a tissue acts collectively as a single entity, or whether distinct regions take-on independent function—it is the latter case that we might expect to give rise to cancer. Information theory offers attractive methods for precisely quantifying such notions of integration. We review two information-theoretic formalisms that attempt to capture various aspects of integration: integrated information theory (IIT) [461, 462] and integrated spatiotemporal patterns (ISTP) [463].

6.1. Integrated information theory

One promising direction is provided by the concept of integrated information. Integrated information theory (IIT) is one of the most widely discussed measures of integration. IIT quantifies how much information a system generates as a whole, above and beyond its individual parts [464]. While IIT was originally developed as a measure of consciousness (which clearly must have some 'wholeness'), its applicability is broad. We discuss here two measures from IIT: effective information (EI) and *integrated information* (φ). Unlike in information dynamics, both EI and φ characterize entire network *states*, rather than individual nodes, and they do not generally require time series data to compute.

Effective information quantifies the information generated by a system when it enters a state G. More formally, the effective information for each realized state of a system, given by $\mathrm{EI}(G')$, is calculated as the relative entropy of the *a posteriori repertoire* with respect to the *a priori repertoire*:

$$\mathrm{EI}(G') = H(p^{\max}(G)) - H(p(G \rightarrow G')). \quad (6)$$

The *a priori repertoire* is defined is as the maximum entropy distribution, $p^{\max}(G)$, where all system states are treated as equally likely. The *a posteriori repertoire,* $p(G \rightarrow G')$, is defined as the repertoire of possible states that could have led to the state G'. In other words, $\mathrm{EI}(G')$ measures how much knowledge of how the system behaves reduces the uncertainty about the possible states that might have preceded G'. EI is then used to calculate *integrated information*, which quantifies by how much the 'sum is more than the parts'. φ is quantified as the information generated by a system when it enters a particular state G', as compared to sum of information generated independently by its parts. More specifically, φ can be calculated as follows: (1) divide the system entering a state G' into distinctive parts and calculate EI for each part, (2) compute the difference between the sum of EIs from every part and EI of the whole system, (3) repeat the first two steps with all possible partitions. φ is then the minimum difference between EI from the whole system and the sum of EIs for its parts (we refer readers to [461, 462, 464] for more details on calculating φ). If $\varphi(G') > 0$, then the causal structure of network generates more information as a whole, than as a set of independent parts when it enters the state G'. For $\varphi(G') = 0$, there exist connections in the system that can be removed without loss of information. φ can capture how much a system is 'more than its parts' suggesting that it is the right sort-of measure for understanding when a collective is really a single entity. In major transitions we might expect systems to become more integrated as the transition proceeds and in cancer we should expect the combined system of healthy and cancerous tissue to become less integrated as the disease progresses.

Integrated information theory has been used to study the structure of the fission yeast cell cycle network, and the network as a whole has been found to maintain integration through the sequence of states corresponding to the phases of the cell cycle [465]. A subgraph of the network in figure 3(A), known as a 'backbone motif', was also analyzed [466]. This backbone motif is the minimal sub-network of the original fission yeast cell cycle Boolean network capable of the same function as the original network, namely it can reproduce the sequence of states for each phase of the cycle. IIT analysis of this reduced network demonstrated that while it could produce the same function, it did not maintain integration through each step of the cycle. Extrapolating to the case of cancer, one can separate function from integration, and loss of the latter does not immediately imply loss of the former. However, due to the rapid increase of the number of partitions necessary to calculate φ as system size increases, IIT is impractical to calculate for systems larger than about ten elements (roughly the size of the fission yeast network). Other measures that approximate φ, or quantify different aspects of integration [467], will be necessary for application to the cancer problem.

6.2. Agency and integrated spatiotemporal patterns

Colloquially, integrated information theory (IIT) focuses on whether a system is greater than the sum of its parts. It attempts, in a rigorous way, to make clear whether the system can be subdivided, and to quantify how much 'more' the system is as a whole. While this concept of integration is powerful, it says little about how the system in question is integrated *with its environment*. An alternative approach to assessing integration, integrated spatiotemporal patterns (ISTP) [463], offers a less assertive take on integration that can account for environmental context in a more flexible way. Specifically, ISTP attempts to provide a quantitative notion of *agency*. Since describing cancer requires not just understanding how it behaves as a collective, but also how it interacts with its environment, ISTP is a promising tool for understanding cancer dynamics.

One intriguing possibility is that tumorigenesis amounts to increased agency of collective and/or constituent cells. Phenomena such as metastasis and angiogenesis lend credence to this hypothesis, though few experiments address this possibility directly. The degree to which the cancer cells are collectively integrated could, based on known relationships between gap junction connectivity and proliferation [468, 469], translate into more aggressive disorders. This section lays out how ISTP could prove experimentally valuable in quantifying the agency of tissues, with cancers as an example of interest.

The notion of agency is notoriously difficult to define much less rigorously quantify. However, there are properties that are commonly accepted as requirements for agency: *individuality*, *perception*, and *action* [470]. Individuality expresses the idea of an 'entity', something to which perception and action can be attributed. This generally requires a larger context than the individual itself, e.g. a tumor is defined in the context of a tissue or a body, an organism in the context of an environment, etc… Within the realm of information theory, individuality is typically quantified in terms of either mutual information or relative entropy between the constituent parts of the individual and the environmental setting. More formally, individuality can be expressed in terms of the *integration* of a subsystem with its environmental context—low integration suggests that the entire system is well understood in terms of how the individual interacts with its environmental context (and vice versa). Given such an individual, *perception* amounts to the individual's interactions with its environment and *action* is the subsystem's response to external stimuli.

Within the context of a given tissue, each cell has some degree of agency—it is an individual that perceives changes in its environment and responds accordingly. However, tissues themselves are reasonably

homogeneous and each cell is functionally similar, if not equivalent, to every other cell. What makes cancer cells distinct is that they break this homogeneity and take on a different function; they become distinguishable from their surrounding tissue. What's more they begin to decouple from their environment, which arguably allows for metastasis and greater proliferation, and makes them easier to culture [471–473]. The expectation is that they become less integrated with their surroundings and take on greater agency than their neighboring cells. However, this is not to say that one should expect that all tumors themselves are integrated structures. This said, the most prolific or metastatic scenarios show signs of cooperative behavior or swarm-like behavior, and as such may be identified in terms of their increased degree of agency and integration.

The concept of *integrated spatiotemporal patterns* was introduced in the work of Biehl *et al* [463] to make explicit the notion of agency in terms of spatiotemporal integration. The authors build upon the works of Krakauer *et al* [39] and Friston [474] to provide a framework which can represent agents. Biehl *et al* began by expressing the structure of discrete, finite-time dynamical systems in terms of dynamical Bayesian networks [463]. These directed, acyclic networks are composed of nodes, each associated with a finite random variable, and directed edges signifying correlational dependence. Essentially, each node represents some aspect of the system, e.g. a chemical concentration, the expression of a gene, the expressed phenotype of a cell, etc, and the edges represent conditional dependence between those variables, e.g. phenotypes may be conditionally dependent on gene expression. As noted by Ay and Polani [475], Bayesian networks have temporal structure; the nodes can be partitioned into sets $\{V_0, V_1, \ldots\}$ such that if a node $A \in V_{t+1}$ then there exists a node $B \in V_t$ with an edge from B to A. In other word, the nodes in the network can be broken into *time slices* where nodes in subsequent time slices have correlational dependence on nodes in the previous time slice.

Given such a Bayesian network, a spatiotemporal pattern is defined to be a collection of nodes in the network together with specific values for those nodes [463]. For example, given a network $G \to P$ which represents the correlational dependence of a phenotype P on the expression of some gene G, then a spatiotemporal pattern may be $x_O = \{1 \in G,\ 0 \in P\}$ representing the pattern 'the gene is expressed while the particular phenotype is absent'. Such a pattern has associated with it a probability $p_O(x_O)$ of occurrence. In a practical situation, this probability would be approximated by the observed frequency of the pattern relative to every expressible pattern of those nodes, here G and P.

The integration of a pattern can then be assessed in terms of local mutual information, first introduced by Fano and Hawkins (1961) [476],

$$mi(X_1 = x_1, \ldots, X_n = x_n) = \log \frac{p(x_1, \ldots, x_n)}{\prod_{i=1}^{n} p(x_i)} \quad (7)$$

which is an unaveraged, multivariate form of the mutual information discussed in equation (2)). Unlike mutual information, local mutual information can take on negative values. This signifies that observing the random variables $X_1, \ldots, X_n$ in the states $x_1, \ldots, x_n$ together is less likely than would be expected if the variables were fully independent. The evidence for integration for a spatiotemporal pattern x_O relative to a partitioning π of the pattern is then defined by

$$mi_\pi(x_O) = \begin{cases} 0 & \text{if } p_O(x_O) = 0 \\ \log \dfrac{p_O(x_O)}{\prod_{Q \in \pi} p_Q(x_Q)} & \text{otherwise.} \end{cases} \quad (8)$$

The pattern x_O is *integrated* if and only if $mi_\pi(x_O) > 0$ for every partitioning π of x_O. In other words, the pattern is integrated if considering all the components of the system jointly is always better than assuming that they are independent, regardless of how you group those components.

Continuing the example above, there is only one proper partitioning of the pattern $x_O = \{1 \in G, 0 \in P\}$, namely $\pi = \{\{1 \in G\},\ \{0 \in P\}\}$. Using equation (8), the evidence for integration of x_O relative to π is

$$mi_\pi(x_O) = \begin{cases} 0 & \text{if } p_O(x_O) = 0 \\ \log \dfrac{p(G = 1, P = 0)}{p(G = 1)p(P = 0)} & \text{otherwise.} \end{cases}$$

In this case, if $p(G = 1,\ P = 0) > p(G = 1)p(P = 0)$, then we would say that the pattern x_O is integrated. As such, from the point of view of the ISTP formalism, x_O would represent an agent in the dynamical system $G \to P$.

The simplest approach to applying this formalism to real systems proceeds as follows.

1. Identify the degrees of freedom of interest, e.g. phenotypes, genes, chemical concentrations, etc…
2. Observe the state of each degree of freedom over a sufficiently long period.
3. Construct an approximation of the system's Bayesian network from the time-series data.
4. Assess the integration of each spatiotemporal pattern in the system using equation (8).

Unfortunately, the systems of interest to cancer biology would likely consist of hundreds or thousands of degrees of freedom. Some of these degrees of freedom may be binary, e.g. a gene is expressed or suppressed, but most would likely admit many more

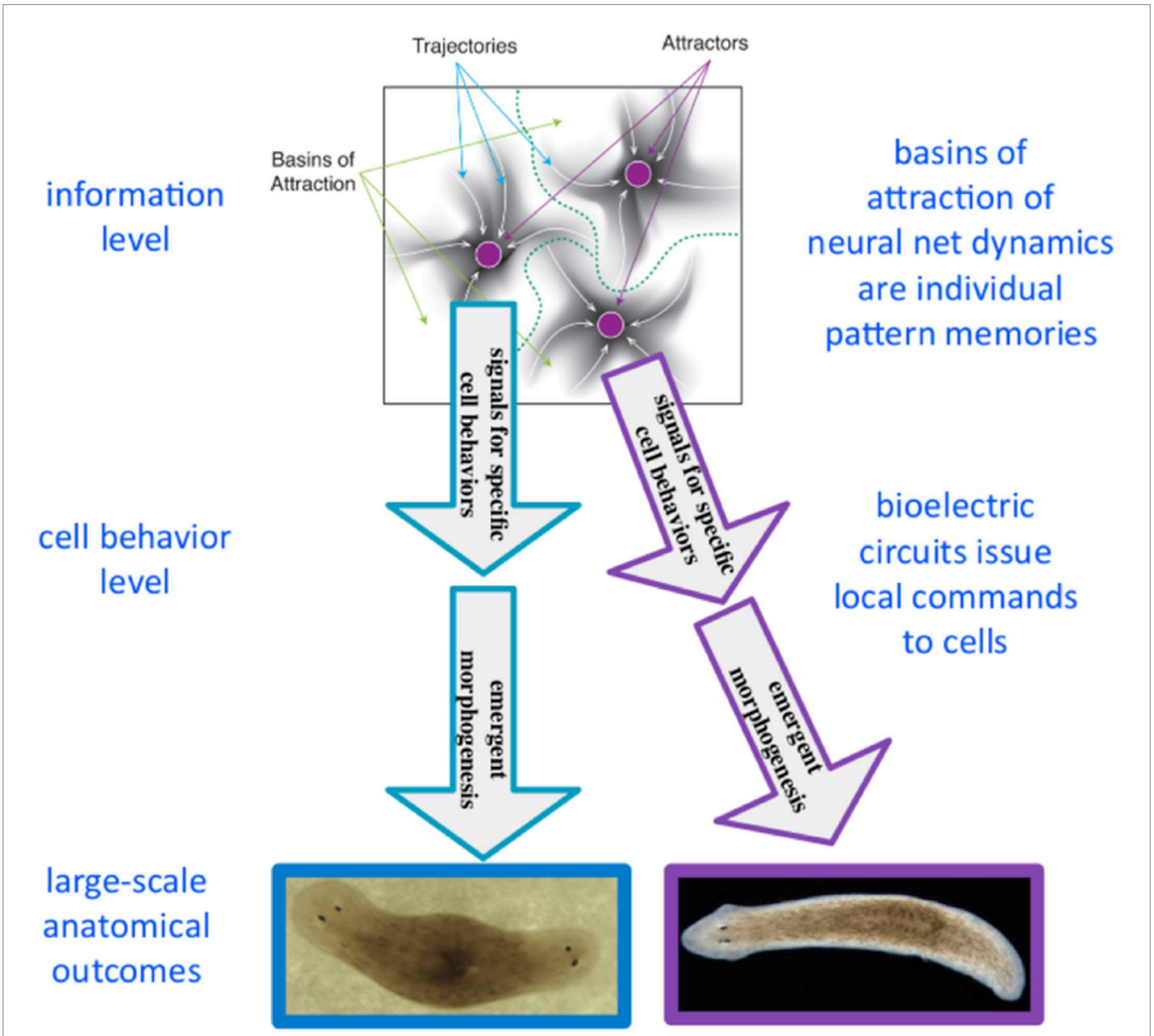

Figure 6. A model of encoding anatomical pattern memories via bioelectric states of tissues. One way to conceptualize how specific anatomical configurations (target morphologies) are encoded in tissues is to visualize the bioelectric network as a kind of (non-neural) neural network. As is known from the field of artificial neural network modeling, such networks store specific memories as basins of attraction in the state space of the electrical network. *In vivo*, the bioelectric network states are transduced into changes of cell behavior—proliferation, differentiation, migration, etc that implement distinct pattern outcomes (such as the 1- and 2-headed planaria shown here). Thus, we propose that target morphologies are encoded as pattern memories in bioelectric network. This allows pattern homeostasis to be addressed (via modeling and experimental approaches) at multiple levels, from cell/molecular mechanisms to the informational level that facilitates the kind of top-down pattern control needed to exploit tumor reprogramming. Graphic by Jeremy Guay of Peregrine Creative; reproduced with permission from [20].

states, e.g. chemical concentrations or cell membrane potentials. Identifying agents using the formalism thus described would prove computationally challenging, if not impossible, due to fact that the number of partitionings of a spatiotemporal pattern grows faster than exponentially with the number of nodes in the pattern. To overcome this limitation, Biehl *et al* suggest only computing the evidence for integration in the finest partitioning (the partitioning in which each node is in its own partition). This approximation is computationally tractable for all but the most pathological cases. Using this approach, Biehl *et al* present preliminary evidence that ISTP can accommodate metabolism, motility and counterfactual variation as intended [463].

As tools in the cancer biologist's toolkit, IIT and ISTP offer powerful new ways of understanding how cancer develops and progresses over time. While measures themselves are likely computationally intractable, approximations exist that will make analyzing the systems of interest possible [463, 467]. The concept of integration may provide insight into phenomena such as metastasis and angiogenesis which could provide targets for treatment. The hypothesis that cancer virulence is related to its degree of integration, internally and with its environment, can be assessed head on with these measures. Establishing such a connection could provide new biomedical techniques for treating cancer, possibly even reverting the cancer state altogether.

7. Conclusion

Over the last several decades we have made tremendous advances in understanding the molecular constituents of living matter. Nonetheless, we are still far from a general understanding of what life is, or how the millions of components of a cell orchestrate to produce the properties we associate with the living state.

The phenomena of complex organ regeneration, and of developmental reprogramming of cancer, challenge our field to augment the increasing resolution of cellular and molecular analysis with the equally necessary integration that explains the information content of (not only mechanisms involved in) higher levels of organization (figure 6). In cancer, many of these properties fail in ways that still preserve features necessary to persist as a living system. Cancer thus represents a functioning example of a living alternative that of healthy tissue, one that is operating with nearly identical molecular components, but very different growth and patterning dynamics. This is perhaps one reason the problem of cancer has been so intractable: reductionist approaches that focus on molecular components alone are hard pressed to distinguish between a cancerous and healthy cell as they share much of the same molecular biology, albeit differentially expressed. Treating cancer as a disease therefore cannot be disentangled from understanding more fundamental aspects of living organization, including what leads to the robustness of the living state, and what alternative forms this robust state of order might take on.

These properties are perhaps best characterized by adopting an informational [416, 431] perspective. Practical advances in this field will require quantitative analyses of patterning information processing in tractable animal models. Key open questions include: (1) determining (perhaps using integrated information metrics) the organizational level at which decisions in cancer are made—which types of tumors are their own integrated entity and which are simply reversions of somatic cells to a unicellular past, and using tools of connectionist computational neuroscience to understand the representation of anatomical pattern states in bioelectrical properties of tissues (figure 6), (2) identifying effective ways to couple cells back to the morphogenetic field (perhaps through the development of gap junction opener drugs), (3) using physiological reporter modalities (such as voltage-sensitive dyes) to detect pre-cancer signatures of incipient patterning failures *in vivo*, and (4) identifying ionoceuticals (blends of the many available and already human-approved ion channel drugs) that can directly mimic specific patterning cues to induce normalization (transition existing successes in amphibia to mammalian models). Recent technologies in interrogating cell perception space [477] suggest numerous approaches to quantify information processed within and among cell collectives, which could be applied to bioelectric signaling to better understand this important layer of the morphogenetic field and then impose states that increase whole-body integrated pattern dynamics. Of course, interventions derived from this perspective will have to be integrated into a biomedical program that functions despite the real-life stressors to which human patients are continuously exposed.

Here we have demonstrated how novel empirical data on cancer progress can be combined with new insights from information-based approaches to the characterization of cancers to provide new insights into the cancer problem, and hopefully new pathways for diagnosis and treatment.

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