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Trends in Cancer

Special Issue: Quantitative Cancer Biology

TrendsTalk

Integrating Quantitative Approaches in Cancer Research and Oncology

Cancer is a complex disease that requires a multidisciplinary approach to address the mechanisms by which cancer progresses, evolves, and causes treatment resistance in patients. Quantitative and systems biology approaches can propel our understanding of the physical, biological, and evolutionary principles that drive cancer progression and treatment resistance. Here, we ask experts what they see as the challenges and opportunities for incorporating physical science concepts into cancer biology and oncology.

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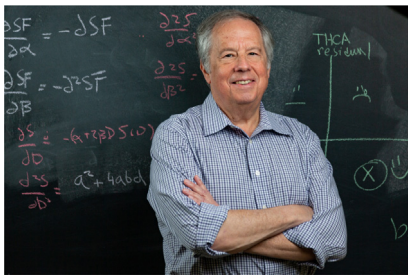
Deconvoluting the Complexity of Cancer Depends on Understanding the Dynamics of Dysregulated Information Flow across Biological Scales

Cancer comprises many 'agents' in a self-organizing complex adaptive system (CAS) that generally operates via simple rules at scale, exhibits redundancy, and operates far from equilibrium at the edge of chaos. Viewing and studying cancer as a CAS requires that the investigator understand that these elements may function somewhat independently or together to drive the development of emergent properties. Cancer exhibits two of the defining features of a CAS, emergence and coevolution, which are inexorably linked through information. Driven by advanced technologies, cancer research is now awash in data from dysregulated molecular pathways and networks, but this data 'tsunami' has yet to produce much useful information to address the two most challenging problems in cancer: metastatic disease and therapeutic resistance. Thus, realizing the concept of precision oncology remains elusive.

Over the next decade, the application (and merger) of information [1] and evolutionary theories will become a primary theoretical organizing model for developing a fundamental understanding of cancer across scales and time. Cancer is defined by the dynamic nature of the digital and analog computing that drives the myriad functions that occur to support complex decision-making and other functions at scale and across scales. It is remarkable that, since the sequencing of the human genome, we have accumulated vast amounts of data in oncology, but still know very little about the quantitative and mathematical aspects of how to identity, monitor, and predict the management and flow of dysregulated information in cancer. To address these challenges in oncology will require unprecedented advances in fundamentally understanding the quantitative aspects of the dysregulated information driving cancer, including long-needed progress in context-dependent algorithm development, computational modeling, simulation, and visualization. Additional advances in computing and the convergence of disciplines will also be needed to decode the nature and dynamics of this information, paving the way for new targets and strategies to prevent and cure cancer.



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Cancer Biology and Treatment: Is the Obvious Answer also Correct?

In 1756, Benjamin Franklin's plan to view a lunar eclipse was disrupted when a violent nor'easter (i.e., a storm with winds coming from the north east) struck Philadelphia. Franklin, like all scientists of his time, assumed that the wind carried the storm so that his brother in Boston would similarly have missed the eclipse. He was shocked to learn the storm actually arrived in Boston after the eclipse, leading him to develop new models of storm movement guided by atmospheric pressures.

Franklin was neither the first nor the last person to experience the divergence of linear human intuition from the nonlinear dynamics of complex dynamic systems. That is, his

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assumption that wind carries storms is both intuitively compelling and completely wrong.

The task of oncologists is eradication or control of the complex, adaptive, dynamic systems that form each cancer. To do this, the oncologist applies some perturbation(s) (e.g., chemotherapy) and then measures the outcome. This process is simultaneously highly sophisticated and surprisingly crude. Cancer medications are often the result of decades of research requiring investment of billions of dollars. Yet, the oncologist knows almost nothing about the components of the system of their governing dynamics beyond the total size of the tumor. Similarly, the applied perturbation elicits complex, probably nonlinear, responses in the tumor, but the only outcome metric is change in tumor size. Thus, it is not surprising that treatment agents are applied according to a decades-old tradition of continuous maximum-tolerated dose (MTD) until progression. This ignores the complex, evolutionary dynamics elicited by each application of the drug(s). In fact, the second drug dose is probably treating a tumor that bears little resemblance to the one that received the first dose. Therefore, it is not surprising that cancer treatment has focused on new drug development, increasing the dose density of existing drugs and simultaneous application of multiple drugs. Yet, most metastatic cancers remain as fatal now as they were 100 years ago. To repeat, in complex dynamic systems, simple assumptions can be both 'intuitively obvious' and completely incorrect.

In many ways, quantitative cancer biology allows cancer biologists and oncologists to follow the trail pioneered by Benjamin Franklin and set aside intuitive approaches. Like the current approach to weather prediction, more sophisticated cancer treatment strategies can be developed using mathematical models built upon evolutionary first principles to capture the complex and nonlinear dynamics during therapy. It will require new clinical data streams to parameterize and validate the mathematical models. Oncologists and mathematicians must learn to speak a common language necessary for true collaboration. It will not be easy, but cancer will not be eliminated as a cause of death until it occurs.

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Mathematical Models and Experimental Data: Chicken or Egg?

I work in the field of mathematical oncology, where my research group develops mechanistic mathematical models to understand cancer. These models not only establish correlative relationships between tumor characteristics and response to treatment, but also uncover why those relationships exist and how they can be exploited. Mathematical modeling is a much-needed approach to study cancer, given the complexity of the tumor microenvironment (TME), which includes many cells and a range of time and length scales over which cell-specific behaviors arise. Completely recreating the TME experimentally and studying how it evolves are time-consuming and resource-intensive processes. Excitingly, mathematical models can simulate the spatiotemporal behavior of cells in the TME, in less time and with fewer resources.

However, we need to improve the process of model building. We usually follow one of two paths: (i) model-first: we outline a specific biological question to answer, decide on the right modeling approach to use, and then look for published experimental data for model fitting; or (ii) data-first: we talk to experimental researchers who have a new data set, and they ask if we can build a model to explain that data. In both cases, we are left to (magically) transform the data or the model into something that might help

us better understand cancer. A third path is more ideal, though less-traveled: (iii) Model+Data: simultaneously generate a mathematical model and the exact data set needed to build and validate the model. Some of my most impactful and satisfying work happened when I sat with a collaborator to design the experiments and model together. No retrofitting the model or the data. No chicken or egg dilemma. Thus, to better understand tumor initiation and progression and impact patients with cancer, mathematical oncologists and experimental researchers must thoughtfully collaborate to build new models and novel data sets at the same time.

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Where Is the EMT? Computer Vision at the Frontline of Precision Medicine

In the era of new and rapidly evolving digital technologies, advances in image analysis have given new meaning to the adage, 'A picture is worth a thousand words'. Computer vision enables the extraction of vast numbers of quantifiable metrics from digital images, which can be interpreted in high-dimensional space via advances in data science (dimensionality reduction, machine learning, etc.). Digital imaging and cutting-edge microscopy techniques have revealed insights into the mechanisms of cancer development and malignant progression at high spatiotemporal resolution; these span the length scales of subcellular (super-resolution) to body-level (whole-animal) imaging. However, it has been challenging to address the high degree of heterogeneity observed in carcinomas. For instance, the epithelial–mesenchymal transition (EMT) can generate subpopulations of tumor cells with striking morphological and functional diversity. EMT may enhance invasive capacity, metastatic potential, and drug resistance, and has been observed in patient biopsies. As such, image analysis pipelines have been created to detect the changes in morphology and biomarkers associated with EMT, to score the epithelial–mesenchymal nature of patient tumors. Overall, digital pathology represents a powerful approach to detect rare or specialized subpopulations of cells, which may improve diagnostics and precision medicine. However, there is still much to learn about the fundamental biology of tumor heterogeneity that is necessary for interpreting digital pathology data to inform therapeutic decision-making. We anticipate that advanced 3D culture and *in silico* models, which 'reverse-engineer' tumor heterogeneity, will shed light on cell–cell and cell–matrix interactions within complex tumors. An intriguing possibility is to combine these techniques to advance precision medicine: we envision a future where digital pathologists generate profiles of tumors from individual patients that can be used to build personalized predictive *in silico* models of tumor evolution and therapeutic response, thereby enabling informed culture models of patient biopsies for preclinical testing.

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Forecasting Tumor Progression

Cancers are the product of somatic evolutionary processes, fueled by the acquisition of mutations and mediated by cellular interactions within a structured tissue microenvironment.

Adaptation and evolution within such genetically and phenotypically heterogeneous populations limits therapeutic efficacy and cancer control. Mathematical and computational models are powerful tools to investigate the complex, emergent, and dynamic properties of cancers, much of which is unobservable. For example, *in silico* tumor models have yielded quantitative and mechanistic insights into the dynamics and parameters that govern disease progression. These measurements, in turn, provide a basis for the development of models to forecast tumor evolution and to evaluate the impact of specific interventions. Such quantitative models can generate testable

predictions and inform experimental design. However, a key challenge is to build predictive models that bridge biological scales and are sufficiently realistic, ideally grounded in data.

Despite the advent of the 'big data' era, current genomic data are often suboptimal for these modeling tasks. A chief limitation is that most data sets record a single molecular measurement at a single snapshot in time and space. Thus, new technologies that probe the tumor-immune microenvironment *in situ* and that enable the repeated noninvasive measurement of circulating tumor DNA can improve spatial and temporal resolution. More generally, the generation of clinically annotated longitudinal, radiographic, genotypic, and phenotypic measurements of tumor progression will be an invaluable resource for the community that spurs new computational techniques to interpret and assimilate such data. Indeed, it is increasingly apparent that the integration of mechanistic computational modeling and experimentation is critical for accelerating our understanding of cancer biology and for advancing a more personalized and precise approach to the detection and clinical management of malignancy.

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Staying One Step Ahead: How Predictive Modeling of Tumor Progression Can Delay Therapeutic Resistance

One of the greatest clinical challenges in cancer today is resistance to therapy. If a heterogeneous tumor contains even one resistant clone or the probability of generating a resistance mutation is nonzero, tumor recurrence is theoretically inevitable: the question becomes not if but when will a tumor come back resistant. Despite extraordinary efforts, new therapies for common resistance pathways can take many years before they are available to patients, suggesting that cancers win this arms race against resistance. An additional hurdle is how to predict resistance *a priori*, so that we can optimize treatment decisions and stay one step ahead of the evolving cancer. Wouldn't it be great if we could take the initial tumor characteristics and predict the long-term trajectory and time to relapse using mathematical models of cancer progression? This challenge provides an exemplary opportunity for integrating quantitative biology into cancer research and oncology. Cancer centers have historical data and continue to gather new data that could be used to develop models. The limiting step is to develop new mathematical tools to accurately model different treatment scenarios and help doctors choose the best strategy to delay resistance. Present models have problems that prevent their application. Their predictions are too sensitive to the input data: small errors in the initial conditions change the trajectories severely. Accuracy requires precise knowledge of the clonal composition of the cancer and the penetrance of resistant mutations, which are unavailable in clinical settings. Tracking tumor sizes during a patient's treatment could help, by correcting an early model and adjusting the treatment in real time. Although the obstacles in front of us are significant, we have hope that a concerted effort among scientists and clinicians will improve the predictive power of mathematical models, an important step toward proactively treating patients with cancer.

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Advances in Computation Herald a New 'Golden Era' for Biology and Medicine

Many of today's quantitative sciences, from economics to physics to meteorology, have gone through a 'golden era' during which they have experienced a profound transformation from a mostly empirical to an almost completely analytical formulation. The most revealing element of that transformation has been the ability to supplement the

classical inductive processing based on experimental evidence with model-based, analytical predictions that could then be validated experimentally. In physics, for instance, experimental tinkering has been all but replaced by analytical framework suggesting, for instance, the existence of 37 subatomic particles on a completely theoretical basis. Yet, existence of every one of them has later been demonstrated, the last one being the Higgs boson, the existence of which was proven in 2012, having been proposed in 1964. Today, largely driven by the relatively new field of systems biology and by the increasing power of supercomputing, biology and medicine are undergoing a similar transformation, which may dramatically alter the way we conduct experiments or treat patients. Some examples include the ability to use increasingly accurate and tumor-specific regulatory and signaling networks to predict critical dependencies of human malignancies directly from molecular profiles of human samples, without the need for cancer models, such as cell lines, mouse models, or organoids. Rather, cancer models can then be used to test these predictions, with validation rates that now routinely exceed the 70–80% range. When combined with similar model-based methodologies to elucidate drug mechanism of action, including polypharmacology and toxicity, these approaches are leading to the ability to predict drugs that can be therapeutically relevant in specific tumor types, with accuracy that surpasses that of targeted therapy, especially in malignancies that present with no actionable mutations, fail to respond to immunotherapy, or become drug resistant following relapse. These models can be helpful in simplifying a problem that may be too complex to be solved empirically in a generalizable manner. For instance, simple math reveals that there are more possible tumorigenic mutation patterns than atoms in the universe. By contrast, recent work [2] shows that such an extraordinary complex mutational landscape may be coalescing to produce only a handful of transcriptionally distinct states, each one presenting highly conserved, targetable dependencies.

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Artificial Naturalism: Coevolving Pathology and Artificial Intelligence

Our goal is to improve the treatment response and prognosis of patients with cancer; the trajectory to that goal might also be a goal, and it requires us all. At the Centre for Evolution and Cancer, we aim to understand how the evolutionary trajectory of cells within a tumor co-emerges with their diverse environmental contexts or local ecology. Quantitative tools following cell detection and classification by artificial intelligence (AI) allow us to depict geographical patterns of the reorganized tumoral multicellularity (i.e., as an artificial naturalism approach). These tools are reminiscent of studies of ecological systems; measuring diversity (Shannon's index), distribution (hotspot detection), coexistence (Morisita's colocalization and immune scores) to quantify habitats and infer niches. By quantifying the tumor biogeography, we seek to contribute new insights into cancer development and evolution.

Current and future challenges are establishing multidisciplinary platforms and developing reproducible science by leveraging genetic, molecular, cellular, and clinical data to improve personalized oncology. However, to advance, it is necessary to quantify intratumor spatial and temporal variability by obtaining multiregion sampling and a temporal track, allowing us to follow its evolution. Such spatiotemporal integration promises to move us closer to a mechanistic framework of solid tumors. We aim to direct these efforts studying the multiscale biology of glioblastoma multiforme (GBM), the most common and aggressive of adult brain tumors. In a major interdisciplinary GBM research program, we seek to develop powerful multiscale approaches linking

genetically engineered mouse models with advanced AI tools to discover stem cell niche dependency and direct therapeutic interventions. We aim to decode the underlying processes of phenotypic plasticity between dormant and proliferating states in cancer cells and the immune response in a spatial context, uniquely possible with the tools we have proved useful in oncology. As we advance, the importance of diverse approaches is increasingly recognized; in our view, computer sciences, ecology, and evolution offer tools, paradigms, and theory for dissecting cancer biology. Charles Darwin described how the intimate coexistence between flowering plants and insects leads to reciprocal evolutionary changes; this is now known as coevolution. Today's promising areas of research emerge through the demolition of disciplinary barriers. We think that that is how to achieve our goal, by collaborating and sharing expertise, and finally, coevolving.

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Cancer Is a Window on the Past

Cancer or cancer-like phenomena are found in almost all mammals, as well as birds, fish, insects, plants, fungi, and corals. The pervasive nature of cancer implies that it has deep evolutionary roots, stretching back to the dawn of multicellularity over 1 billion years ago. Unicellular organisms are effectively immortal in that they just replicate whenever they can. However, multicellular life outsources a vestige of immortality to the germ line. The price paid by somatic cells is apoptosis. To ensure that somatic cells do not cheat, many layers of regulatory control have evolved. If something compromises cell and tissue management, cells may rebel and revert to quasi-unicellular behavior, such as turning off apoptosis and indulging in unrestrained proliferation. The result is cancer.

Many hallmarks of cancer recapitulate unicellular modalities, suggesting that cancer initiation and progression represent a systematic reversion to simpler ancestral phenotypes, an idea that dates back to Theodor Boveri. This so-called ‘atavism theory’ may be tested using phylostratigraphy, which can be used to assign ages to genes. Several research groups have confirmed that cancer cells tend to overexpress evolutionarily older genes, and rewire the architecture linking unicellular and multicellular gene networks. In addition, some of the elevated mutation rate (one of the hallmarks of cancer) is in fact self-inflicted, driven by genes found to be homologs of the ancient SOS genes activated in stressed bacteria, and used to evolve biological workarounds. The mutations arise from the switch to error-prone double-strand break DNA repair mechanisms that produce mathematically distinctive patterns of damage around the lesion. Cancer is an ancient deeply embedded, preprogrammed response to stress, such as chemical insults, poor tissue environment, hypoxia, or stroma damage. Rather like ‘safe mode’ on a computer that has suffered an insult, cancer is a deeply protected default state in which the cells run on their core functionality.

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