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Discrete dynamic network modeling of oncogenic signaling: Mechanistic insights for personalized treatment of cancer

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Abstract

Targeted drugs that disrupt proteins that are dysregulated in cancer have emerged as promising treatments because of their specificity to cancer cell aberrations and thus their improved side effect profile. However, their success remains limited, largely due to existing or emergent therapy resistance. We suggest that this is due to limited understanding of the entire relevant cellular landscape. A class of mathematical models called discrete dynamic network models can be used to understand the integrated effect of an individual tumor's aberrations. We review the recent literature on discrete dynamic models of cancer and highlight their predicted therapeutic strategies. We believe dynamic network modeling can be used to drive treatment decision-making in a personalized manner to direct improved treatments in cancer.

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Introduction

Cancer, a disease characterized by uncontrolled cell growth, can lead to devastating effects on the human body. Cancer is one of the most common causes of deaths worldwide. Normal working cells over time accumulate genetic and epigenetic changes that lead to dysregulation of the signaling pathways that regulate cellular behavior and the acquisition of the hallmark features of cancer. These hallmark features include proliferation, evasion of growth suppression and cell death, invasion, and metastasis [1]. More recently, modulation of the immune response has emerged as an important additional feature of cancer [2].

Traditional medical modalities of cancer treatment (when surgical removal is not an option) include chemotherapy and radiation, which disrupt DNA synthesis of all cells and lead to cessation of proliferation and induction of cell death. More recently, targeted and immunological therapy have emerged as promising modalities of cancer treatment. Targeted therapies are drugs that target a specific protein within a signaling pathway that is critical to one of the above cancer hallmarks. They tend to be less toxic than chemotherapy because the targeted protein is usually not expressed in healthy cells. With the growing arsenal of targeted therapies for cancer and other diseases, the question becomes how to most effectively use targeted therapy.

Individualization of oncologic treatment: where we stand now

Currently, targeted therapies are approved as first or second line agents in multiple cancer types and are generally used as single agents. Personalized tumor information is currently used to a very limited extent. There are initiatives for screening for specific genetic or expression features of cancers and targeting the treatment accordingly but the benefit they have so far demonstrated is limited [3,4]. For example, in non-small cell lung cancer, if a tumor contains an EGFR inhibitor sensitizing mutation, the treatment decision would be an EGFR inhibitor such as gefitinib [5]. Gefitinib, compared to traditional chemotherapy, has a slightly improved progression-free period (about 11 months versus 5 months) and overall survival (30 months versus 24 months) [6]. This trend is similar for many targeted therapies in lung cancer [7] and other cancer types [8,9]. But just like traditional chemotherapy, the efficiency of targeted therapies is thwarted by either intrinsic resistance to the drug or the development of drug resistance. We propose that models that incorporate comprehensive tumor information would help improve treatment efficacy beyond the current "single mutation, single treatment" strategy. For example, multivariate models using clinical and epidemiologic information are frequently and successfully used for

making clinical decisions [10–12]. At present there are no clinical multivariate models that incorporate molecular/genomic information.

The critical information required to determine which patients should get a targeted therapy can be formulated as a set of questions:

- What are the characteristics of a specific tumor that would lead it to respond in some way or be outright resistant to a targeted therapy?
- Should we target multiple aspects of cancer in combination? Which targeted drug combinations are optimal?
- As a cancer acquires resistance to our current treatment regimen, how should we augment the regimen to effectively treat this evolved cancer?

We propose that answers to these questions can be elicited by systems biology approaches. Systems biology provides a powerful set of tools that allows the integration of signaling and gene regulatory networks, genomic, and epigenomic information into system-level models [13–17]. These models can be used to incorporate such information from individual cancer cells to understand these cells' individual dynamics, their response or resistance to treatment. Here we describe how these network models can help to understand cancer cell dynamics and to rationally develop individualized targeted strategies to improve oncologic treatment.

Oncogenic signaling networks underlie cancer

Molecular networks inside healthy cells contain so-called proto-oncogenes and tumor suppressor genes. Proto-oncogenes may acquire a mutation that then makes the cell adopt a cancer hallmark phenotype (e.g. proliferation); these altered genes in cancer cells are referred to as oncogenes. Tumor suppressor genes ward against aberrant phenotypes when they are active; alterations that cause their inactivation lead to cancer development. Alterations that activate oncogenes, combined with alterations that inactivate tumor suppressor genes, perturb the cell's signaling pathways, lead to incorrect cellular decisions and behaviors (proliferation instead of quiescence, survival instead of apoptosis), and ultimately to a cancer phenotype [1].

In order to understand the often indirect connection between an alteration and a cellular outcome, we need to consider the network of interactions and regulatory relationships the alteration is embedded in. In a within-cell network, nodes represent proteins, RNA, or small molecules and the edges are the interactions and regulatory relationships between nodes. The edges are directed (indicating the direction of mass- or information flow) and can be positive (activating) or negative (inhibitory). This network usually also involves proxies for one or more cellular outcomes and the external signals that can lead to these cellular outcomes. The receptor tyrosine kinase (RTK) signaling network shown in Figure 1 and described in detail in Box 1 illustrates several features of signaling networks that underlie cancer phenotypes.

The network representation of a signal transduction process, such as the one described above, is static, while biological processes happen over time. In order to understand the dynamic behavior of a system, each node needs to be characterized by a state variable that can change in time and that is affected by the state variable of the nodes that regulate it. Both quantitative models (using continuous state variables) and qualitative models (using discrete state variables) exist. Quantitative models, generally using systems of ordinary or partial differential equations, can be highly accurate and provide quantitative information (e.g. drug dosage information, drug response time, or fold-changes of protein concentrations) that is either difficult or impossible to obtain with qualitative models because of their use of discrete state variables. Phenomenological pharmacokinetic/pharmacodynamic models of the physiological response to drugs are an integral part of drug testing and discovery. The use of quantitative models for mechanistic modeling of signal transduction networks is highly desirable, and there are multiple examples of the unique insights such a quantitative approach can provide [18–23], but their widespread use is limited by the scarcity of high-quality quantitative data these models require, such as kinetic and temporal information about individual nodes in the network and/or quantitative microscopy time course data to fit the unknown model parameters. Discrete and quantitative models are often consistent in capturing the response repertoire of signaling networks (e.g. their potential bistability or response to perturbations) [17,20,21,24,25].

Discrete dynamic network models in biology

Discrete dynamic network models (DDNMs) can be constructed using widely available biological information. In DDNMs each node i is assigned a variable s_i that can take one of a small number of discrete states, where each state is characterized (and defined) by its influence on the state of the nodes j that have an incoming edge from node i ($i \rightarrow j$). Thus, the direct regulators of each node determine its future state, and this is encoded in the regulatory function f of the node. In the simplest case, the Boolean scenario, each node takes one of two states: $s_i = 0 (OFF)$ or $s_i = 1 (ON)$, assuming that an implicit threshold exists above which the node is sufficiently active to regulate its target nodes. Each regulatory function f can be expressed in terms of Boolean