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Cancer hybrid automata: Model, beliefs and therapy

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ABSTRACT

This paper introduces Cancer Hybrid Automata (CHAs), a formalism to model the progression of cancers through discrete phenotypes. The classification of cancer progression using discrete states like stages and hallmarks has become common in the biology literature, but primarily as an organizing principle, and not as an executable formalism. The precise computational model developed here aims to exploit this untapped potential, namely, through automatic verification of progression models (e.g., consistency, causal connections, etc.), classification of unreachable or unstable states and computer-generated (individualized or universal) therapy plans. The paper builds on a *phenomenological* approach, and as such does not need to assume a model for the biochemistry of the underlying natural progression. Rather, it abstractly models transition timings between states as well as the effects of drugs and clinical tests, and thus allows formalization of temporal statements about the progression as well as notions of timed therapies. The model proposed here is ultimately based on *hybrid automata*, and we show how existing controller synthesis algorithms can be generalized to CHA models, so that therapies can be generated automatically. Throughout this paper we use cancer hallmarks to represent the discrete states through which cancer progresses, but other notions of discretely or continuously varying state formalisms could also be used to derive similar therapies.

1. Introduction

Cancer is generally thought of as a *progressive disease* – in particular, a disease which exhibits certain discernible cancer phenotypes (modeled as a finite set of *discrete* states), through which it progresses towards a terminal phenotype (e.g., metastasis).

Among other theories, this view is reflected in the so-called *hallmarks of cancer* proposed by Hanahan and Weinberg [1], and it has become one of the predominant ways of thinking about cancer, solidified through many further publications and experiments. A recent article by the same authors [2] reviews and consolidates the new insights of the last decade. Similar models have also been explored by a mechanistic agent-based simulation in [3].

According to the model proposed by Hanahan and Weinberg, tumors must necessarily acquire certain "intermediate" hallmarks culminating in the "final" hallmarks of tissue invasion and metastasis. As the authors write,

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> Simply depicted, certain mutant genotypes confer selective advantage on subclones of cells, enabling their outgrowth and eventual dominance in a local tissue environment. Accordingly, multistep tumor progression can be portrayed as a succession of clonal expansions, each of which is triggered by the chance acquisition of an enabling mutant genotype [2, p. 658].

The current list of cancer hallmarks includes the abilities to reproduce autonomously, to ignore anti-growth signals, or to signal for formation of new blood vessels, as well as handful of other phenotypes. Hallmarks can be obtained in various different orders, but not every order is viable. Intuitively, a hallmark can be acquired by a dominant sub-population of cells if it conveys a selective advantage compared to the other phenotypes acquired in that population. For example, in a wildly growing cluster of cells, the ability to signal for new blood supply, and thus nutrients, oxygen, and waste disposal, will allow the respective sub-population to outgrow the others.

Most hallmarks are acquired through mutations (point mutations, copy number changes or epigenetic modifications) of very specific sets of oncogenes and tumor suppressor genes. Thus, many of the targeted drugs, administered individually or combinatorially in a cocktail, which have been developed in recent years, aim to influence the function of the products of these genes [4] and thus cancer's evolution from specific hallmarks. For example, the vascular endothelial growth factor (VEGF) signals for creation of new blood vessels (*angiogenesis*), and the drug Avastin inhibits the associated signaling pathway, thus preventing growing tumors from obtaining the needed blood supply. While current therapies target only the observed hallmark at any instant, they rarely take into account the potential hallmarks that may evolve in the future and the temporal structure of the underlying evolution. By connecting therapy design to the theory of supervisory control of hybrid automata, we aim to build a framework for better therapy design (e.g., that avoids drug-resistance, exploits synthetic lethality, oncogene addiction, etc., and avoids undesirable side-effects on other organs).

In this view of cancer, its progression through discrete states and therapy bears a striking resemblance to formal models of state-transition machines in computer science.

In this paper, we first present a logical framework called *Cancer Hybrid Automaton* (CHA) that allows us to formally capture cancer progression through accumulation of successive discrete states. States in CHA models represent states of the progression, and directed edges among pairs of states define possible progression paths. Drugs can then be thought of as inhibiting or prolonging specific transitions in the automaton. We then show how this approach enables us to formally describe cancer progression, automatically verify/model-check its temporal properties, and manipulate its evolution to satisfy certain therapeutic goals.

We illustrate our approach through a highly simplified running example of a cancer hybrid automaton in which states represent hallmarks, and progression paths represent successive hallmark acquisitions. However, the states of the automaton can represent any set of discrete states at varying levels of abstraction. Examples include stages of cancer, a set of affected pathways, and a set of specific genomic aberrations. By ignoring complex structures such as heterogeneity, geometry, circulating tumor cells, tumor growth dynamics, genomic instability at this point, we avoid obscuring the key ideas inherent to the therapy design algorithms. However, the framework is flexible enough to include such structures as well as detailed mechanistic models of the discrete states.

An earlier version of this paper appeared in [5]. We now extend this earlier work by explicitly modeling partial knowledge of the therapist and tests in the framework (Section 6) as well as interaction of the cancer with different subsystems of the organism (Section 7).

2. Overview

The rest of this paper is organized as follows. In Section 3, we introduce a basic CHA formalism. In this section, a CHA is modeled as a *finite non-deterministic automaton*. The edges, representing transitions from one progression state (e.g. hallmarks) to the next, are labeled with drugs that can inhibit the transition. A *therapy* is defined as a function that assigns a set of drugs to each finite progression history, or *run*. An execution of a therapy is defined as a run of the CHA that respects the therapy, that is, no transition of the execution is inhibited by the therapy. Our model includes costs by associating a cost vector with each state and each cocktail. Therapies may be selected by comparing costs of possible executions using a notion of Pareto dominance, in addition to the required qualitative properties specified in CTL.

In Section 4 we extend the CHA framework to include real time. In this model, transitions take certain durations of time, and drugs can prolong (or stop) the transition process. This is modelled using a hybrid automaton with multiple clocks.[3] Clock constraints on the edges and clock invariants at the states restrict the possible progressions of the system. Multiple clocks are needed to allow for the scenario that a drug affects the transition to possible next states in different ways. Possible runs and therapies of a timed CHA now include the clock values. An extension of CTL, Timed CTL, is used to specify extended goals about the system.

In Section 5, we discuss the problem of automatically generating therapies, i.e., controller synthesis for CHAs. For simple untimed CHAs this is a well-studied problem and algorithms exist. For timed CHAs, we show that if we allow only for control at discrete moments in time the problem is decidable for CTL goals.

[3] Thus the continuous dynamics of these clocks justify the term *hybrid* in 'cancer hybrid automaton'.

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