Cancer Hallmark Automata

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Hallmarks of Cancer – Background and Motivation for a Formal Model

Cancer is a progressive disease which traverses certain discrete states (hallmarks) towards its full-blown phenotype of tissue invasion and metastasis. [...] 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. [Hanahan&Weinberg, 2011]

- Useful abstraction level: The hallmarks view is abstract enough to allow analysis of different cancers in one framework, yet detailed enough to connect to low-level mechanisms of gene regulation, metabolism and signaling, and to therapeutic agents.
- Advantage of formalization: Helps to better understand progression and resilience against therapeutic interventions.
- Advantage of computation: Models are becoming too complex for manual planning of a therapy. A formal model of cancer progression will allow for therapies to be automatically generated.

Timed CHA

Let D be a set of drugs, X a set of clocks and C(X) a set of clock constraints.

A Timed CHA is a tuple \( H = (V, E, v_0, l, \rho) \) where

- \( V \) is a set of states, corresponding to hallmarks
- \( E \subseteq V \times C(X) \times V \) is a set of directed edges labeled with a clock constraint
- \( v_0 \in V \) is the initial state
- \( l : V \times X \rightarrow \mathbb{N} \) specifies the invariant for each clock and state
- \( \rho : V \times D \rightarrow X^{\mathbb{R}_+} \) specifies how a given drug influences the clocks at a given state

Computation Tree Logic (CTL)

CTL can be used to specify control goals for the CHA.

\[
AG(\neg G_{\leq 20}^{\neg})
\]

"It is known that metastasis will not be reached within 20 years"

\[
AG(\neg) \rightarrow (G(\neg \land AX(\neg)) \lor K(\neg))
\]

"Whenever the tumor acquires angiogenesis, this will be known (strictly) before the tumor reaches metastasis"

A Simple Cancer Hallmark Automaton (CHA)

Models possible progression trajectories:
- Edges labeled with minimum time needed for transition
- In the example, the drug Avastin can be given in two states to locally slow down progression to \( \neg \) by a half
- Invariant (7) restricts time tumor can stay in those states
- System is forced back to Normal if transition to \( \neg \) is not made in time

Therapy strategies may include:
- Giving drug when in a state where it is effective
- Giving drug temporarily to slow down progression
- Giving drug until forced back to normal (complete cure)
- Repeated testing to determine current state
- Scheduling tests so that transition to state where certain drug is effective will be detected as early as possible

Partial Observability and Tests

Timed state: pair \((v, val) \in V \times R^X\)
Belief set: set of timed states
Belief state: tuple \((v, val, b)\)
Finite runs starting from \((v, val, b)\): \(\text{Runs}_1((v, val, b), H)\)
Let \( T \) be a set of tests, and \((v_0, val_0, b_0)\) the initial belief state.
A therapy maps finite runs to therapeutic actions:

\[
\pi : \text{Runs}_1((v_0, val_0, b_0), H) \rightarrow 2^D \cup T
\]

It is assumed to be uniform: Runs that agree on the belief set sequence map to the same action.
A therapy can be translated into a conditional plan.

Extensions and Future Work

- The state of other systems (e.g., stroma, liver, immune system, stem cells, etc.) can be affected by a therapy and needs to be monitored. As an example, we propose a simple liver automaton in the paper that can be composed with a CHA.
- Expand the formalism to include other mechanisms, like mitotic stress, into the framework.
- Develop algorithms to generate therapies automatically by applying and improving algorithms from the hybrid automata control theory literature.
- Connecting to data: by automatically generating fine-grained hallmark models from data using statistical model inference methods like GOALIE, and by mining clinical data to discover progression “bottlenecks” (promising drug targets).