Cancer Hallmark Automata

Loes Olde Loohuis Andreas Witzel Bud Mishra
New York University and City University of New York

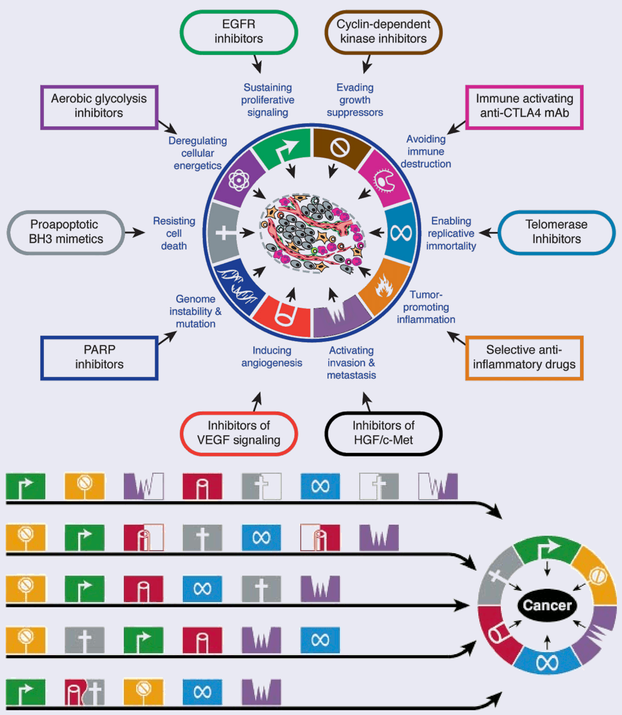
NSF Expeditions in Computing

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.

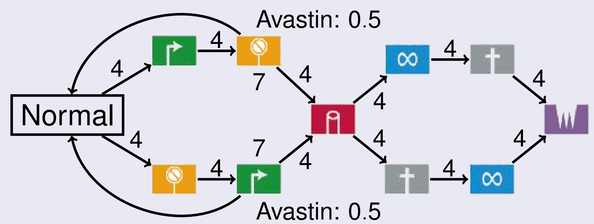
> *[...] multistep tumor progression can be portrayed as a succession of clonal expansions, each of which is triggered by the chance acquisition of an enabling mutant genotype. [Hanahan&Weinberg, 2011]*

- 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.
  Modeling time allows us to aim for slowing down (chronic disease) instead of completely curing cancer.
- 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.



D. Hanahan and R. A. Weinberg. *The Hallmarks of Cancer*, Cell, vol. 100, no. 1, pp. 57-70, 2000.
D. Hanahan and R. A. Weinberg. *Hallmarks of Cancer: The Next Generation*, Cell, vol. 144, no. 5, pp. 646-674, 2011.
J. Luo, N. L. Solimini, and S. J. Elledge. *Principles of Cancer Therapy: Oncogene and Non-oncogene Addiction*, Cell, vol. 136, no. 5, pp. 823-837, Mar. 2009.

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 by a half
- Invariant (7) restricts time tumor can stay in those states
- System is forced back to Normal if transition to 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

Timed CHA

Let D be a set of drugs, X a set of clocks and $\mathcal{C}(X)$ a set of clock constraints.

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

- V is a set of states, corresponding to hallmarks
- $E \subseteq V \times \mathcal{C}(X) \times V$ is a set of directed edges labeled with a clock constraint
- $v_0 \in V$ is the initial state
- $I : V \times X \to \mathbb{N}$ specifies the invariant for each clock and state
- $\rho : V \times D \to X^{\mathbb{R}_{\geq 0}}$ 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.

$$K\mathrm{AG}_{\leq 20}\neg$$

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

$$\mathrm{AG}(\to ((\neg \wedge \mathrm{AX}\neg) \,\mathrm{U}\, K))$$

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

Partial Observability and Tests

Timed state: pair $(v, \mathbf{val}) \in V \times \mathbb{R}^X$
Belief set b: set of timed states
Belief state: tuple $(v, \mathbf{val}, b)$
Finite runs starting from $(v, \mathbf{val}, b)$: $\mathrm{Runs_f}((v, \mathbf{val}, b), H)$

Let T be a set of tests, and $(v_0, \mathbf{val}_0, b_0)$ the initial belief state.
A therapy maps finite runs to therapeutic actions:

$$\pi : \mathrm{Runs_f}((v_0, \mathbf{val}_0, b_0), H) \to 2^D \cup T$$

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).