Individualized Dosing Sequences in Dynamic Precision Medicine

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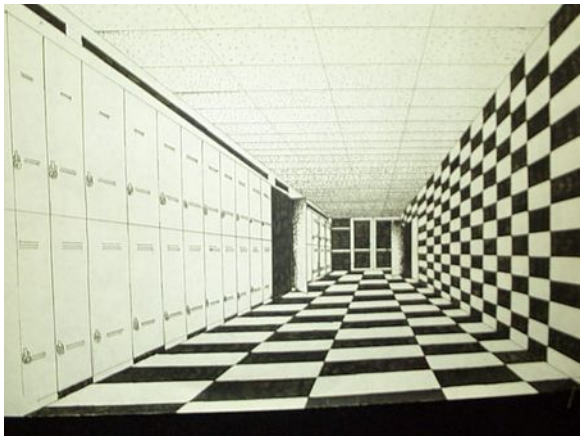
A Different Perspective

- Mathematical biology
- Cancer therapy development
  - 23 therapies first in man
  - 5 therapies advanced to late development
    - Her3 antagonist antibody
    - Pan-alpha integrin antibody
    - Anti IL6 antibody
    - Anti IGFR antibody
    - DR5 agonist antibody
  - 2 therapies approved:
    - Topotecan for small cell lung cancer
    - Bicalutamide for adjuvant therapy of prostate cancer
  - Small and large molecules targeting
    - Signal transduction
    - Repair
    - Angiogenesis
    - Developmental pathways
  - DNA vaccines, immunoliposomes, antibody-drug conjugates



Agenda

- Precision medicine and dynamic precision medicine for cancer
- Detailed background on dynamic precision medicine
- Role of combination therapy
- Role of planning ahead
- Results of dynamic precision medicine with long-range planning
- Conclusions concerning:
  - Dynamic precision medicine
  - Long range planning
  - Role of combinations vs monotherapy: a false choice?

Current Precision Medicine of Cancer

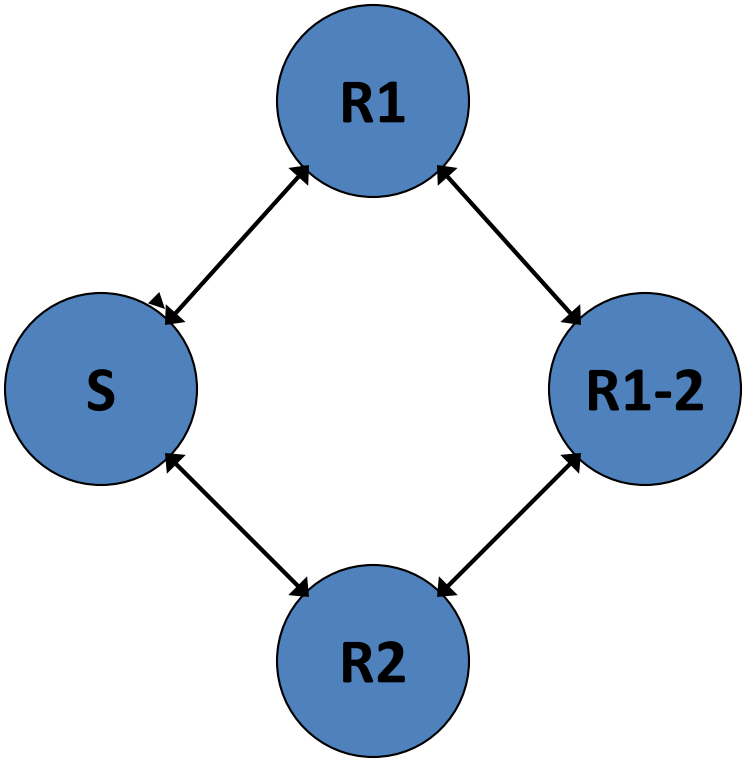
- Tumors are genetically unstable, increasing the clinical importance of evolutionary dynamics. Analysis by:
  - Efficiency of carcinogenesis
  - Focused quantitative modeling
  - Predicted features of current experimental data before TCGA
- Current precision medicine strategies focus on:
  - Average molecular properties of a tumor sample
  - At a particular point in time (usually at diagnosis)
  - With the goal of optimizing the next 1-2 therapeutic maneuvers
- But:
  - No two tumor cells are alike within one tumor: why treat the consensus?
  - Tumors evolve: why perform static matching?
  - Strategies which plan ahead are generally superior to reactive one move strategies: why not try to plan ahead?

Dynamic Precision Medicine

- Explicitly considers subclonal heterogeneity
- Explicitly considers tumor evolution
- Decisions based on probabilities and risk states
  - May consider factors that are not observable at that time
- Frequent adaptation of therapy
- Long range planning

A Simple Model

- Two non cross resistant drugs or drug combos: Drug-1 and Drug-2 (i.e. RAF-MEK, PI3K)
- Four cell types:
  - Sensitive cell S, killed by both Drug-1 and Drug-2
  - Resistant cell R1, killed only by Drug-2
  - Resistant cell R2, killed only by Drug-1
  - Incurable doubly resistant cell R1-2
- Genetic and epigenetic transitions between cell types
- Cell growth and death affected by drugs in dose dependent manner
- Partial resistance
- Patient can have a **mixture** of cells, which **evolves** over time
  - **Different subclones may evolve at different rates**
- **Combination therapy requires dose reduction**



Current Model Condenses Complex Information and Should Be the Hub of a System of Linked Models

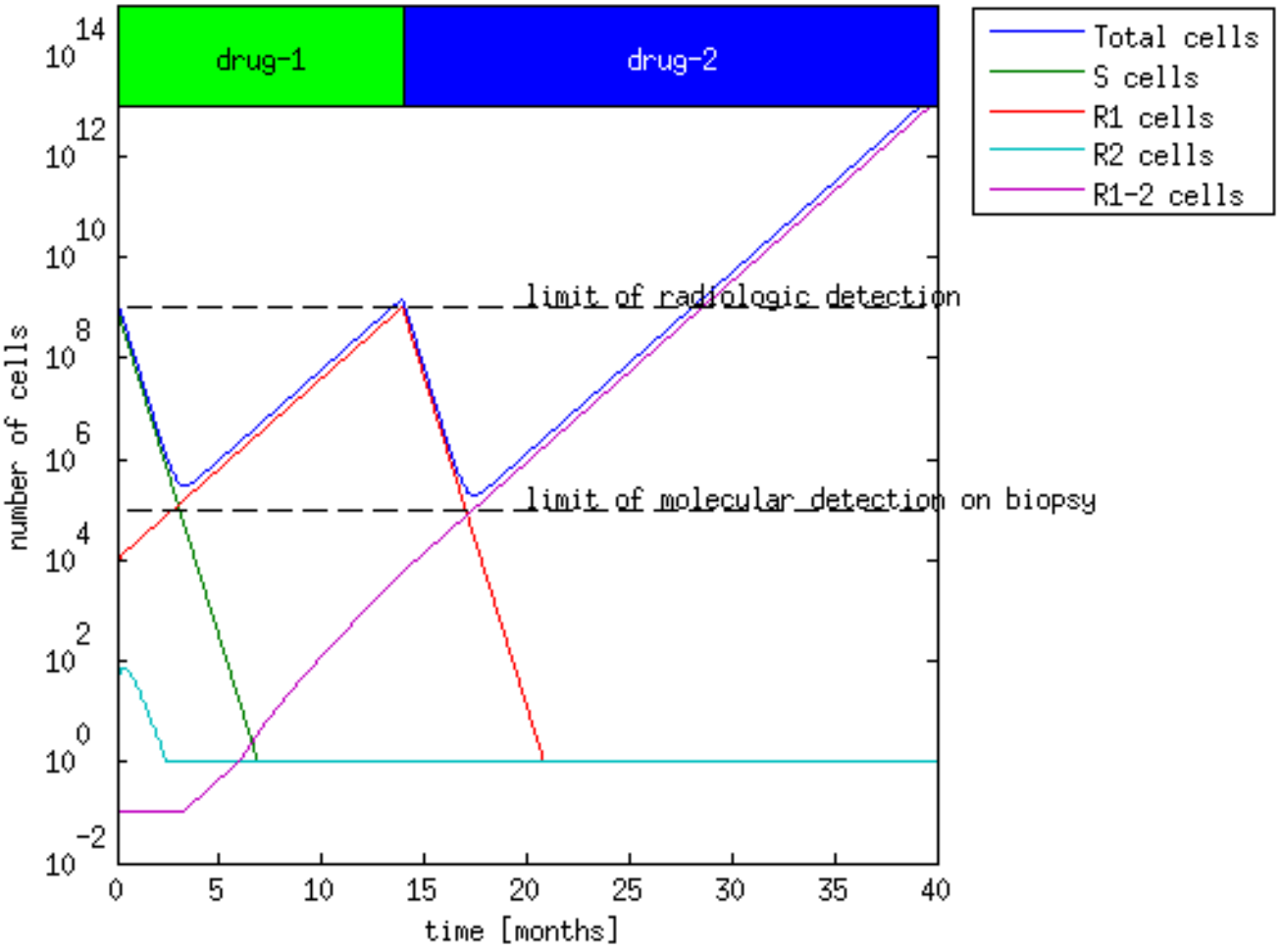
- Simplicity is required to allow computationally feasible assessment of a variety of complex treatment strategies
- **Other linked models would feed detailed information about tumor and therapy from bioinformatics sources into the core model**
  - information would influence the probability distribution of parameters
- **Organized around clusters of phenotypic combinations of sensitivity/resistance to available therapies**
  - Any phenotypic cluster may correspond to millions of heritable molecular states, each with
  - **Each has substates including non-genetic resistance mechanisms**
  - **A "drug" may refer to a combination directed at a heritable state**
- **Net transition rates between phenotype A and B represent the sum of rates of all possible transition mechanisms**
  - Summed over all mechanisms of genetic and epigenetic change
  - Summed over all relevant loci that can lead to phenotype
  - Example: mechanisms of crizotinib resistance*

*Katayama R *et al*. (2012) Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers *Sci Translational Med* 4: 120ra17.

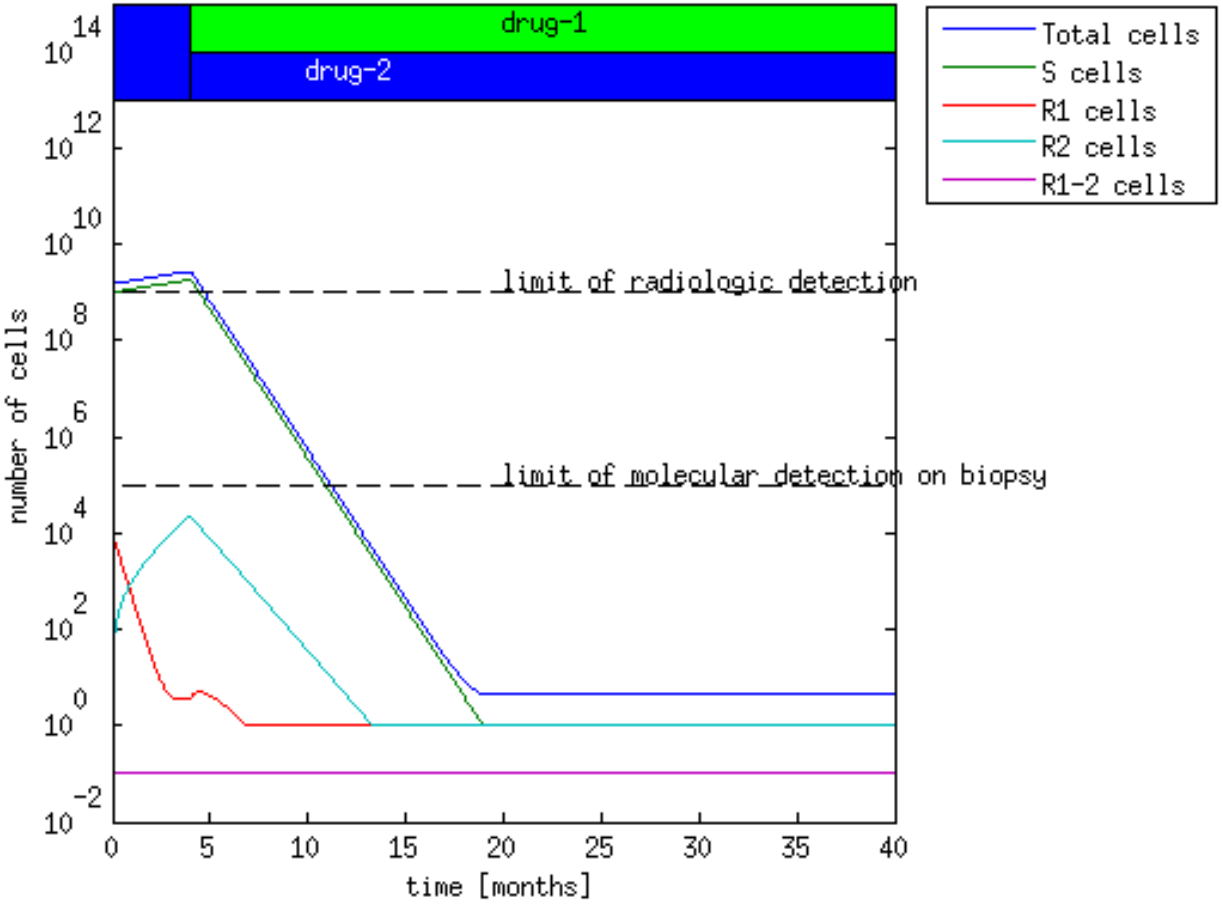
Strategies

- A **strategy** is a data-driven method for planning a sequence of therapies
  - When to treat with a combination and when to treat with sequential monotherapy
  - When to change therapies
- Like therapies, ***strategies*** may be individualized
- A simulation compared 6 strategies
  - Strategy 0 is the current precision medicine strategy: the patient is treated with the best drug for the observed predominant cell type and switched to the alternative drug upon tumor progression or relapse.
    - **note: each "drug" may itself be a combination designed to kill a single subclone**
  - Strategies 1, 2.1, 2.2, 3, and 4 (see backup for detail):
    - Used the evolutionary model to predict the total cell number and the likelihood of forming an incurable cell at the next 45 day timepoint
    - Gave therapy that minimized either total cell number or incurable cell likelihood
    - Differed in method of prioritizing total cell number vs incurable cells

Current Precision Medicine: 28 months to incurable relapse



Dynamic Precision Medicine: Cure



In Silico “Clinical Trial”: 3 million “patients”

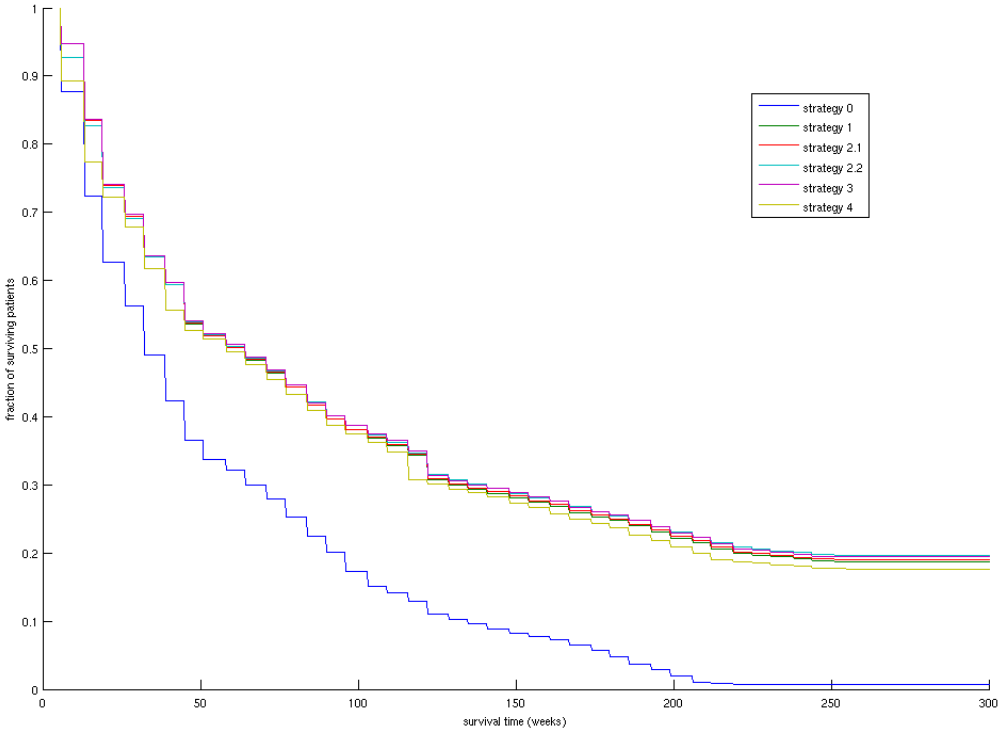
Examined 30 million parameter configurations encompassing:

- Different initial populations
- Different growth rates
- Different transition rates
- Different levels of sensitivity and resistance to drugs

Choosing the Parameter Ranges

- Parameters varied over broad ranges to encompass all possibilities as found in the experimental literature and clinical experience
  - Transition rates varied over 8 orders of magnitude
  - Growth rates varied over 340 fold range
- Possible parameter value combinations filtered by 2 criteria
  - Must correspond to a strategic choice: both drugs must provide at least minimal efficacy
  - Worst strategy must provide no more than 4 years survival time
- Chose over 3 million parameter combinations; explored them all
- **Net result is sensitivity analysis across known tumor and therapy characteristics with strategic choices between 2 drugs and survival in the range of up to 4-5 years**

Benefit of dynamic precision medicine is very general



Simultaneous Combinations: History

- Holland, Freireich, Frei, 1950s: first combination therapy in oncology, made childhood acute lymphocytic leukemia (ALL) into a curable disease
- DeVita: 1960s: combination therapy for Hodgkin's disease and diffuse large cell lymphoma
- Goldie, Coldman: 1970s: Theoretical basis for combination therapy in subclonal heterogeneity
- Bozic et al 2013: Further math analysis advocates simultaneous combinations

Reasons for Combinations

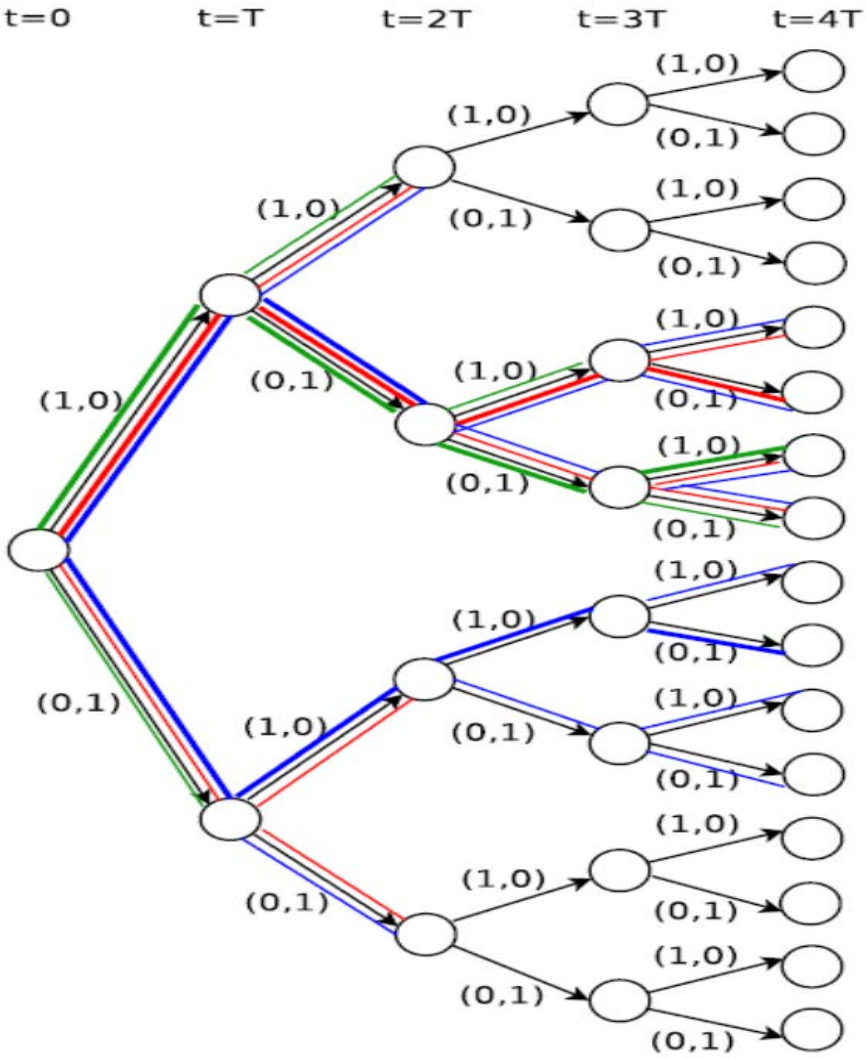
- Robustness of signaling networks within a single genetic state:
  - Redundancy
  - Feedback loops
  - Need to hit multiple nodes with combination therapy to eliminate a single genetic state: **first order combination**
- Multiple genetic states: subclonal heterogeneity
  - Each different subclone may require a different combination for its elimination
  - Thus a mixture of subclones may require a combination of combinations: **higher order combinations**
- Will it be feasible to give simultaneous higher order combinations of sufficient complexity at effective doses?

Prolonged Combination Therapy vs Prolonged Monotherapy: A False Choice?

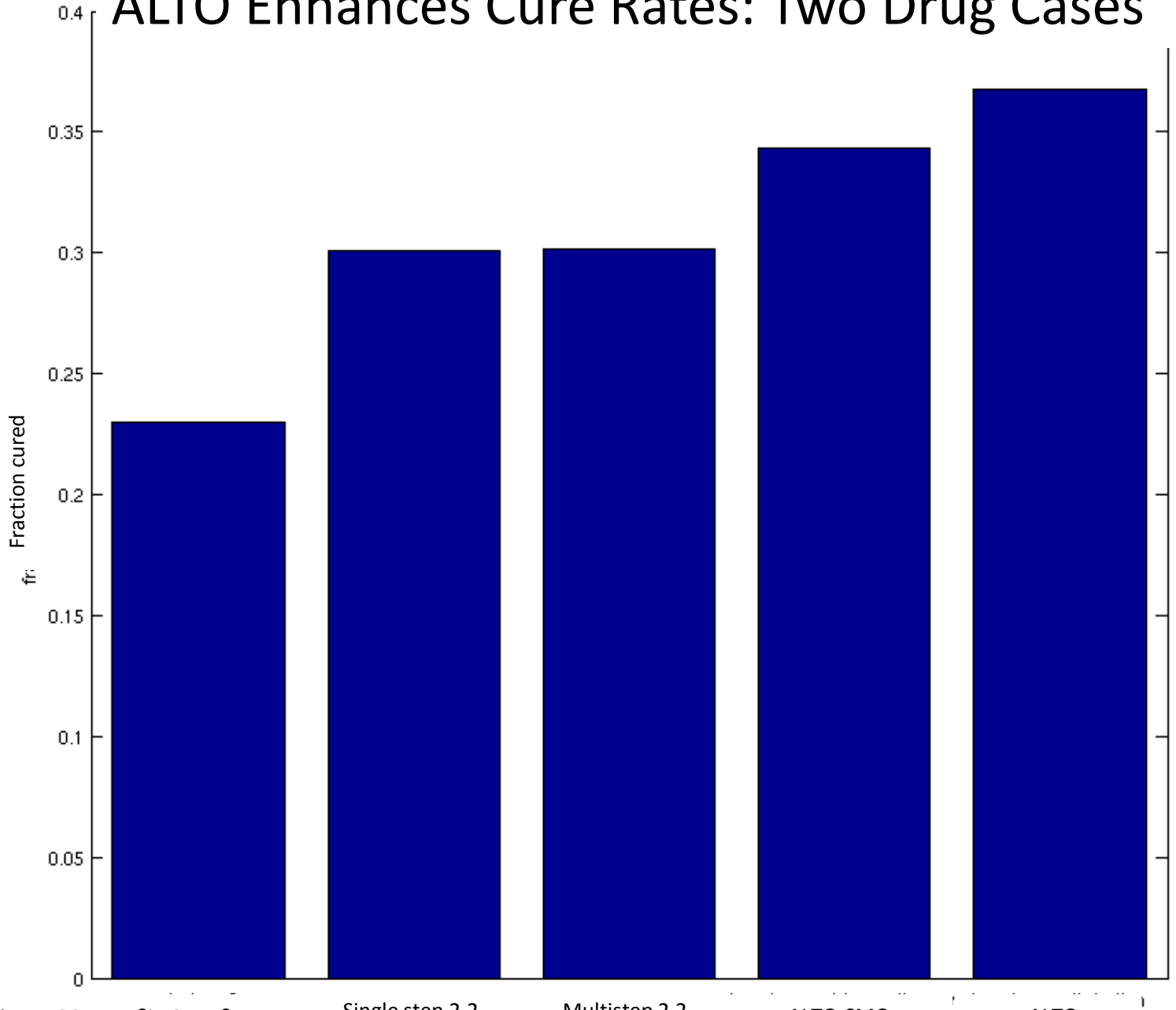
- Bozic elegantly show that prolonged combination therapy is superior to prolonged sequential monotherapy **in the absence of any need for dose reduction due to toxicity**
- However, prolonged therapy with the same drugs “as long as the patient is benefiting” is a great way to teach a tumor to evolve
- **An alternative: individualized sequences adapting frequently, and including monotherapy pulses and simultaneous combination pulses**
  - A high level of complexity of therapy can be delivered in a short period of time if we allow this flexibility
  - An unpredictable, varied therapy schedule creates a jagged evolutionary landscape: hard for tumors to evolve (Kauffman S, The Origins of Order, 1993)

Long Range Planning

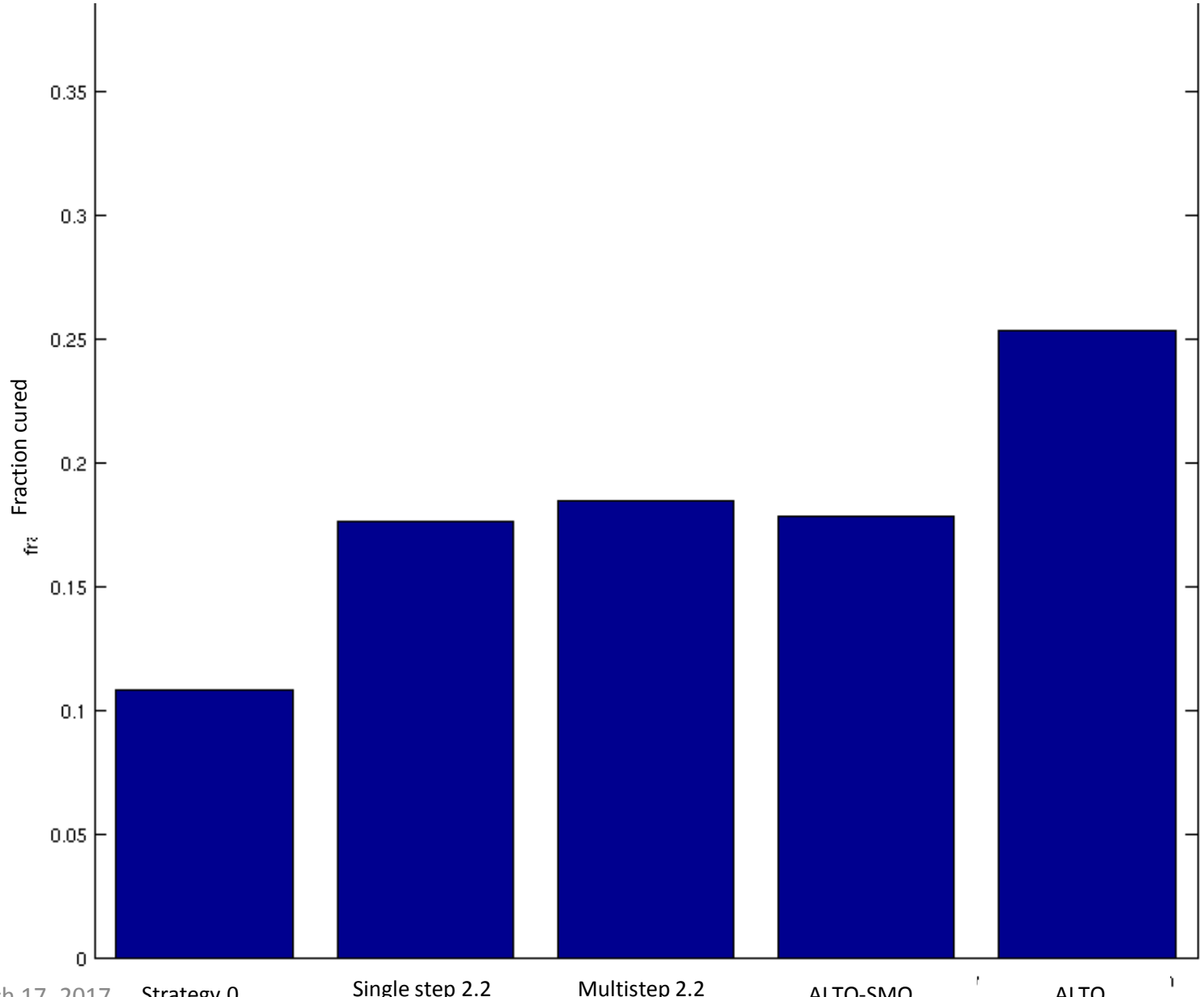
Long Range Planning: Multi-Step Heuristics and Adaptive Long-Range Therapeutic Optimization (ALTO)



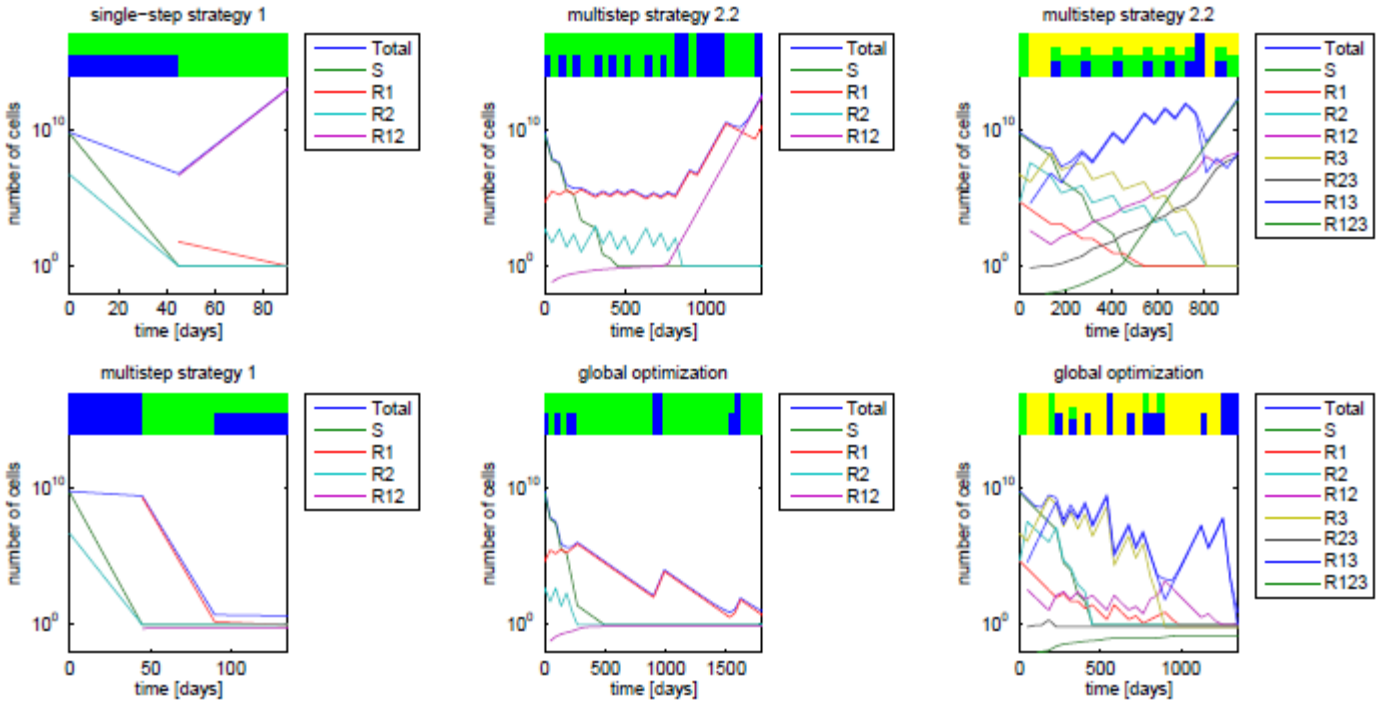
ALTO Enhances Cure Rates: Two Drug Cases



ALTO Enhances Cure Rates: Three Drug Cases



ALTO Enhances Cure Rates



Dynamic Precision Medicine: High Level Conclusions

- The current strategy used for precision therapy of cancer is not the only possible one
- Genetic heterogeneity and evolutionary dynamics can greatly influence the optimal strategy for precision medicine
- The systematic study of **dynamic precision medicine strategies** as a function of population substructure and evolutionary dynamics is an important area for investigation
  - The statement above is not obvious to the oncology mainstream
  - It's not about this model or these strategies
- Benefits are potentially highly significant and very general across a large variety of tumor and therapy characteristics

Long Range Planning: High Level Conclusions

- Long range planning may enhance cure rates
- Optimal treatment sequence are extremely complex and non-intuitive

Combination Therapy: High Level Conclusions

- Effective treatment of cancer will require very high order combination therapy
  - Not generally feasible as simultaenous combinations
- Such higher order combinations may be given as complex individualized adaptive sequences consisting of pulses of lower order combinations and/or monotherapies

References

1. **Beckman, Robert A., Schemmann, Gunter S., and Yeang, Chen-Hsiang. Impact of genetic dynamics and single-cell heterogeneity on development of nonstandard personalized medicine strategies for cancer. *Proceedings of the National Academy of Sciences USA,* Published online before print August 13, 2012, 109: 14586-14591 (2012).**
2. **Yeang, Chen-Hsiang and Beckman, Robert A. Long range personalized cancer treatment strategies incorporating evolutionary dynamics. *Biology Direct,* 11: 1-25 (2016).**
3. Beckman, Robert A., and Yeang, Chen-Hsiang. Nonstandard Personalized Medicine Strategies for Cancer May Lead to Improved Patient Outcomes, *Personalized Medicine*, 35: 705-19 (2014).
4. Beckman, Robert A. Efficiency of Carcinogenesis: Is the Mutator Phenotype Inevitable? *Seminars in Cancer Biology*, 20: 340-352 (2010).
5. Beckman, Robert A. Mutator Mutations Enhance Tumorigenic Efficiency across Fitness Landscapes, *PLoS One*, 4: e5860 (2009).
6. Loeb, Lawrence A., Bielas, Jason H., and Beckman, Robert A. Cancers Exhibit a Mutator Phenotype: Clinical Implications, *Cancer Research*, 68: 3551 (2008).
7. Beckman, Robert A., and Loeb, Lawrence A. Efficiency of Carcinogenesis With and Without a Mutator Mutation, *Proceedings of the National Academy of Sciences,* 103, 14140 (2006).
8. Beckman, Robert A., and Loeb, Lawrence A. Negative Clonal Selection in Tumor Evolution. *Genetics*, 171, 2123 (2005).
9. Beckman, Robert A., and Loeb, Lawrence A. Genetic Instability in Cancer: Theory and Experiment. *Seminars in Cancer Biology*, 15, 423 (2005).

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