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

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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 $R_1$, killed only by Drug-2
  - Resistant cell $R_2$, killed only by Drug-1
  - Incurable doubly resistant cell $R_{1-2}$
- 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*

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
- 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

- Strategy 0
- Single step 2.2
- Multistep 2.2
- ALTO-SMO
- ALTO
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 simultaneous combinations

• Such higher order combinations may be given as complex individualized adaptive sequences consisting of pulses of lower order combinations and/or monotherapies
References


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