Optimizing Adaptive Therapy

Designing novel strategies for tumoral control in late-stage metastatic castration-resistant prostate cancer

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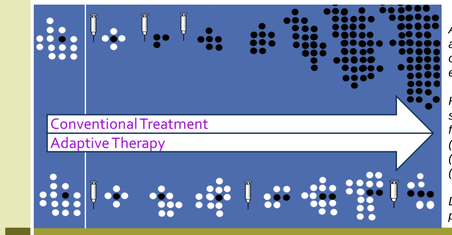
Abstract

Utilizing principles of evolutionary ecology, adaptive therapy seeks to manipulate the tumor micro-ecosystem in order to select against the inevitable rise of resistance that characterizes treatment failure. Adaptive therapeutics views cells as expected and manageable fauna of the body, rather than as microbes to be eradicated, and tailors an adaptive treatment regimen for each patient. Under this new paradigm, cancer shifts from a terminal illness to a chronic condition. Preliminary research has demonstrated significant benefits; however, the current literature lacks understanding of the tumor microdynamics and tests the feasibility of adaptive therapy, often by using simple, highly suboptimal treatment protocols.

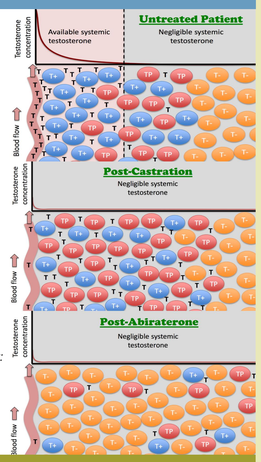
Via an agent-based cellular automata model, we observed spatial dynamics of the intra-tumoral ecosystem in late-stage metastatic castration-resistant prostate cancer. We then use deterministic models and evolutionary principles to create and optimize various treatment protocols utilizing a combination of various therapies that leads to the most stable, controlled, cancer state, one that we theorize could be maintained indefinitely. We both confirm adaptive therapy's effectiveness in significantly prolonging survival time and derive an optimal treatment regimen for clinical application. We then generalize these conceptual findings to treatment of all cancers, and propose several viable avenues of further investigation.

Background

- Adaptive therapy treats cancer as an evolutionary ecosystem, and attempts to engineer competition such that cancer becomes a chronic, rather than acute, condition.
- Tumor cells in late-stage prostate cancer can be separated into three phenotypes based on their relationship with androgens: Producing (TP), Consuming (T+), and Independent (T-).
- We consider 3 medications:
  - Abiraterone, a drug which inhibits the CYP17 enzyme in autoandrogenesis, selects against androgen dependence.
  - Docetaxel, a chemotherapeutic agent, selects against the quickest-growing population.
  - Lupron, the drug used in chemical castration, selects against T+.

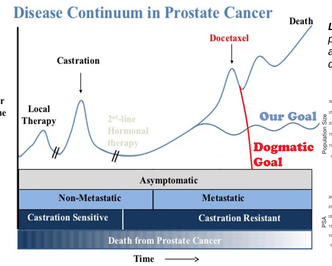


Left: *Adaptive therapy, aimed at control over eradication, explained.*
Right: *Hypothetical subpopulation frequencies under: (1) No Treatment (2) Lupron (3) Lupron + Abiraterone Docetaxel not pictured.*



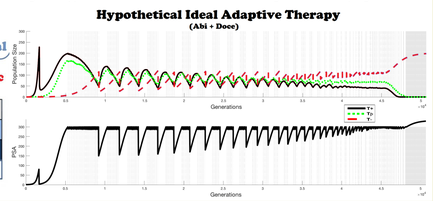
Objectives

- What is the most optimal administration of Docetaxel, Abiraterone, and Lupron to maximize survival time, given stochasticity and granularity of clinical data?
- How can we understand and develop means and markers for monitoring and controlling the development of resistance?



Left: *Typical prostate disease progression, and the contrasting aims of the adaptive and the dogmatic approach.*

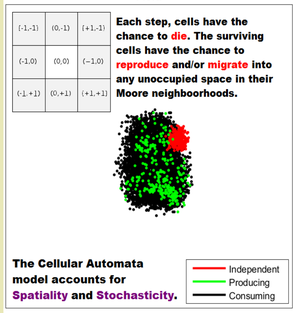
Below: *The hypothetical ideal result as visualized within the deterministic model, wherein the patient likely dies of natural causes long before cancer progression.*



Methods

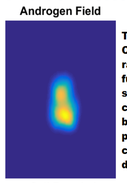
Cellular Automata Model

Naive Therapy #67-629

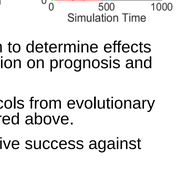


Each step, cells have the chance to die. The surviving cells have the chance to reproduce and/or migrate into any unoccupied space in their Moore neighboorhoods.

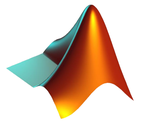
The Cellular Automata model accounts for Spatiality and Stochasticity.



The Producing and Consuming cells' growth rates vary based on a Hill function of Androgen levels, shown here, with greater concentrations depicted as brighter. Androgen is produced by the Producing cells and then undergoes a diffusion function.



Population data is displayed and saved. Treatments are shown as vertical bars, with grey representing Abiraterone, black representing Docetaxel, and Cyan representing external Androgens.



All models built with MATLAB©

Left: *An annotated look at the spatial interface in the Cellular Automata model. Used for observation; data was saved and extracted for analysis.*

Below: *An outline of the four adaptive protocols and the Control. See paper for details, implementation, and specific results.*

After constructing the model, I:

- Conducted real-time observation to determine effects of medication and parameterization on prognosis and resistance.
- Constructed four adaptive protocols from evolutionary principles and knowledge garnered above.
- Ran iterations to determine relative success against control.

Deterministic Model

After analyzing conceptual results of the cellular automata model, and constructing the deterministic model, I:

- Observed long-term evolutionary dynamics to the adaptive protocols.
- Confirmed conceptual findings of the cellular automata model.
- Tested the parameter space for achievement of sustainable cycles.

Below: *The G-Function, used in calculating growth rates during each step.*

$$G_y = r_y\left(1 - \frac{(1-E_y)(x_{T+} + x_{Tp} + x_{T-})}{K(v_y)}\right) - \mu(v_y)$$

See paper for details on model implementation and parameterization

Control

Maximum Tolerable Dose

Current standard of care: Late-stage prostate cancer patients are given the maximum tolerable dose of Abiraterone. Resistance quickly develops. This extends mean survival time by 4 months.

Key:
Abiraterone
Docetaxel
Androgen

Low Freq Abi

Large Dose Low Frequency

PSA Informed

"Classic Adaptive Therapy" – This is the protocol currently being used in the clinical trial. A large-dose Abiraterone regimen is initiated as soon as PSA levels meet a certain threshold. PSA levels are measured every 4 weeks. This therapy seeks to slow tumor growth rather than eradicate, and aims at delaying propagation of resistant populations (T+) by increasing the average fitness of non-resistant populations over **Control**. However, since each dose of Abiraterone is large and discrete, after every dosage T- enjoys temporary competitive release.

Continuous Abi

Small Dose High Frequency

PSA Informed

This protocol is highly ideal – it assumes perfect knowledge of tumor composition and state, and extends the same protocol behind the **Low Freq Abi** regimen to its limit. In this protocol, we give Abiraterone in continuous, small doses, as modulated by an omniscient "insulin pump", which has the effect of offering no momentary competitive release. This significantly slows the expansion of T-.

Abi + Doce

Small Dose High Frequency *Large Dose before Docetaxel*

PSA Informed

Large Dose

T- Informed

Docetaxel, like all chemotherapeutics, targets quickly-dividing cells. Clinically, Docetaxel is currently a last-line therapy that temporarily reduces tumor burden before it too is foiled by resistance. In this protocol, by sparingly administering Docetaxel after a T- threshold and a large dose of Abiraterone, the drug becomes a scalpel to target and select against T-. The hope is that after Docetaxel, tumor composition approaches original composition, enabling indefinite cycles of Abiraterone stalling and Docetaxel "resets".

Tri-Protocol

Small Dose High Frequency *Large Dose before Docetaxel*

PSA Informed

Large Dose

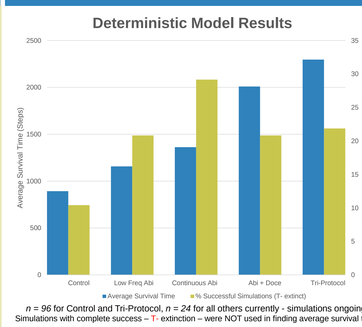
T- Informed

Large Dose

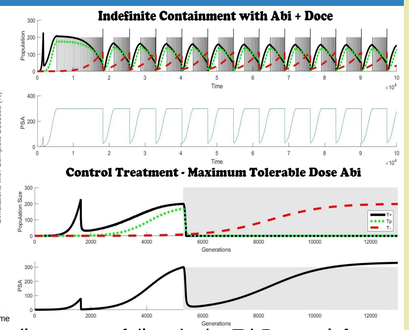
Follows Docetaxel

This protocol follows the approach of the **Abi + Doce** protocol, with the addition of androgens. These androgens, either external or due to the cessation of Lupron, temporarily increases the fitness of T+ and Tp to promote the outcompetition of T-.

Results



n = 96 for Control and Tri-Protocol, *n = 24* for all others currently - simulations ongoing
Simulations with complete success – T- extinction – were NOT used in finding average survival time

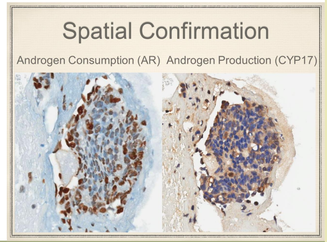


- In the Cellular Automata model, time until treatment failure in the Tri-Protocol, for instances that failed, was 2.57 times longer than control. Other protocols are still undergoing simulation.
- Complete success, defined as T- extinction, was observed in 21.9% of Tri-Protocol simulations, as compared to 10.4% in control.
- In the deterministic model, we observed indefinite containment even in the worst-case parameter set, with the Docetaxel Cycle (Abi + Doce) protocol.

Conceptual Findings

- High frequency, low-dosage "insulin-pump" treatment significantly extends survival time over coarse, status quo, adaptive therapy.
- The slope and behavior of PSA data can be used to determine relative frequencies of subpopulations, and predict failure, assisting end-of-life care decisions.
- Spatial segregation and migration occurs naturally and decreases competition.
- "Forcing Move" therapies, e.g. the Tri-Protocol, cause cancer systems to become highly deterministic and predictable.
- With a rather wide margin of "success", the determination of a "most optimal therapy" ought to include medication costs, quality of life, and logistical constraints.
- Tumors can be classified into "types" based on behavior and state. Classification is key to formulating the most effective therapy regimen, and may be determined from early responses to Abiraterone.

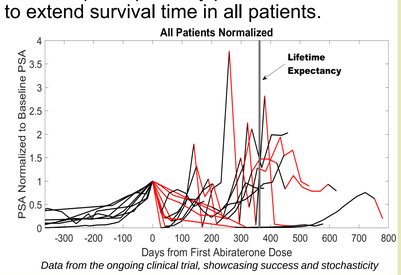
Below: *Imaging of stained tissue from a lymph node biopsy, showing spatial organization of Tp and T+.*



Conclusions and Discussion

- Optimization significantly extends survival times, and makes Adaptive Therapy an extremely viable alternative to status-quo metronomic or tolerance dosage therapies.
- Simple *in vitro* observational studies are sufficient to elucidate key parameters that govern much of tumor development.
- The creation of deterministic tumor behavior implies "perfectly personalized medicine" is a viable means by which to extend survival time in all patients.
- Results are highly generalizable to all forms of cancer with existing pharmacological development.

We envision a future in which cancer becomes a chronic disease, much like diabetes, and is managed by precise continuous administration of control-oriented medication, but otherwise does not impact lifespan nor quality of life.



Data from the ongoing clinical trial, showcasing success and stochasticity

References and Extensions

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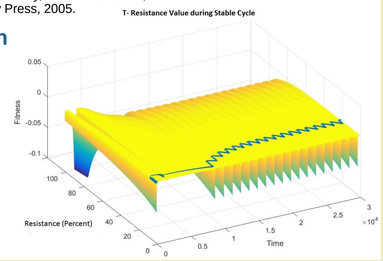
Below: *A fitness landscape for T- resistance over time, generated during a stable cycle in the deterministic model.*

Limitations and Future Investigation

- Parameterization is largely theoretical, can become more concrete via *in vitro* and clinical work.
- Clinical feasibility studies to confirm theoretical results.
- CTC and further PSA analysis to extend work on earlier diagnosis and classification of patients.
- Cross-application to other types of cancer – we're currently looking at breast cancer as a similar avenue.
- Exploration of integration of further treatments – immunotherapy, oncolytic viri, genetic engineering, etc.



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