

Adaptive Therapy and Competition

Cancer Adaptive Therapy Models Virtual Meeting

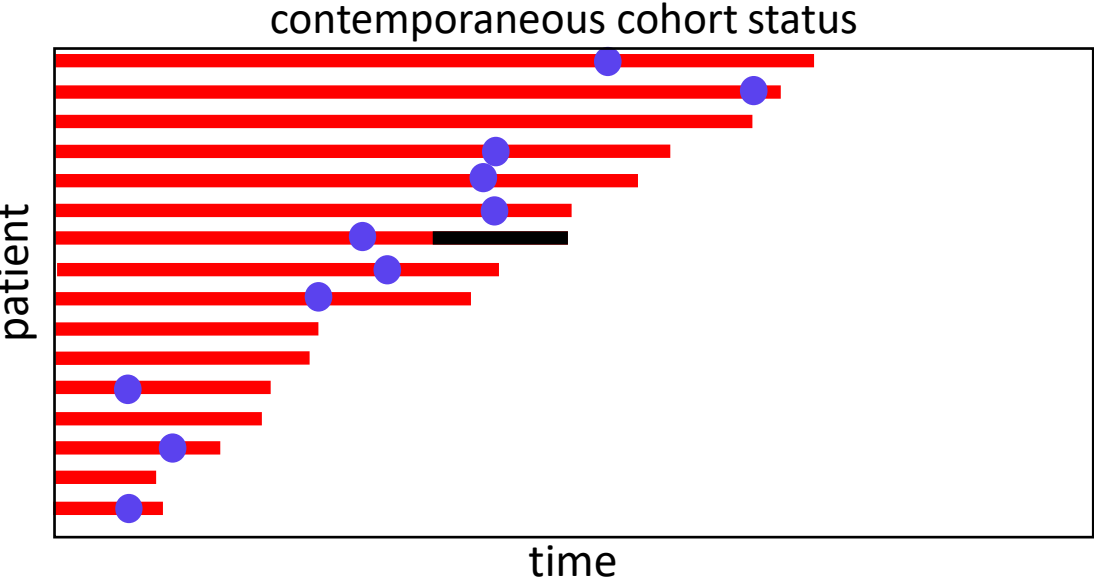
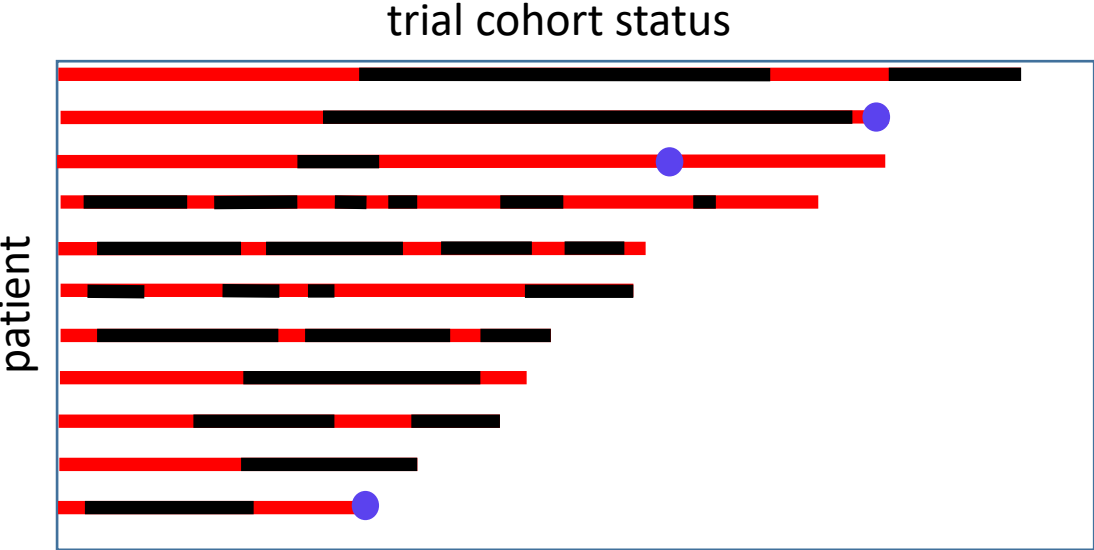
Elsa Hansen

The Pennsylvania State University

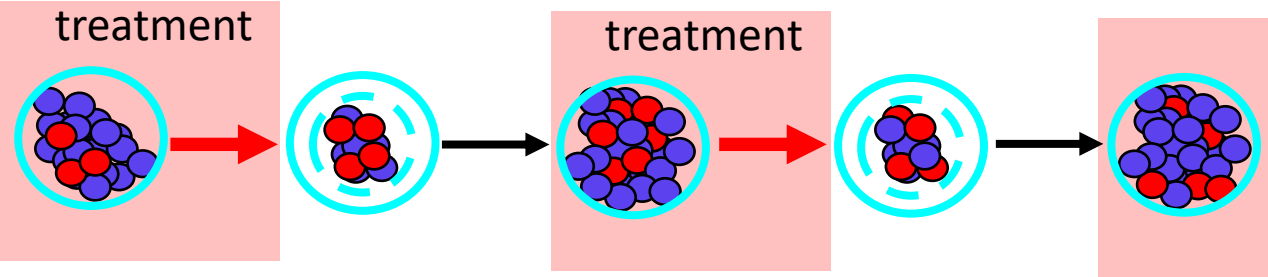
CIDD

Center for Infectious
Disease Dynamics

Treatment of prostate cancer: Recent Pilot Clinical Trial



- treatment failure
- on treatment
- off treatment



- sensitive cell
- resistant cell
- baseline PSA (B_{PSA})

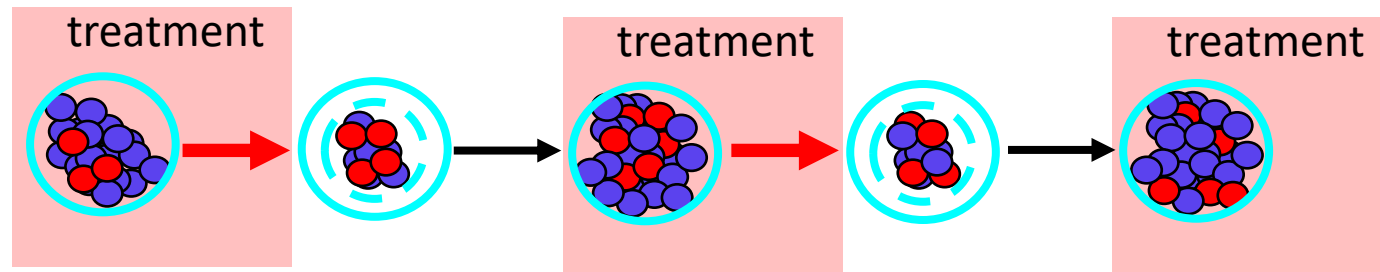
Zhang, Cunningham, Brown and Gatenby.
 Integrating evolutionary dynamics into treatment of
 metastatic castrate-resistant prostate cancer.
 Nature Communications, Nov. 2017

Treatment of prostate cancer: Recent Pilot Clinical Trial

Main advances of trial:

1. Treatment is **adaptive**: dosing depends on the actual tumor dynamics of each individual patient
2. Treatment leverages **competition**: deliberately maintains a sensitive population to slow the growth of the resistant population.

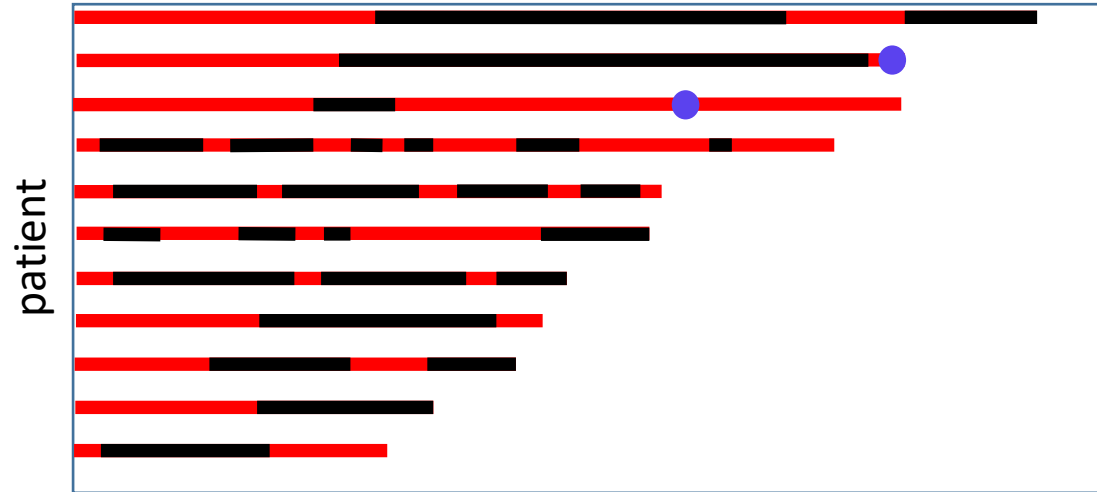
Adaptive Approach



Can we modify the adaptive therapy design and improve results?

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trial cohort status



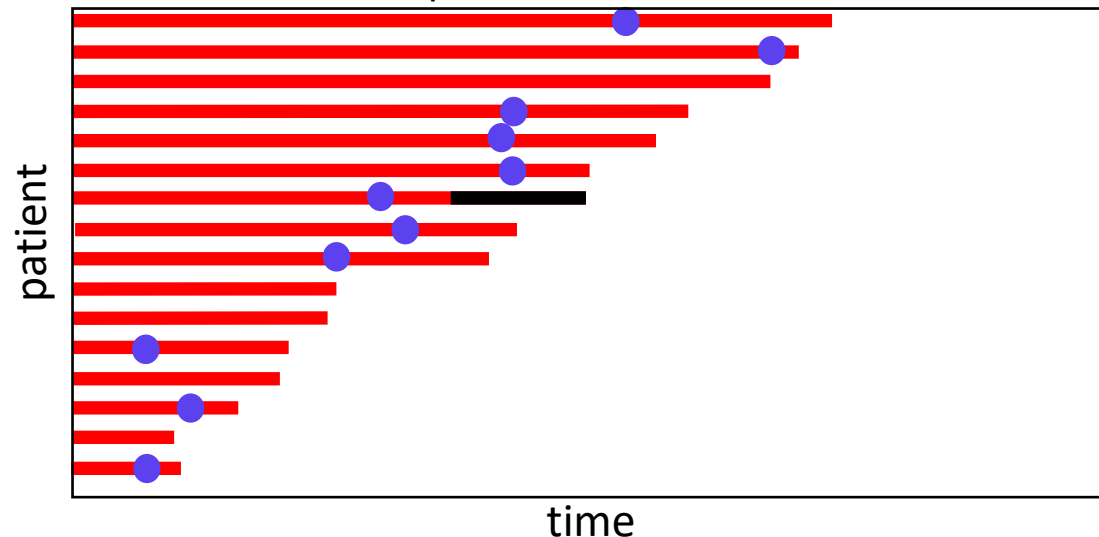
Assumptions

1. Adaptive therapy works because of competition
2. Larger populations generate more competition

Caveats

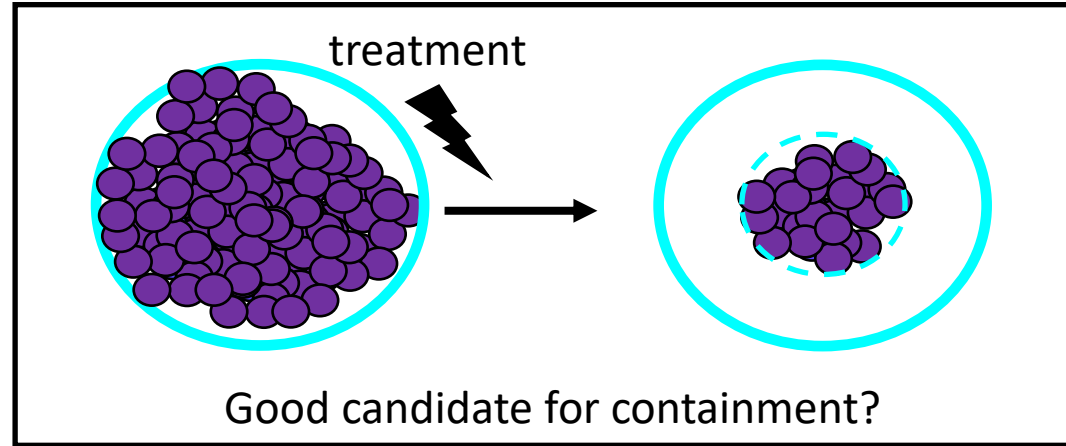
1. Interested in adaptive therapy in general
 - a) Discussion is not restricted to prostate cancer
 - b) Use PSA as a proxy for tumor burden
2. **Adaptive therapy** designed to competitively suppress resistance in order to contain the tumor for longer. **Competitive Suppression** and **Containment**

contemporaneous cohort status

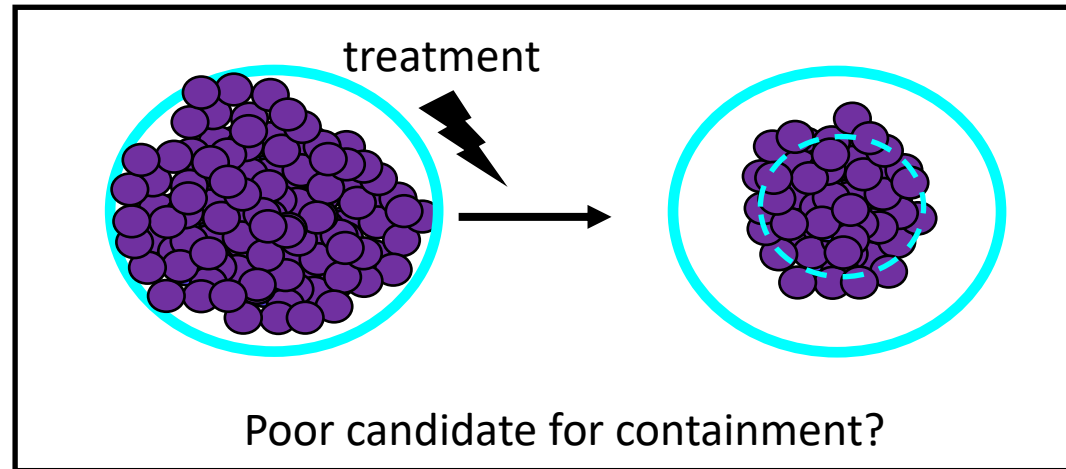





Role of initial tumor response?

Accept To Trial

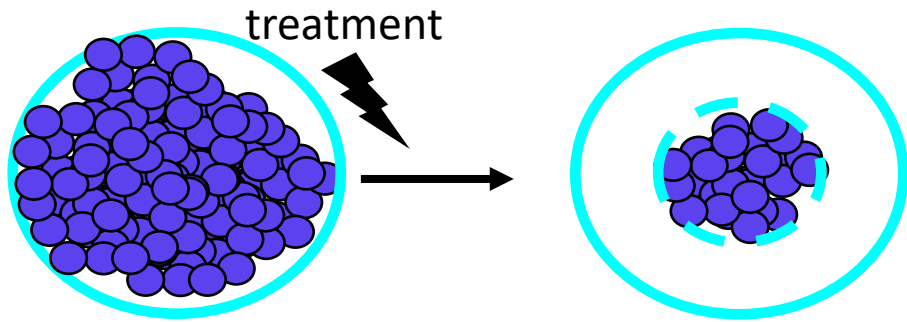


Decline From Trial

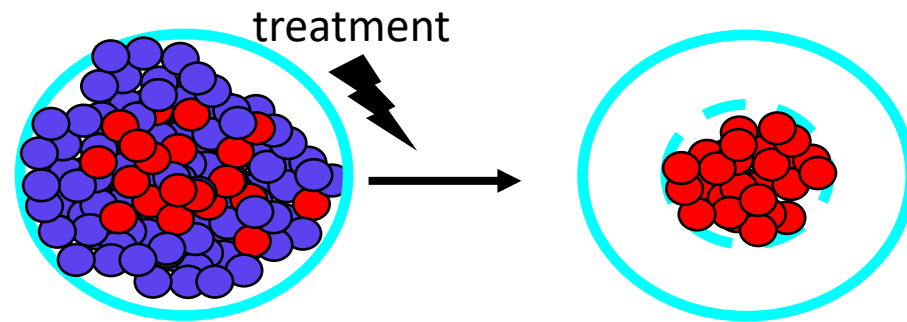


-  baseline PSA
-  50% baseline PSA
-  tumor cell

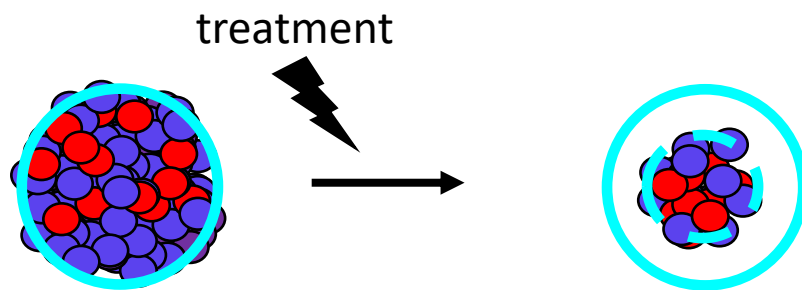
Strong Initial Response BUT Bad Candidate for Containment







standard therapy could clear tumor



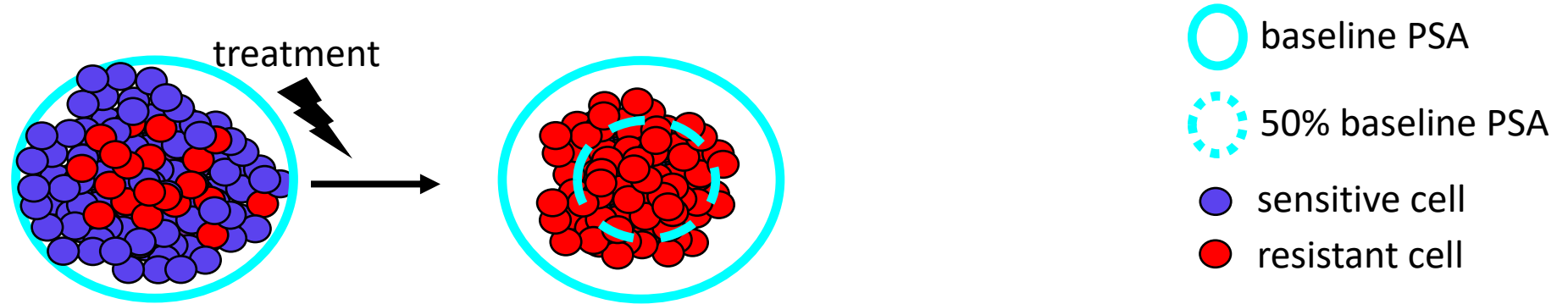
50% reduction in PSA is too much



baseline PSA is too low

-  baseline PSA
-  50% baseline PSA
-  sensitive cell
-  resistant cell

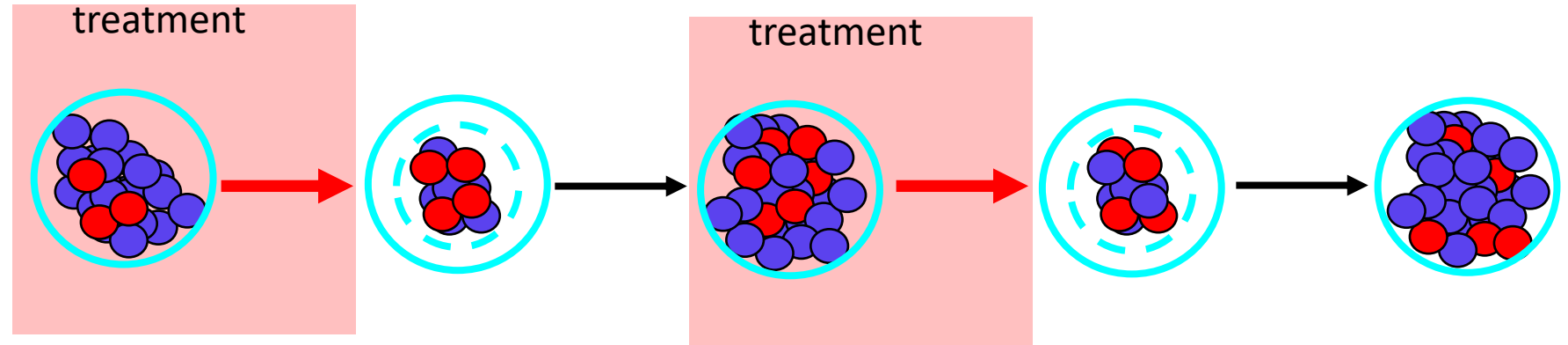
Poor Initial Response BUT Good Candidate for Containment?



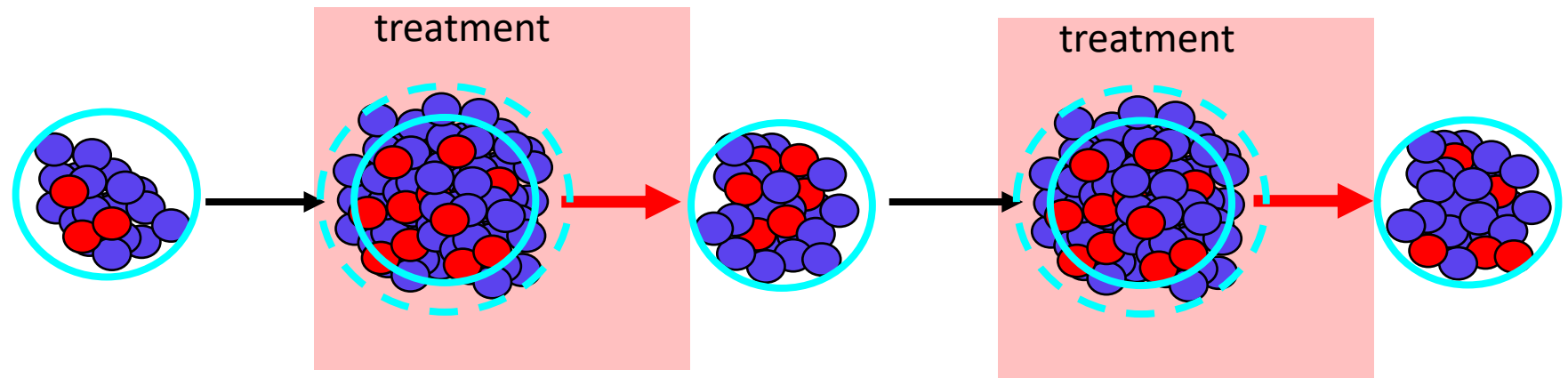
These patients may have excellent potential to benefit from competitive suppression.

Modified Approach to Enhance Competition

Current Approach



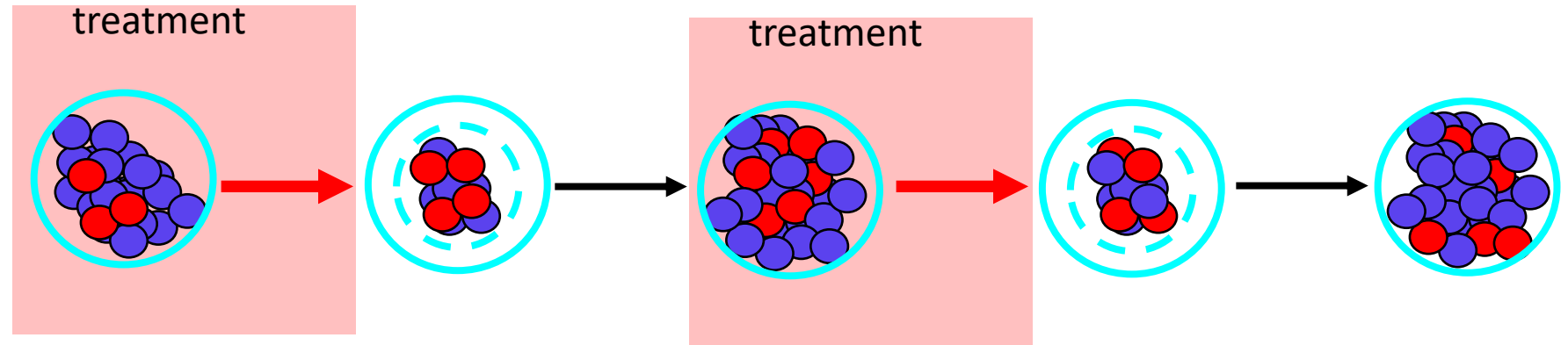
A Possible Improved Approach



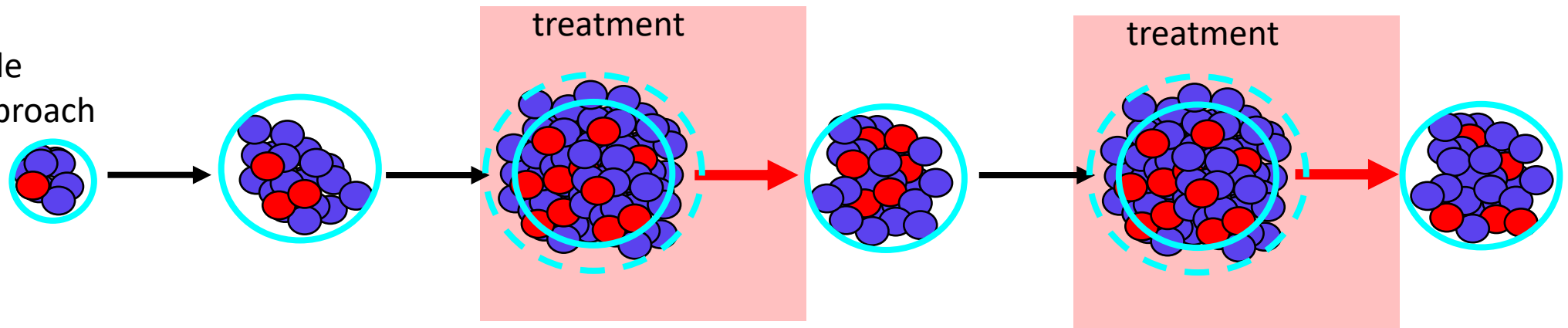
- sensitive cell
- resistant cell

Modified Approach to Enhance Competition

Current Approach



A Possible Improved Approach



- sensitive cell
- resistant cell

Important Reminder

1. Analysis assumes that competition is the main consideration
2. Larger populations generate more competition

But, in general we know

Populations interact in many different ways

1. Competition
 - a) For space
 - b) For nutrients
2. Cooperation
 - a) Production of public goods
 - b) Self-restraint behavior
3. Transfer between populations
 - a) Mutation
 - b) Epigenetic changes

**Populations also interact
with their environment**

CANCER

Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer

Pedro M. Enriquez-Navas,¹ Yoonseok Kam,¹ Tuhin Das,¹ Sabrina Hassan,¹
Ariosto Silva,¹ Parastou Foroutan,^{1*} Epifanio Ruiz,¹ Gary Martinez,^{1,2} Susan Minton,³
Robert J. Gillies,^{1,4} Robert A. Gatenby^{1,4†}

Conventional cancer treatment strategies assume that maximum patient benefit is achieved through maximum killing of tumor cells. However, by eliminating the therapy-sensitive population, this strategy accelerates emergence of resistant clones that proliferate unopposed by competitors—an evolutionary phenomenon termed “competitive release.” We present an evolution-guided treatment strategy designed to maintain a stable population of chemosensitive cells that limit proliferation of resistant clones by exploiting the fitness cost of the resistant phenotype. We treated MDA-MB-231/luc triple-negative and MCF7 estrogen receptor-positive (ER⁺) breast cancers growing orthotopically in a mouse mammary fat pad with paclitaxel, using algorithms linked to tumor response monitored by magnetic resonance imaging. We found that initial control required more intensive therapy with regular application of drug to deflect the exponential tumor growth curve onto a plateau. Dose-skipping algorithms during this phase were less successful than variable dosing algorithms. However, once initial tumor control was achieved, it was maintained with progressively smaller drug doses. In 60 to 80% of animals, continued decline in tumor size permitted intervals as long as several weeks in which no treatment was necessary. Magnetic resonance images and histological analysis of tumors controlled by adaptive therapy demonstrated increased vascular density and less necrosis, suggesting that vascular normalization resulting from enforced stabilization of tumor volume may contribute to ongoing tumor control with lower drug doses. Our study demonstrates that an evolution-based therapeutic strategy using an available chemotherapeutic drug and conventional clinical imaging can prolong the progression-free survival in different preclinical models of breast cancer.

Three Different Treatment Strategies

1. Standard Treatment (ST):

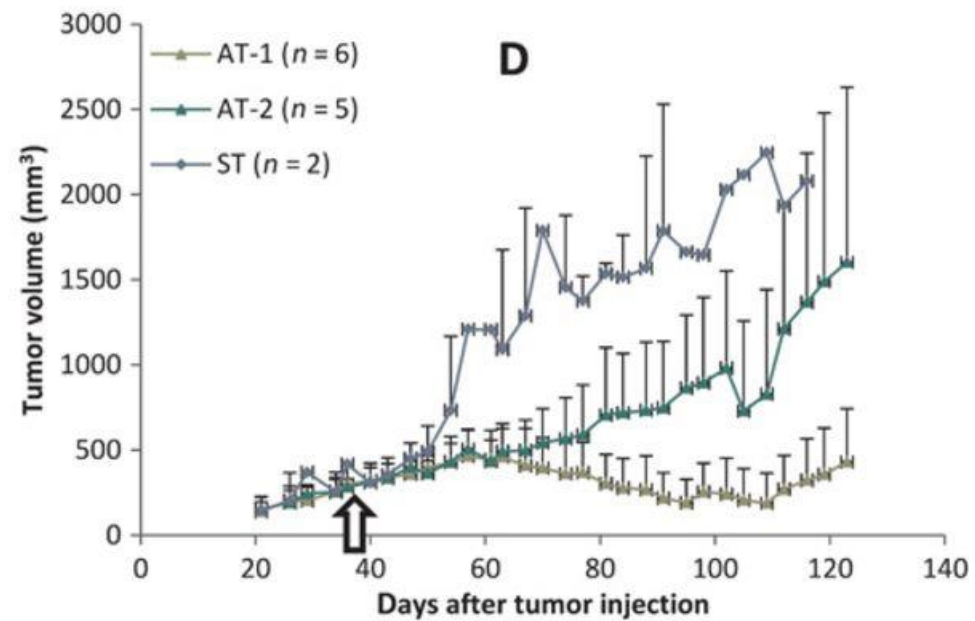
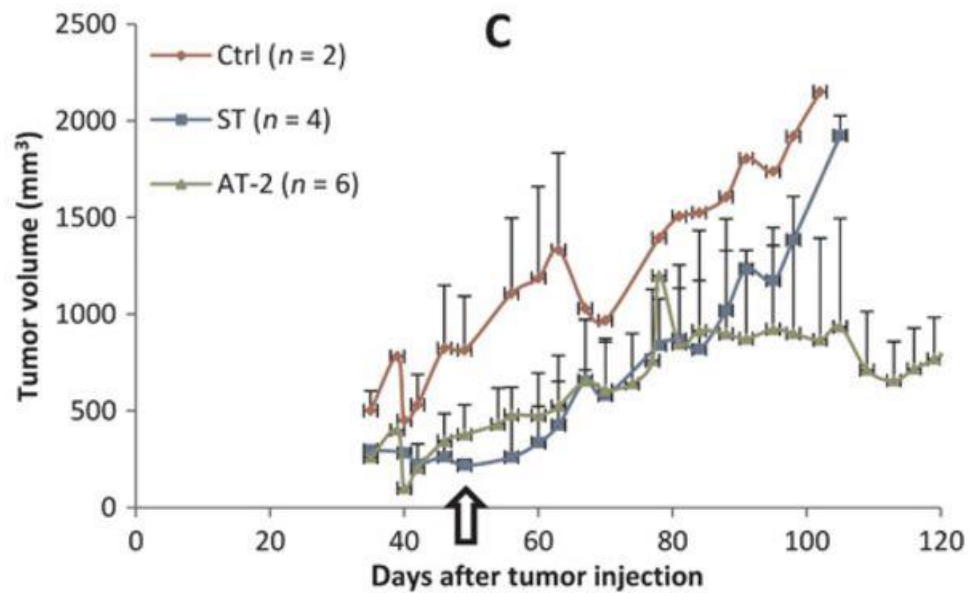
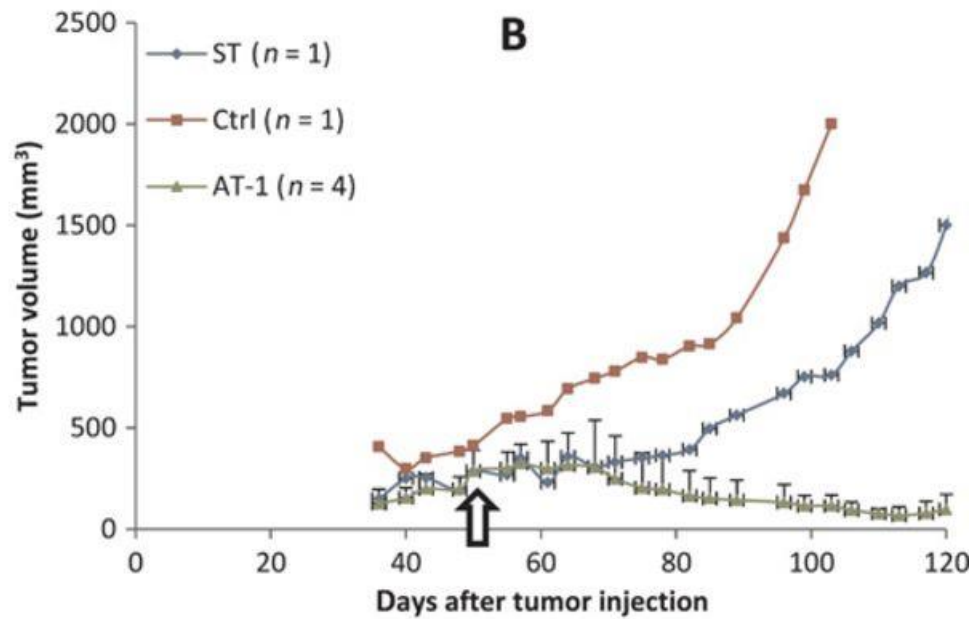
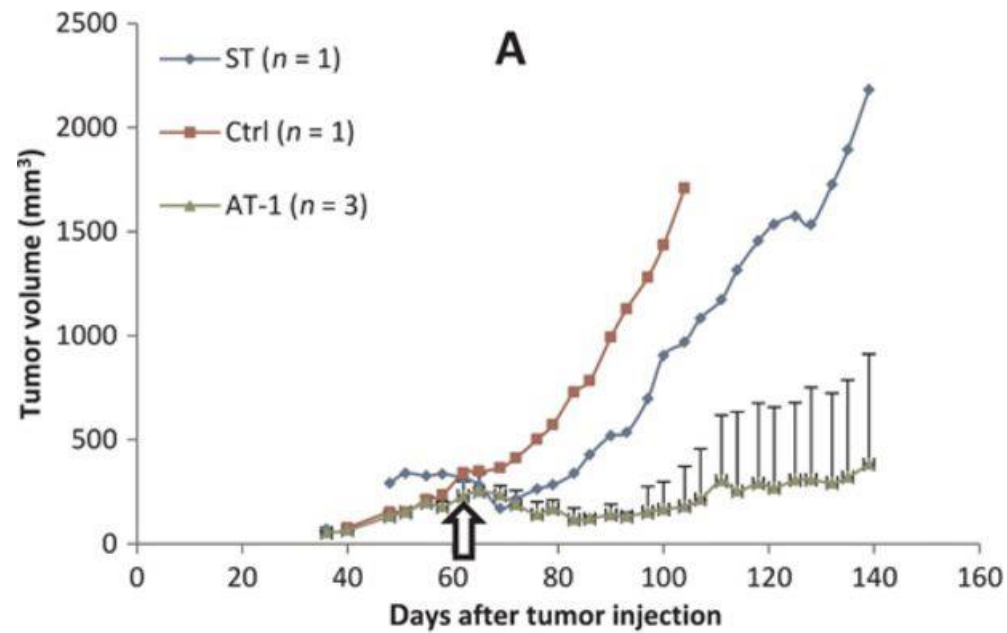
Fixed dose twice a week for 2.5 weeks

2. Adaptive Therapy 1 (AT-1): Dose Modulating

Treatment times fixed. Dose adapted to tumor response.

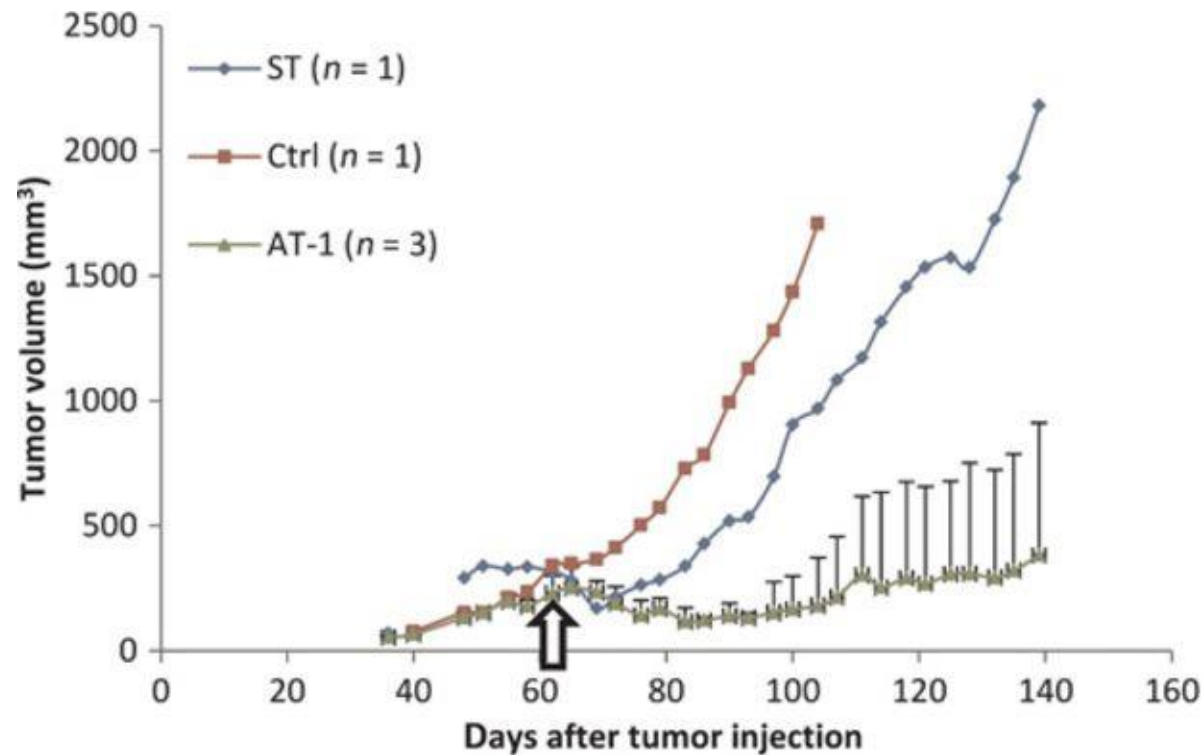
3. Adaptive Therapy 2 (AT-2): Treatment Skipping

Treatment dose fixed. Treatment timing adapted to tumor response.

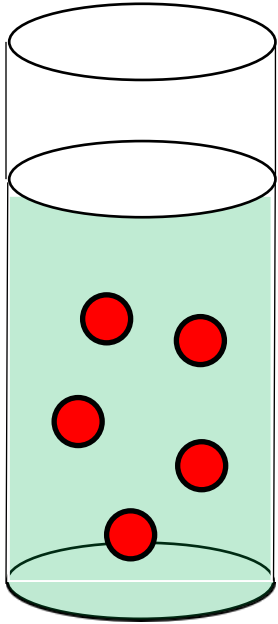


Immediate Questions

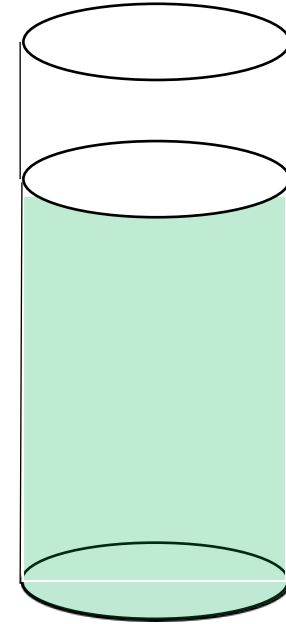
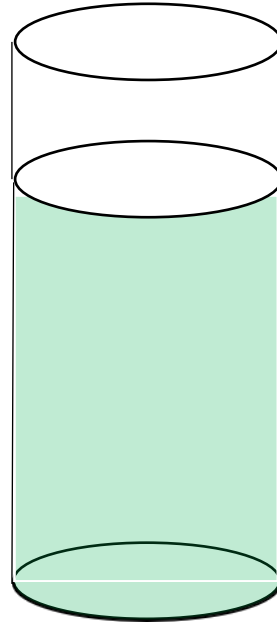
- 1) Is success of adaptive therapy due to competition?
- 2) Is treatment failure (progression) due to drug resistance?



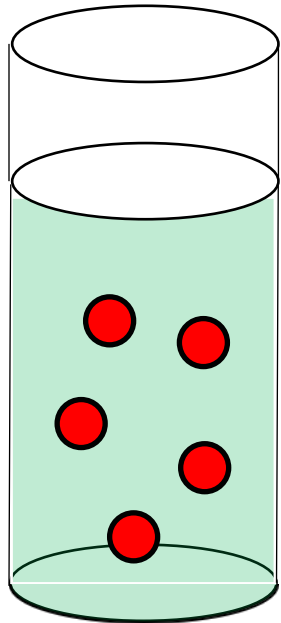
Example using *E.coli* as model system



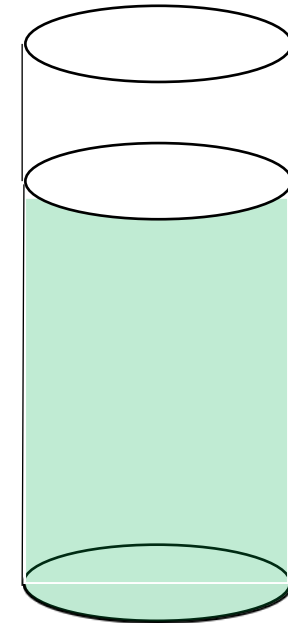
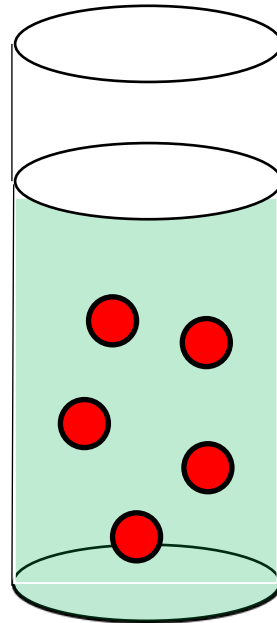
Resistant Only



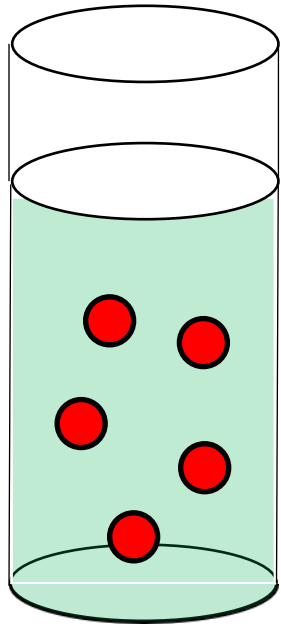
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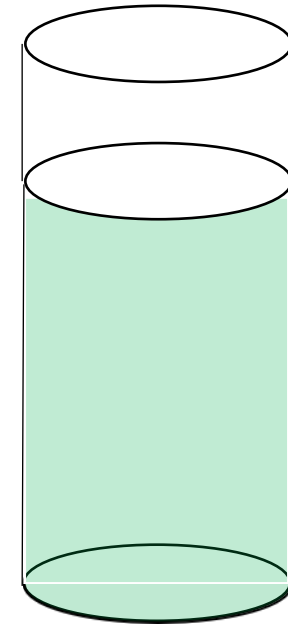
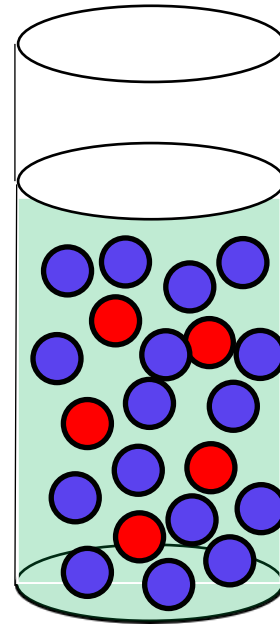
Resistant Only



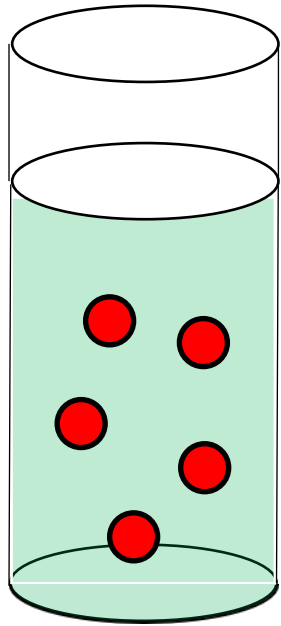
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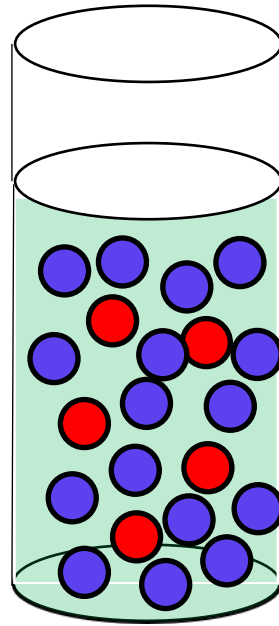
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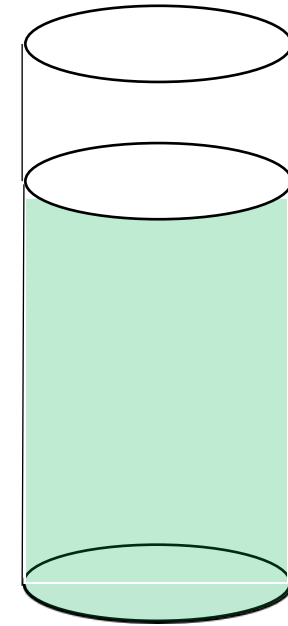
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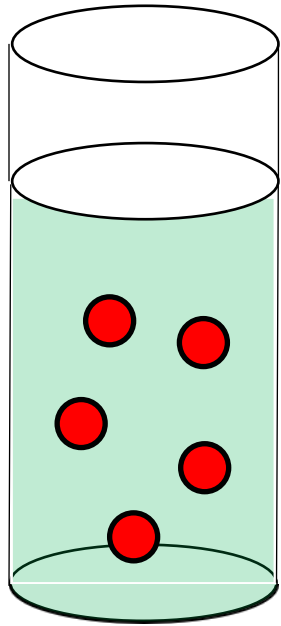
Resistant Only



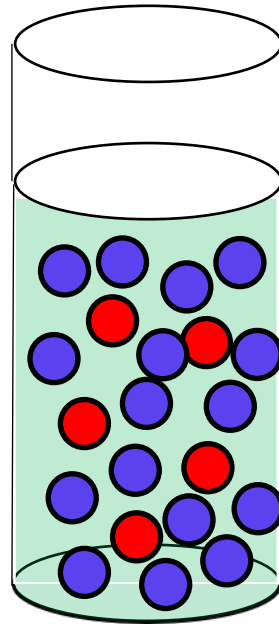
Mixed



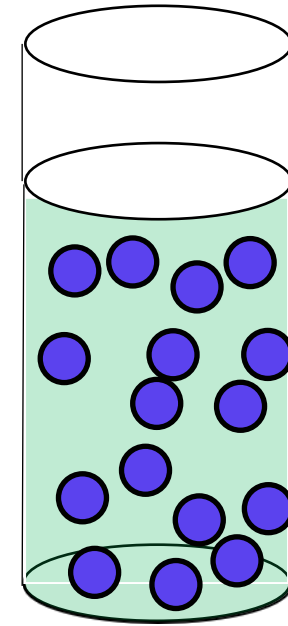
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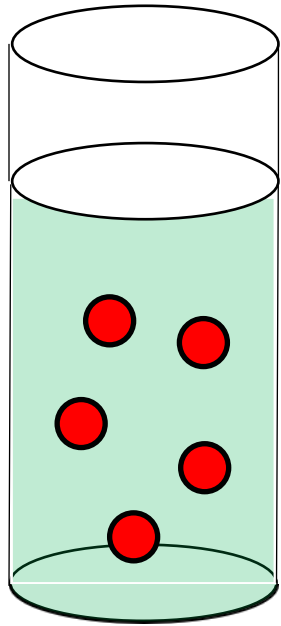
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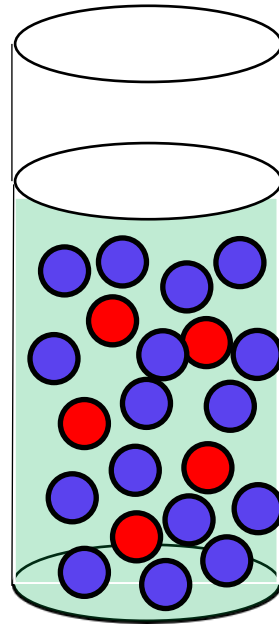
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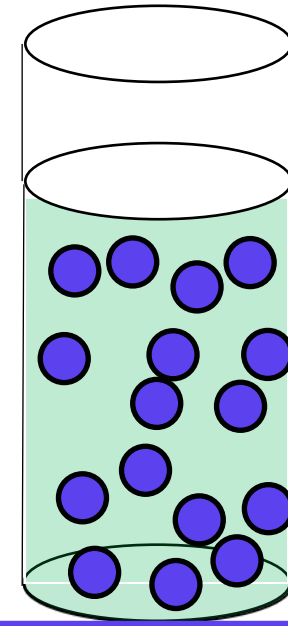
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Resistant Only

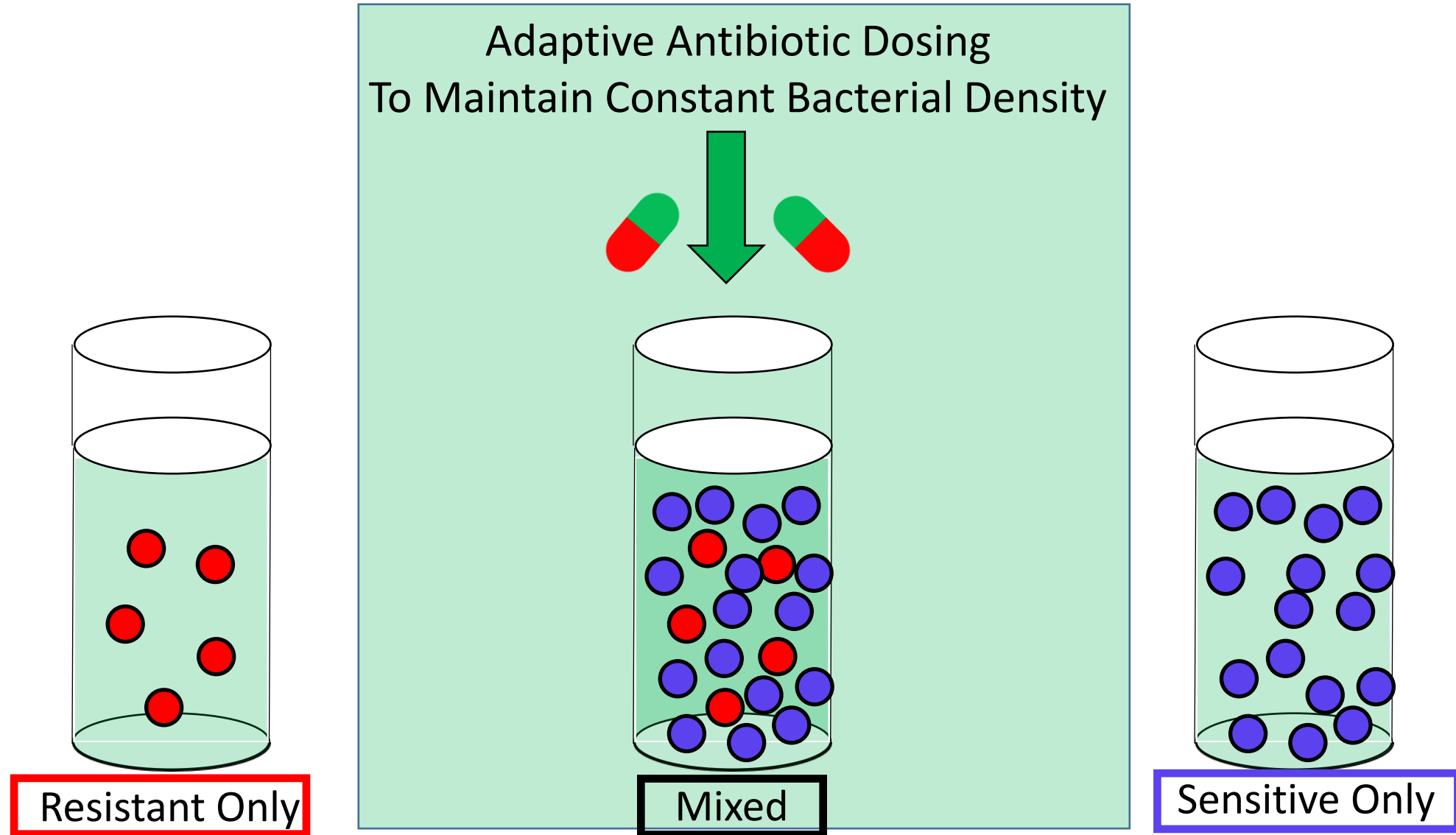


Mixed

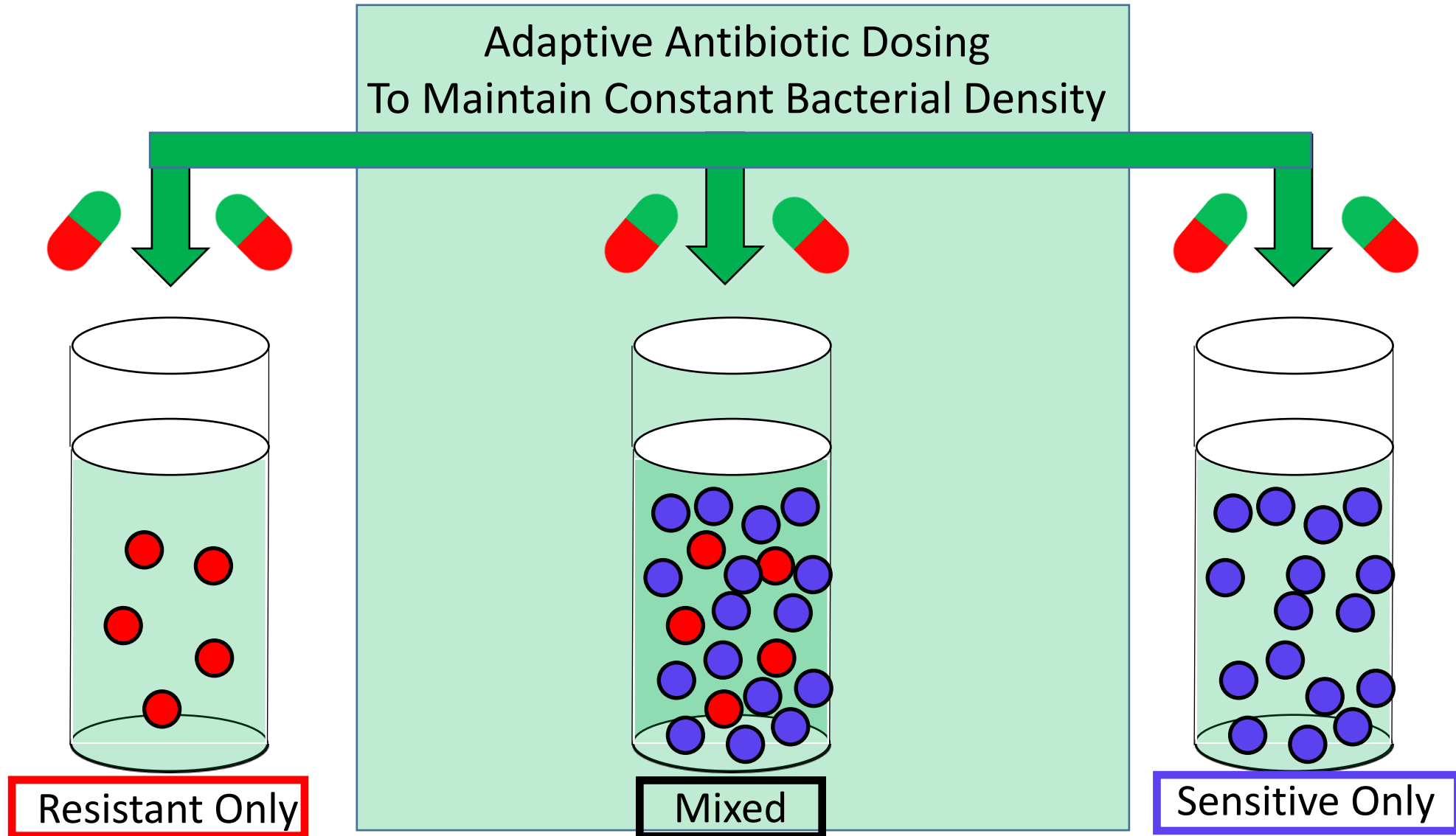


Sensitive Only

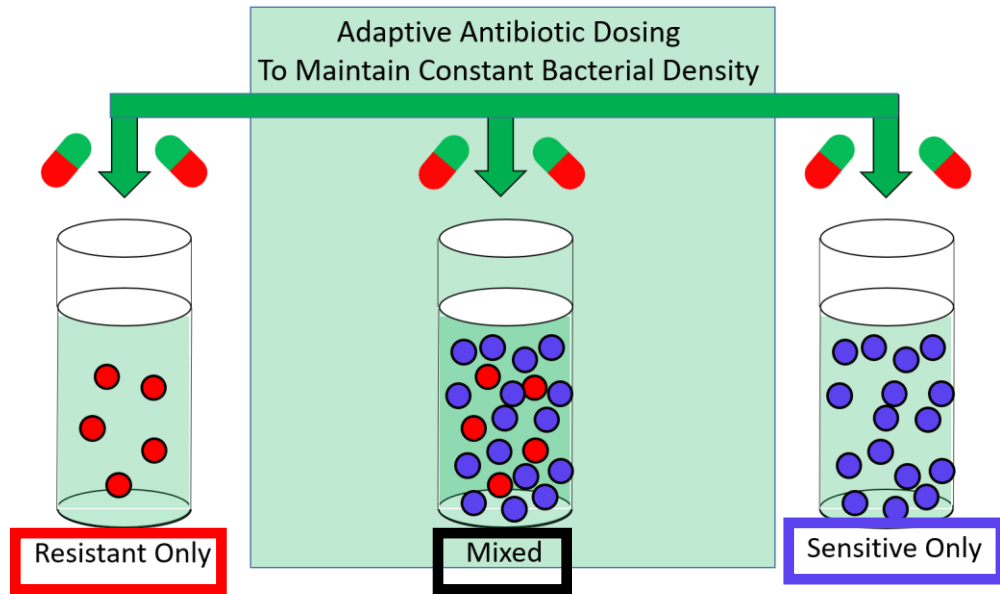
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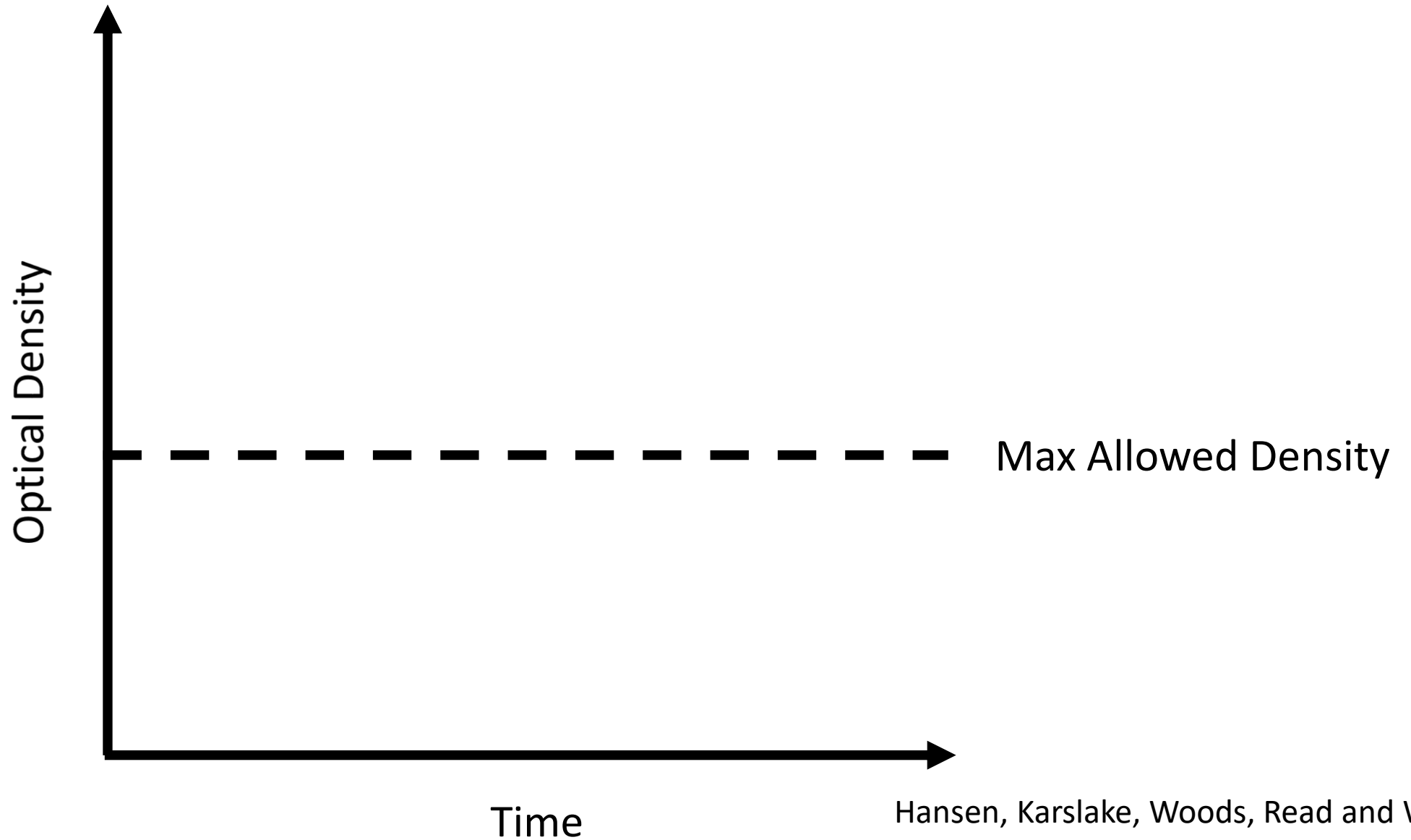
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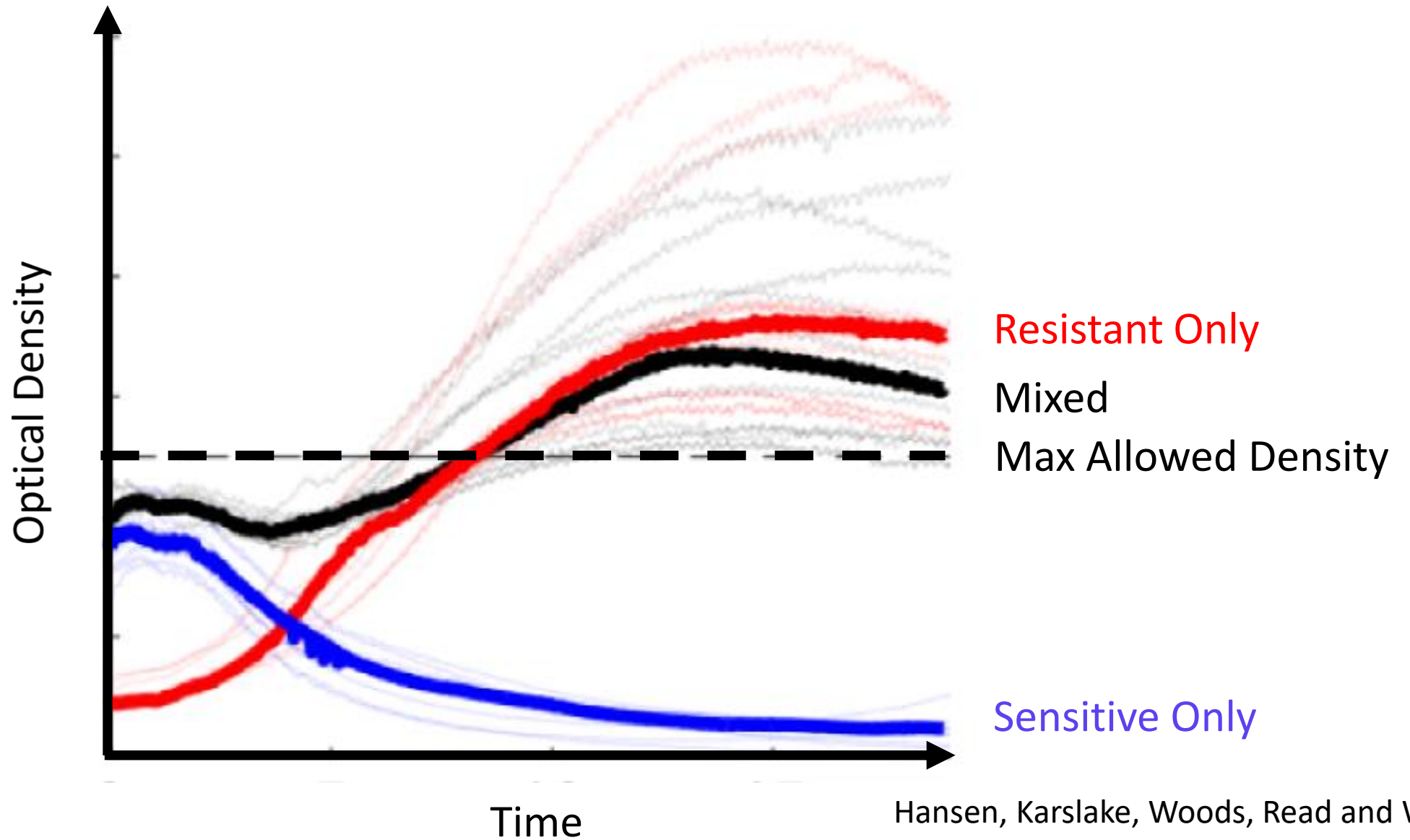
- 1) By matching drug in all vials, only difference between vials is presence/absence of sensitive cells
- 2) By comparing **Resistant Only** and **Mixed** we can measure the effect of sensitive cells.

- 1) Is success of adaptive therapy due to competition?
- 2) Is treatment failure (progression) due to drug resistance?

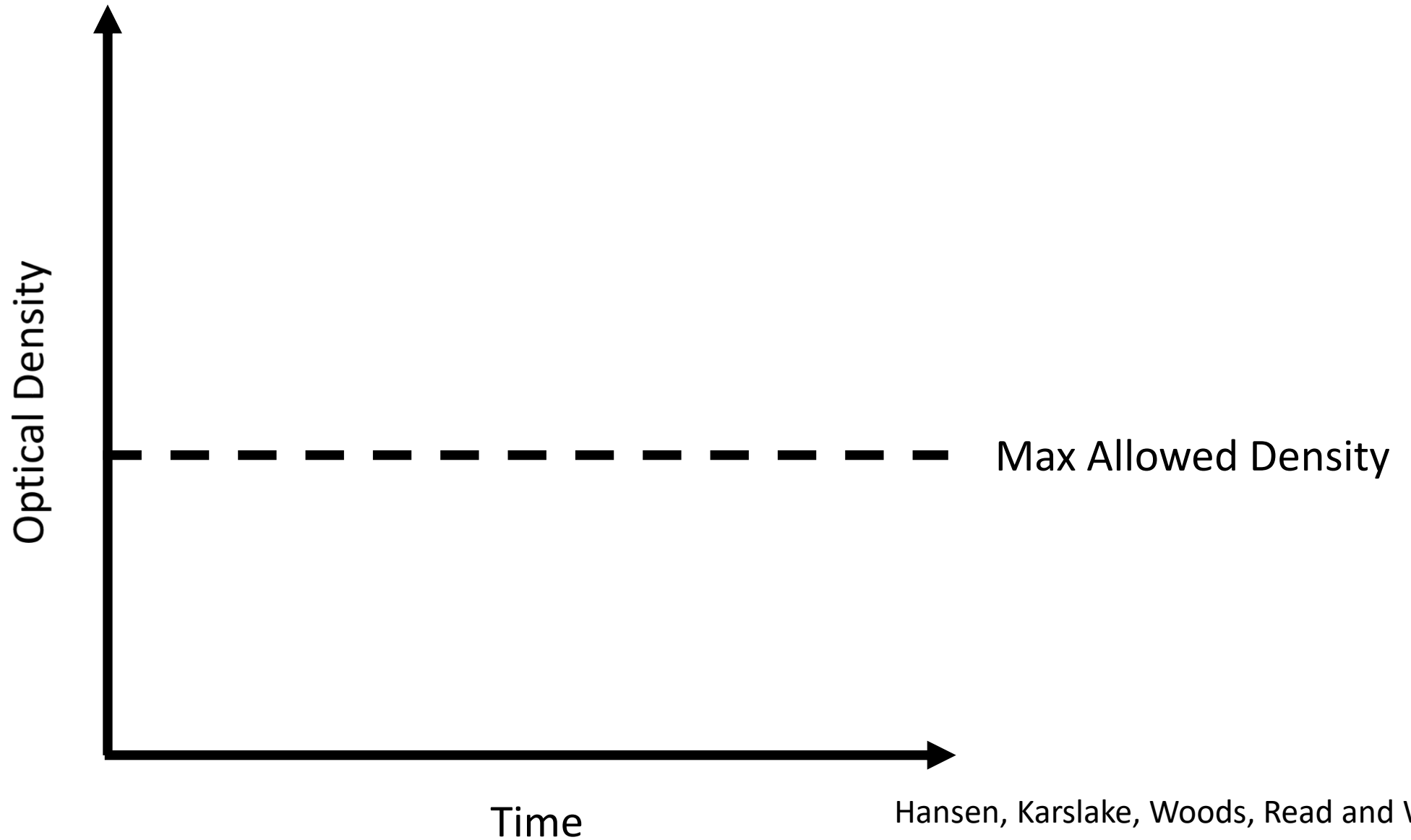
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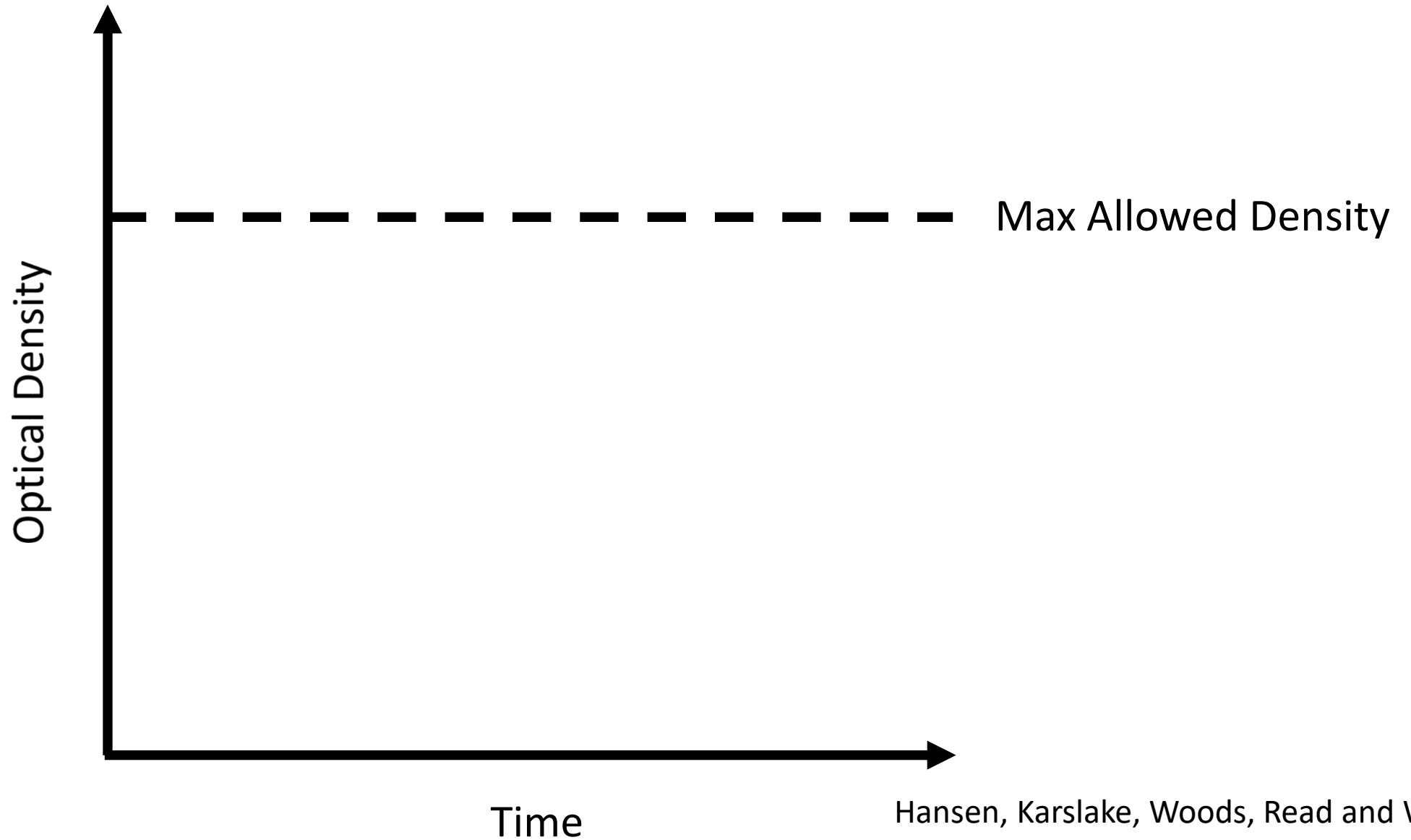
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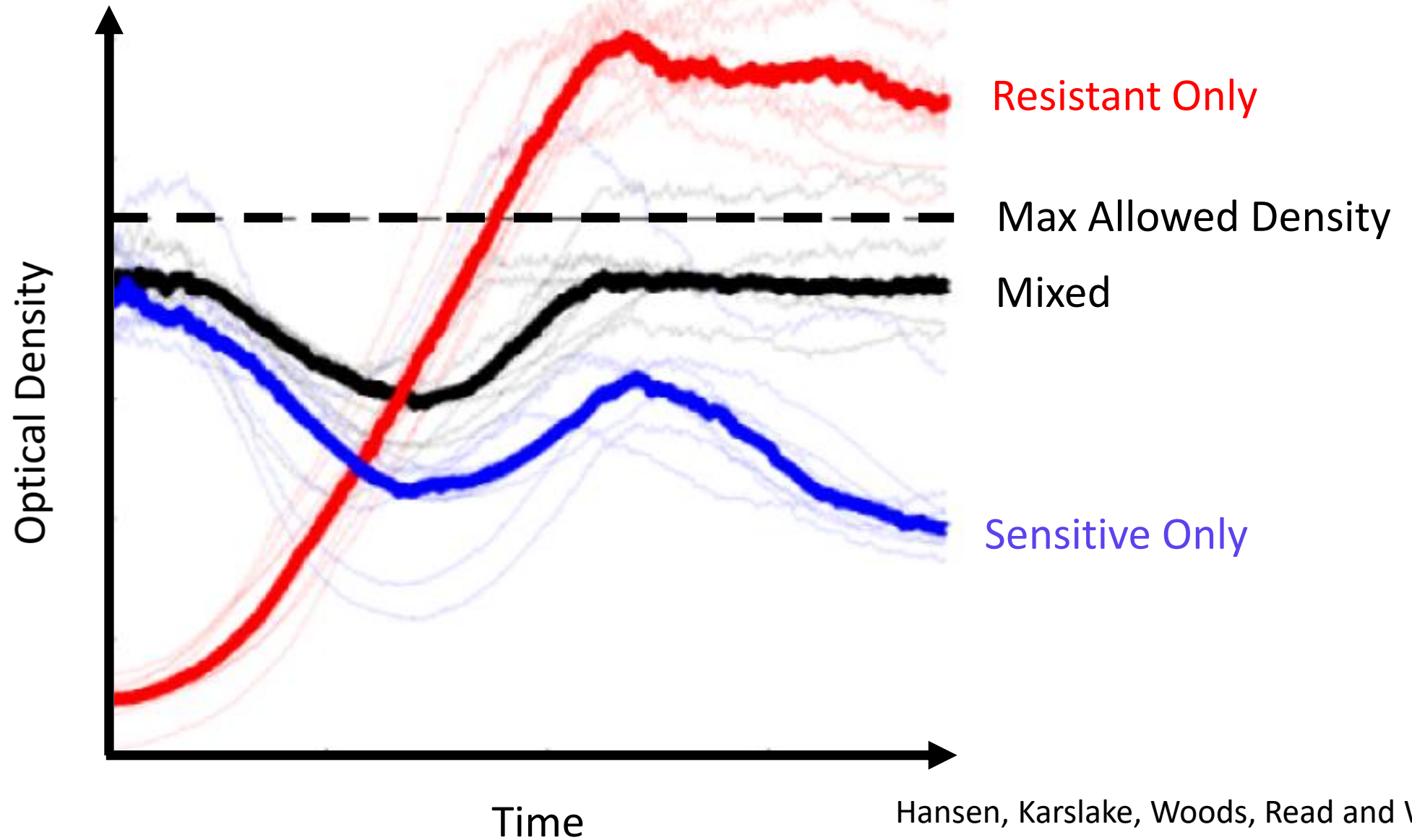
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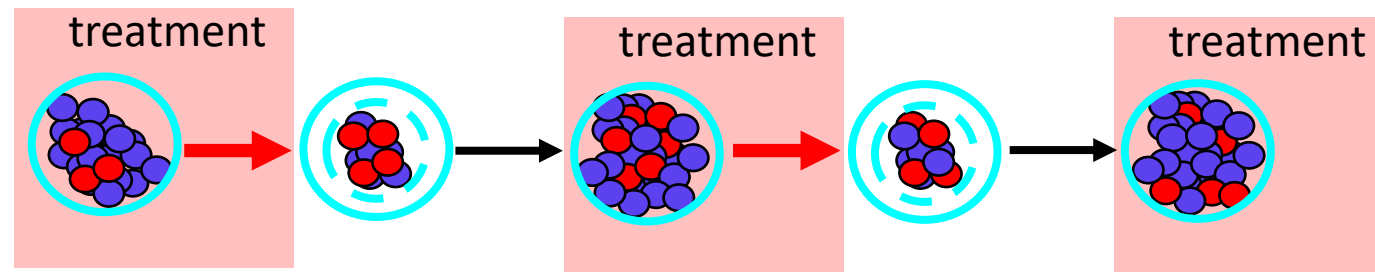


What is adaptive therapy?

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1. Treatment is **adaptive**: dosing depends on the actual tumor dynamics of each individual patient
2. Treatment leverages **competition**: deliberately maintains a sensitive population to slow the growth of the resistant population.

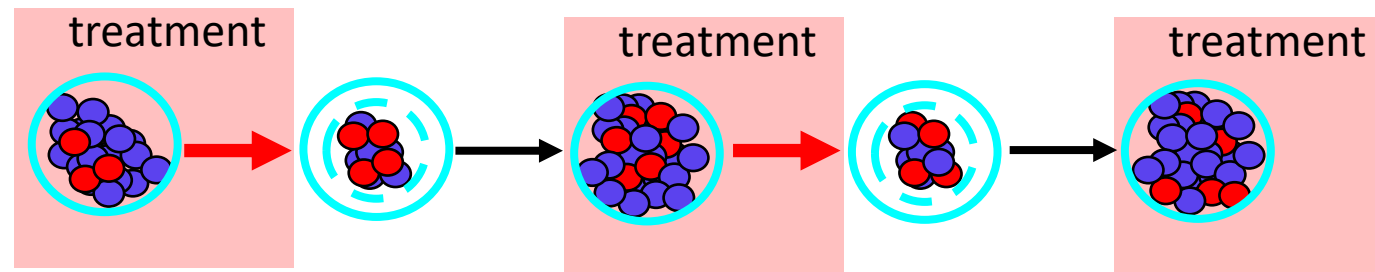
Adaptive Approach



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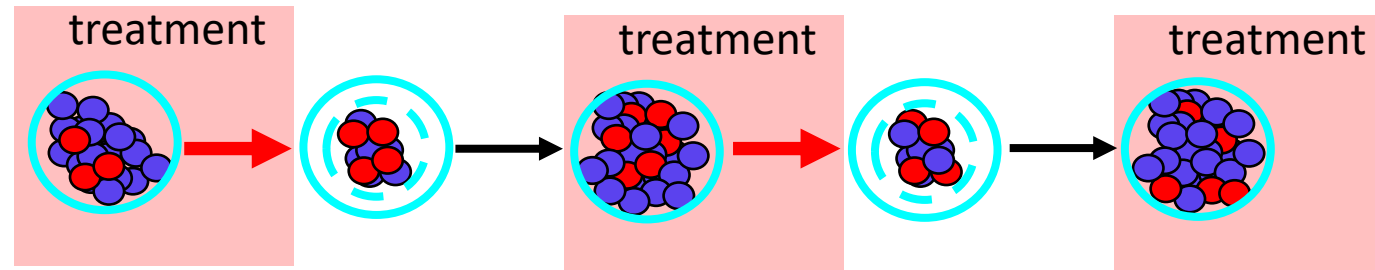
Adaptive Approach



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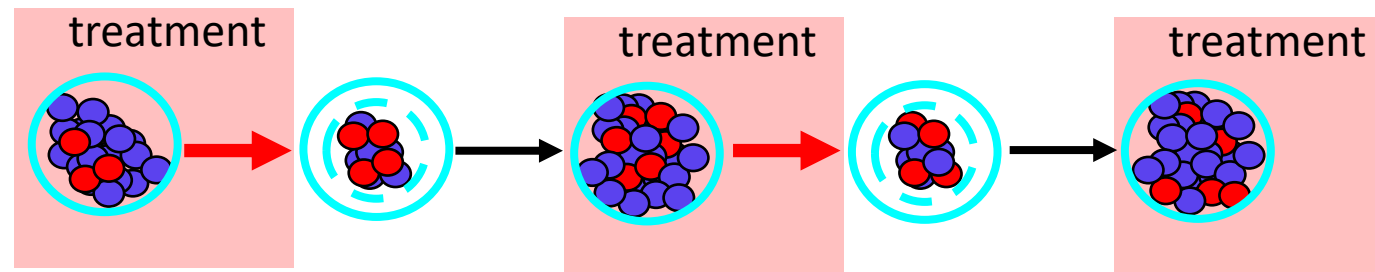
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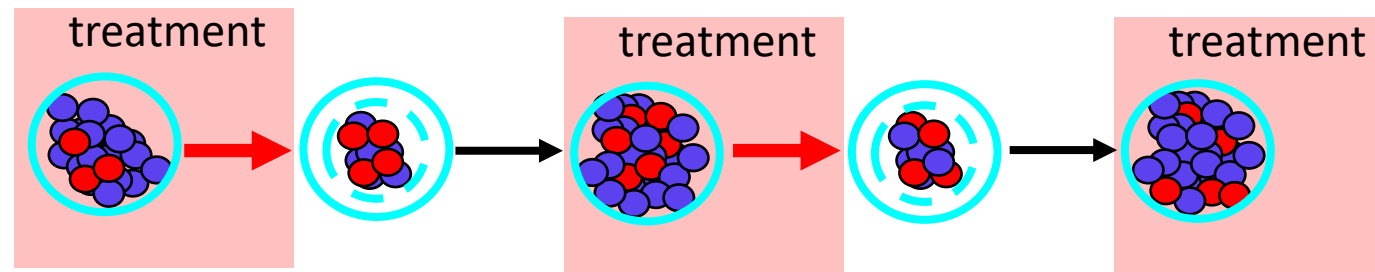
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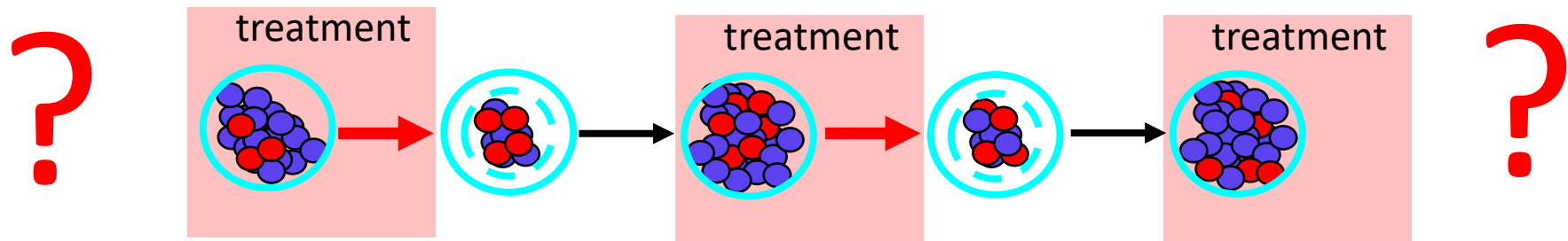
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Adaptive Approach



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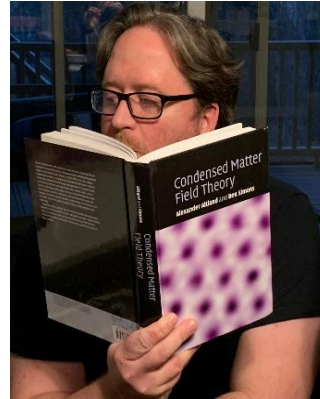
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University of Michigan



Jason Karstlake, PhD
University of Michigan



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University of Michigan