Do models matter? Establishing the conditions for adaptive therapy to control growth and delay emergence of resistance in cancer

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Acknowledgments

- U54 project: Andrea Bild, Jason Griffiths
- Prostate cancer: **Cassie Buhler**, **Rebecca Terry, Katie Link**
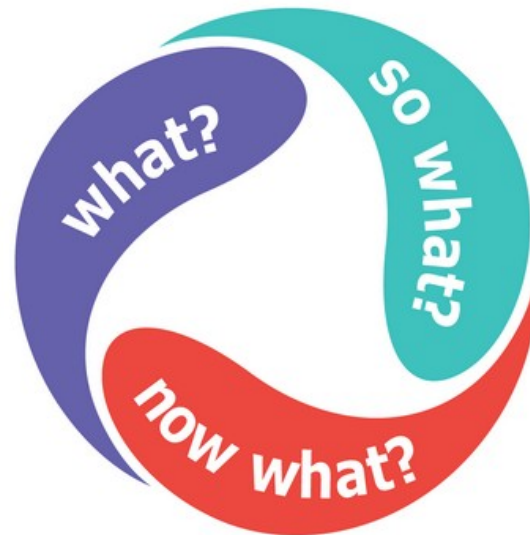- Cancer ecology: Deborah Gordon

Cassie Buhler

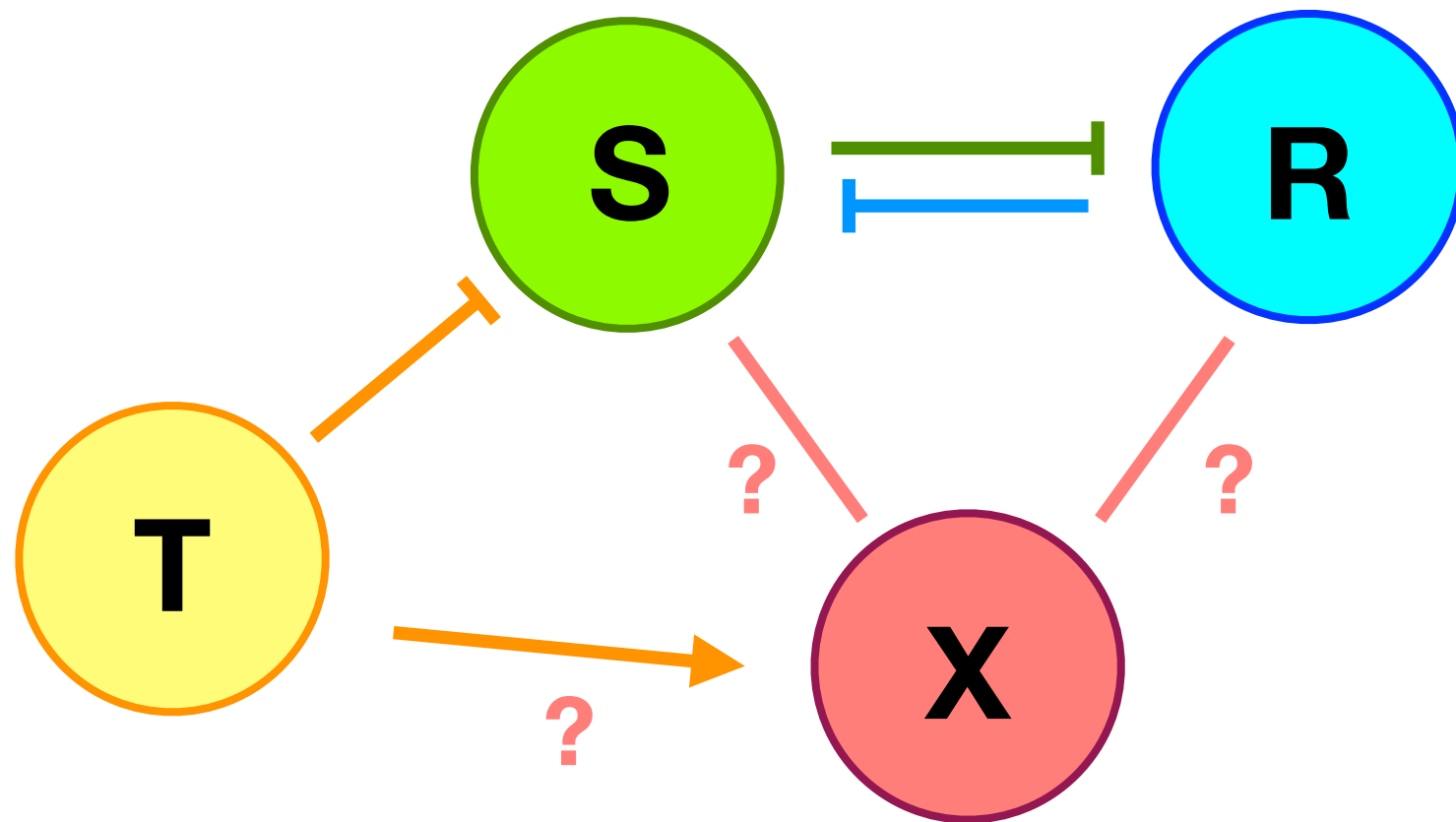No computers were harmed by the use of Microsoft products in creating this talk

Outline

- Modeling framework and special cases

- Comparative results

- Ruminations on modeling and treatment
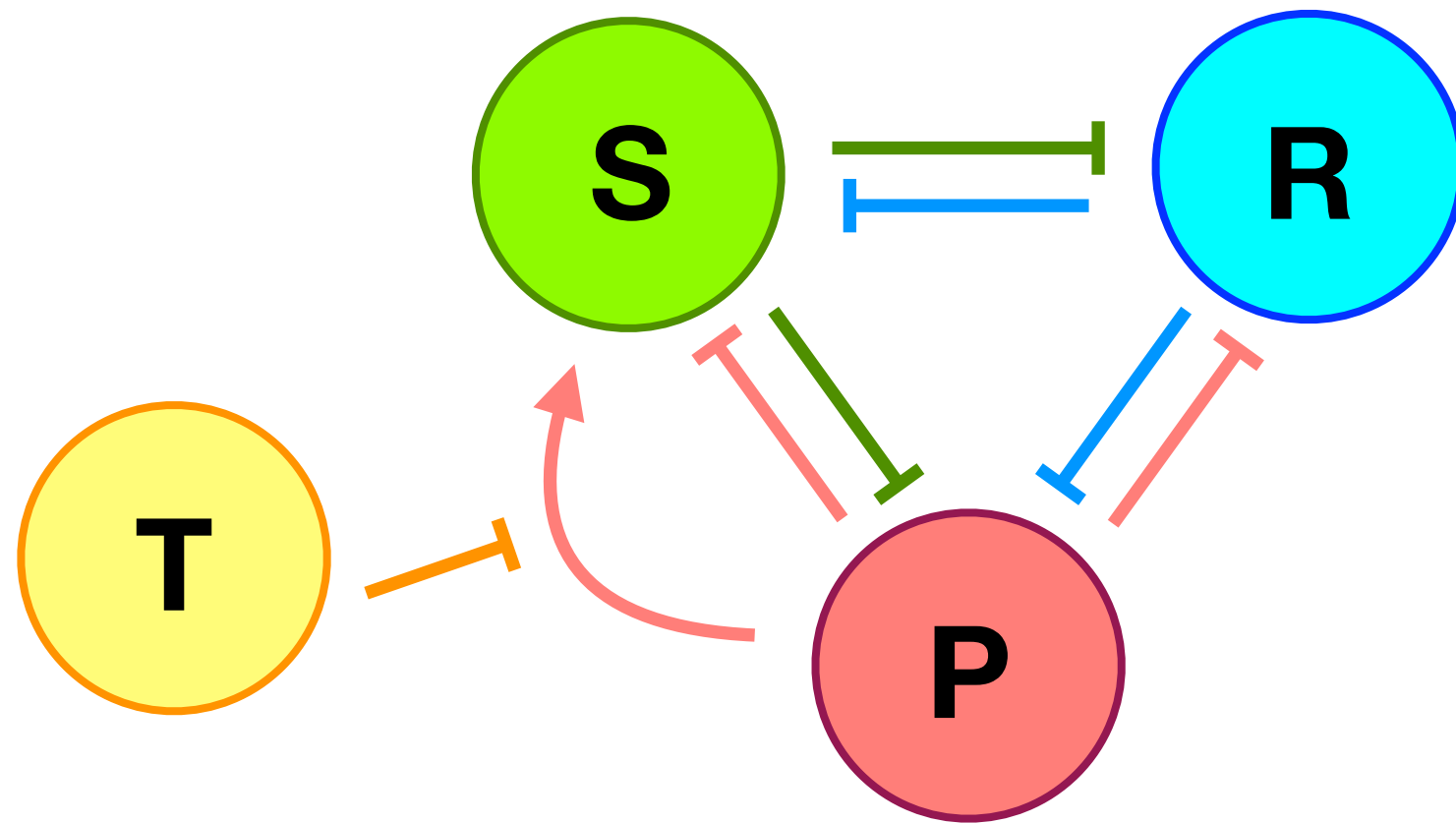
General model framework

- S: Sensitive cells
- R: Resistant cells
- T: Therapy
- X: Mediating factor

Goals

- Minimize cancer burden
- Delay resistance
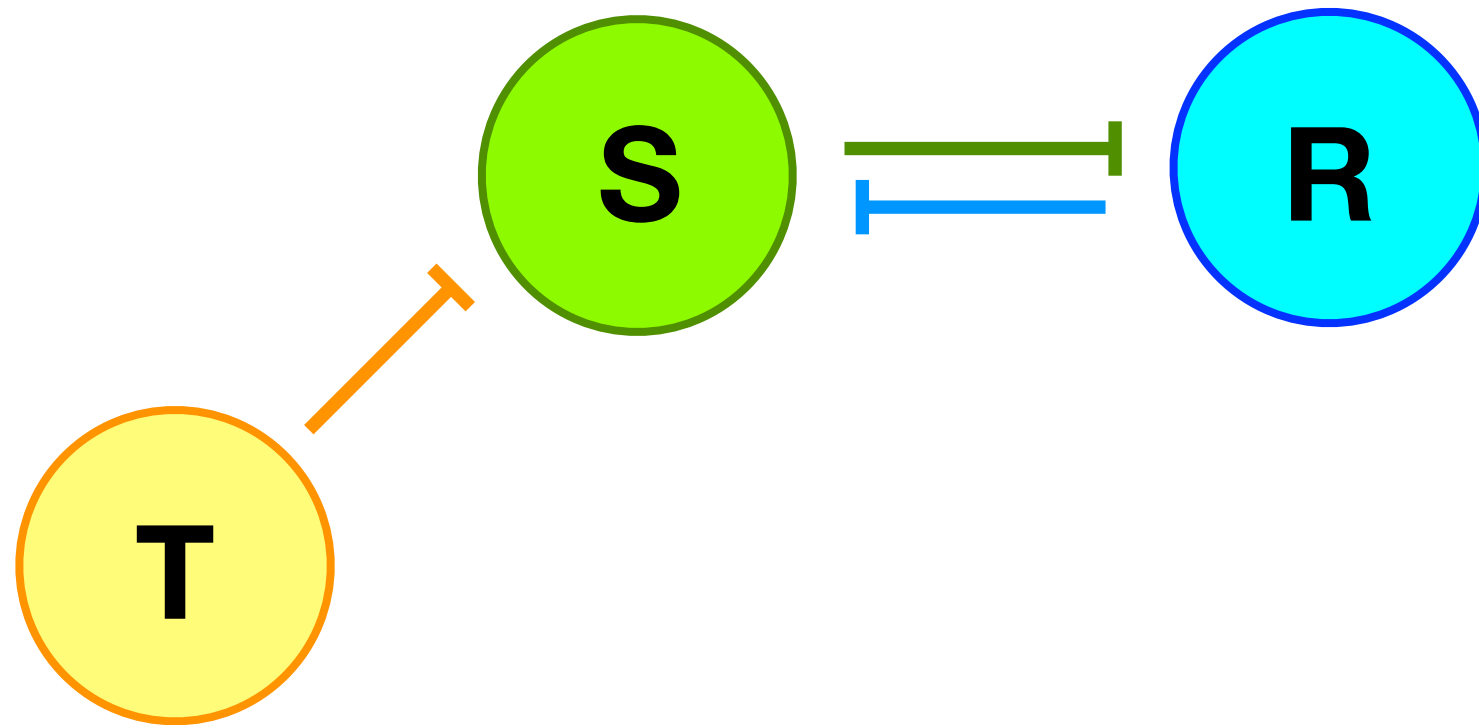- Minimize side effects

Zhang et al model

- S: Sensitive cells
- R: Resistant cells
- T: Therapy
- P: Producing cells

Key Assumptions

- Implicit androgen dynamics
- Sensitive cells dependent on producing cells
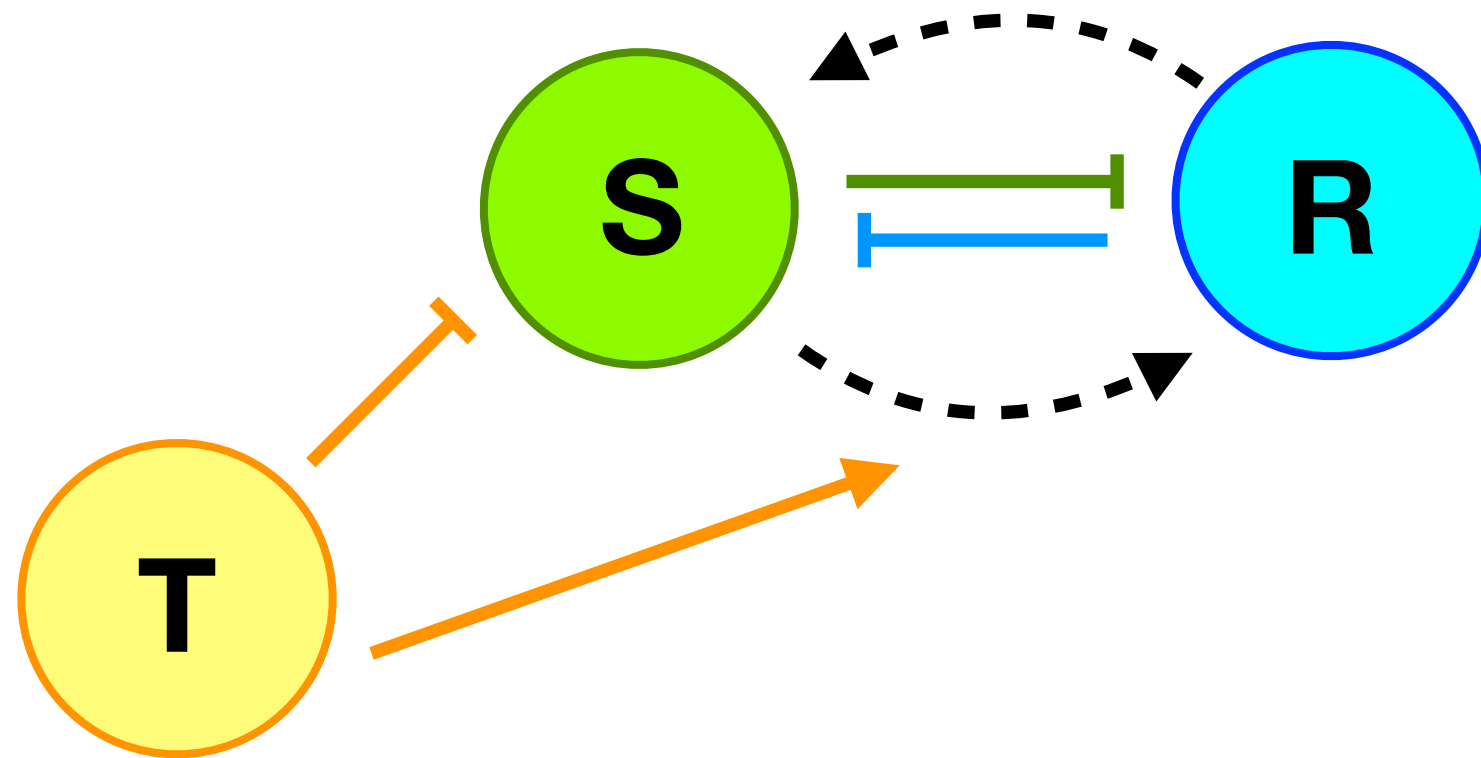- Rapid and strong drug effects

Vanilla Lotka-Volterra model

- S: Sensitive cells
- R: Resistant cells
- T: Therapy

Key Assumptions

- It's all about that competition
- Treatment increases death rate of cells
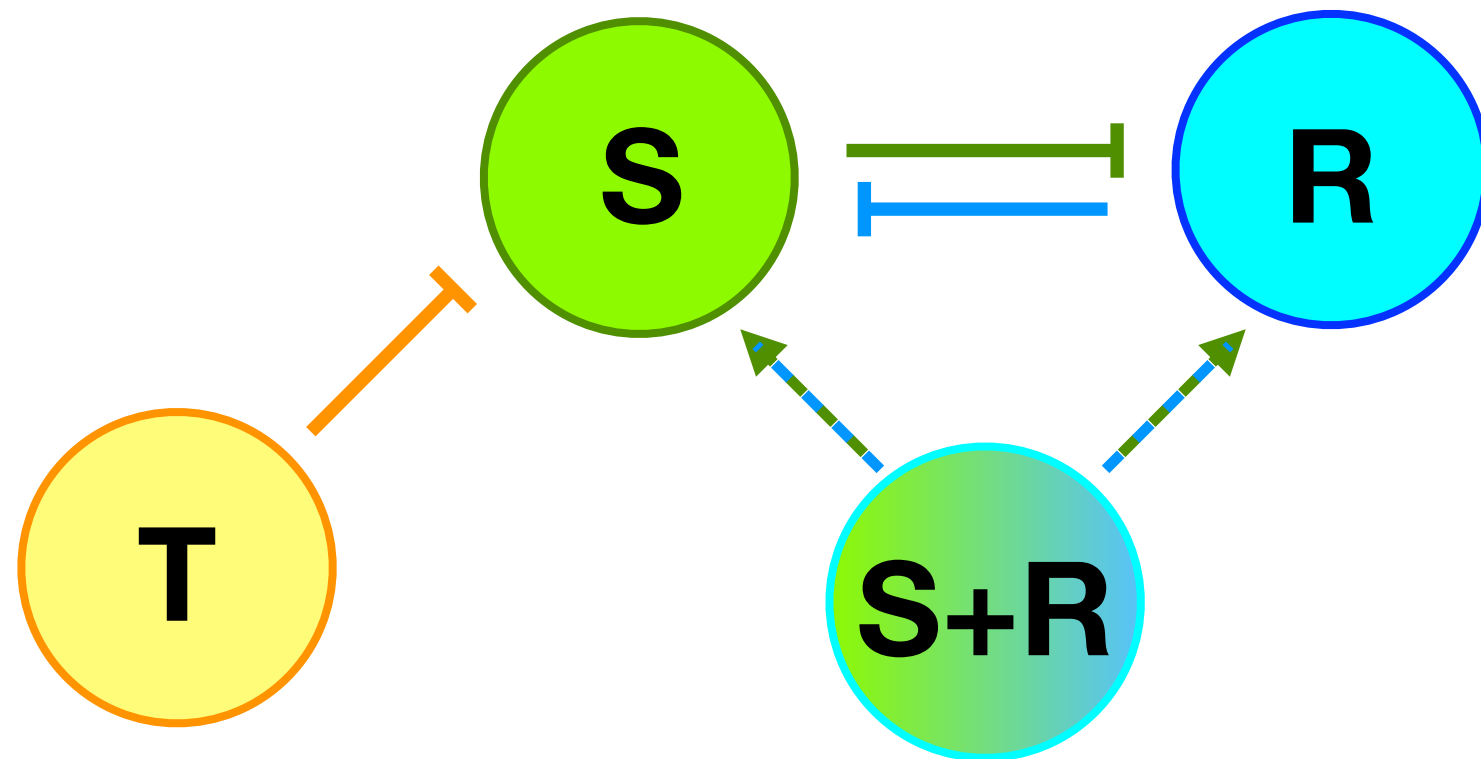
Lotka-Volterra model with plasticity

- S: Sensitive cells
- R: Resistant cells
- T: Therapy

Key Assumptions

- Cells can switch to resistant state when treated
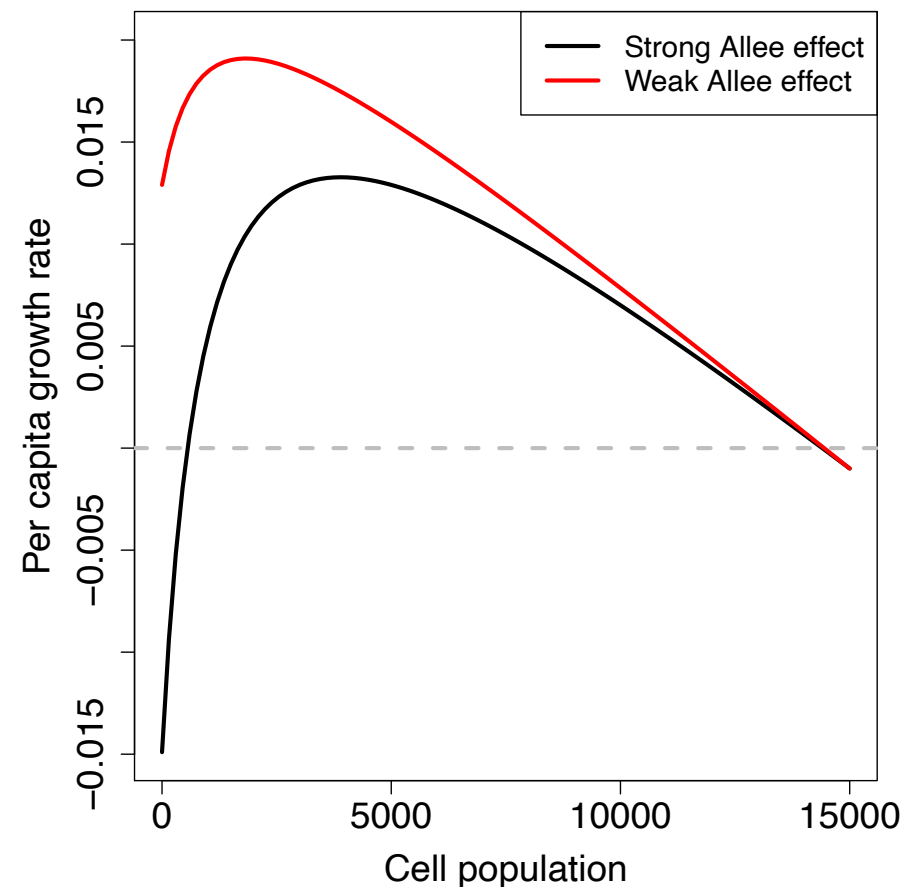- Cells may also switch back to avoid costs
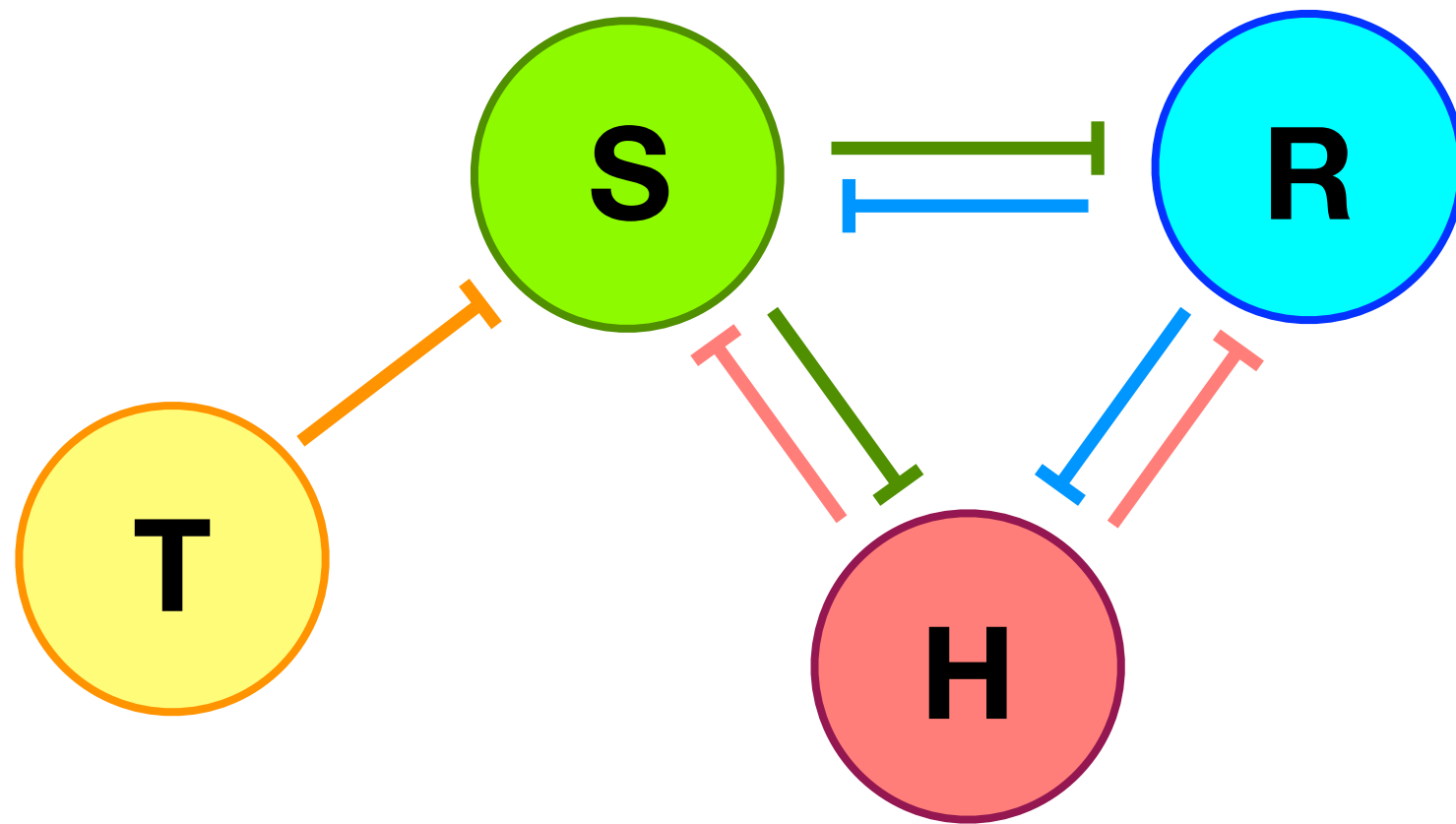
Lotka-Volterra model with Allee effect

- S: Sensitive cells
- R: Resistant cells
- T: Therapy

Key Assumptions

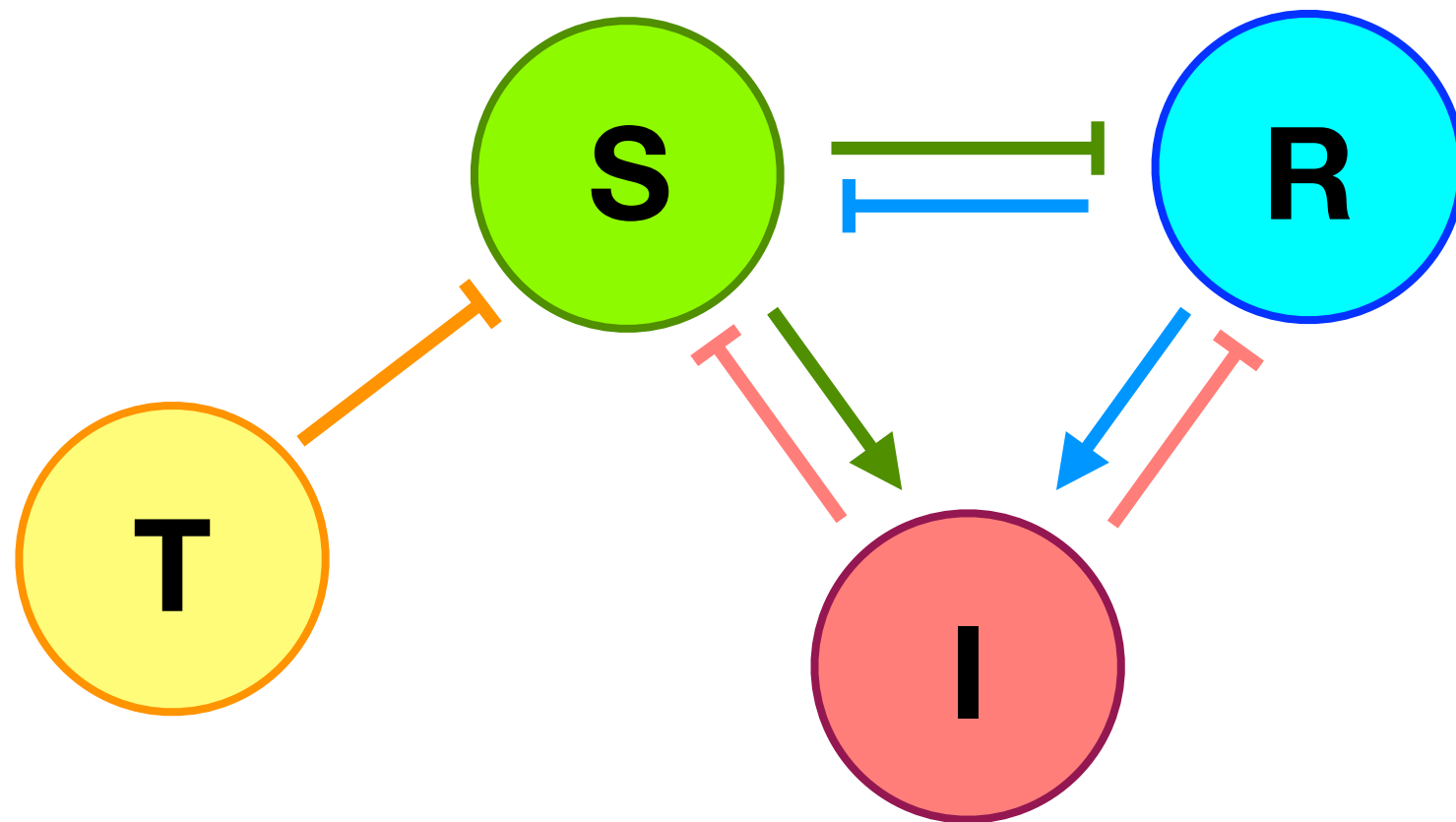- Allee effect: Cells facilitate growth when rare

Healthy cells model

- S: Sensitive cells
- R: Resistant cells
- T: Therapy
- H: Healthy cells

Key Assumptions

- Healthy cells compete with cancer cells
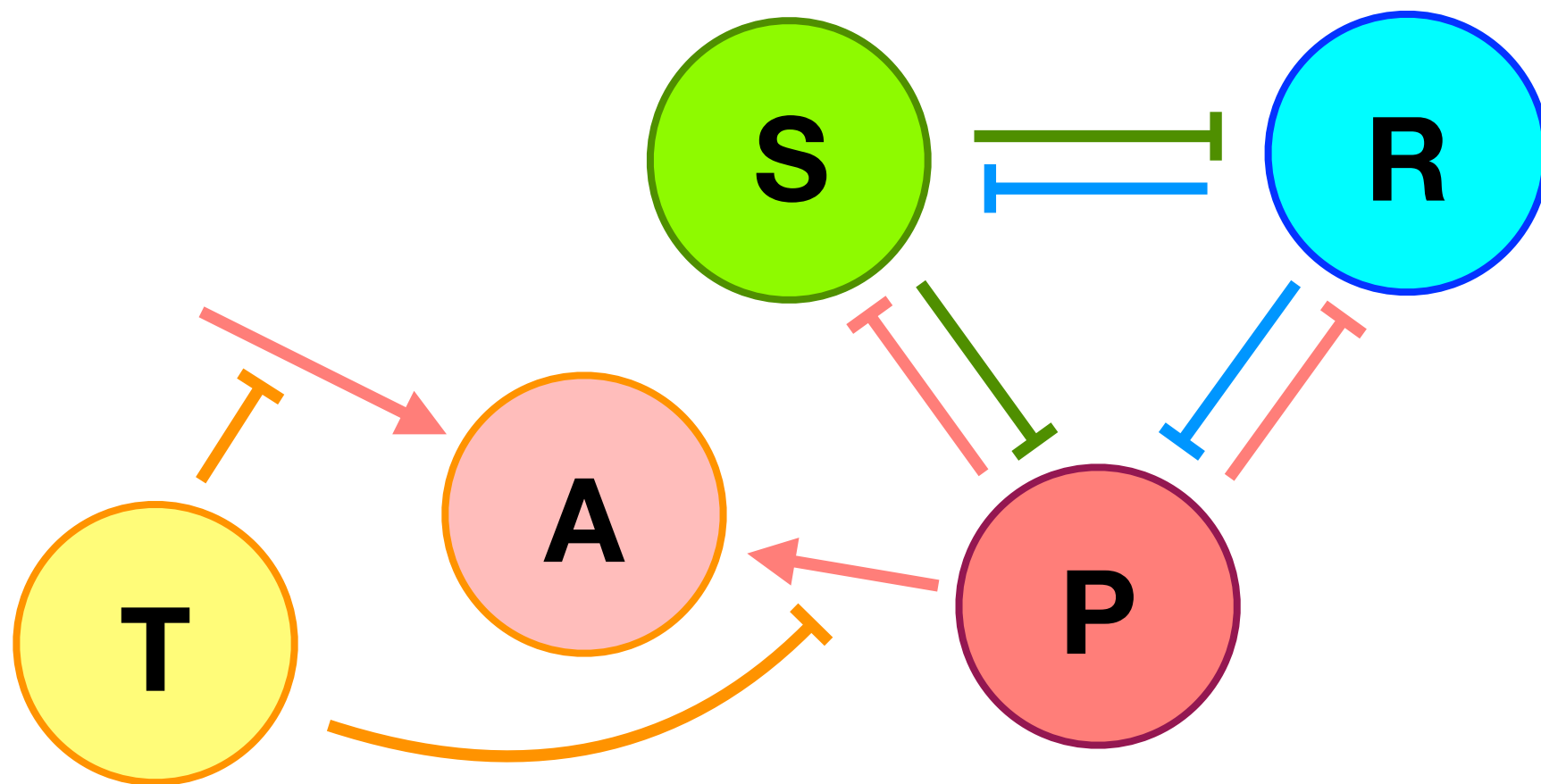- Healthy cells not affected by treatment

Immune cells model

- S: Sensitive cells
- R: Resistant cells
- T: Therapy
- I: Immune cells

Key Assumptions
- Immune cells control cancer cells
- Immune cells not affected by treatment

Mechanistic androgen model

- S: Sensitive cells
- R: Resistant cells
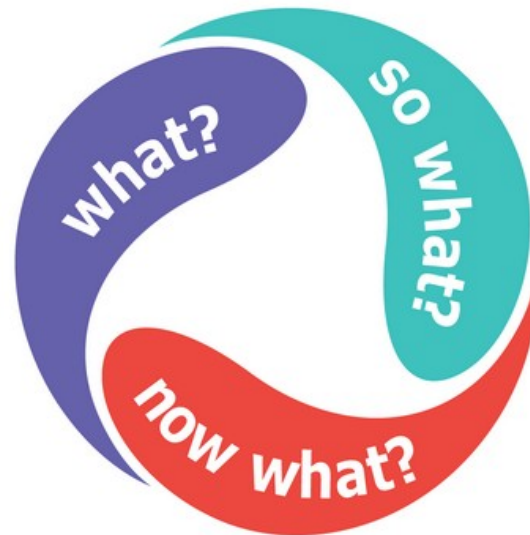- T: Therapy
- P: Producing cells
- A: Androgen

Key Assumptions

- Explicit androgen dynamics in steady state
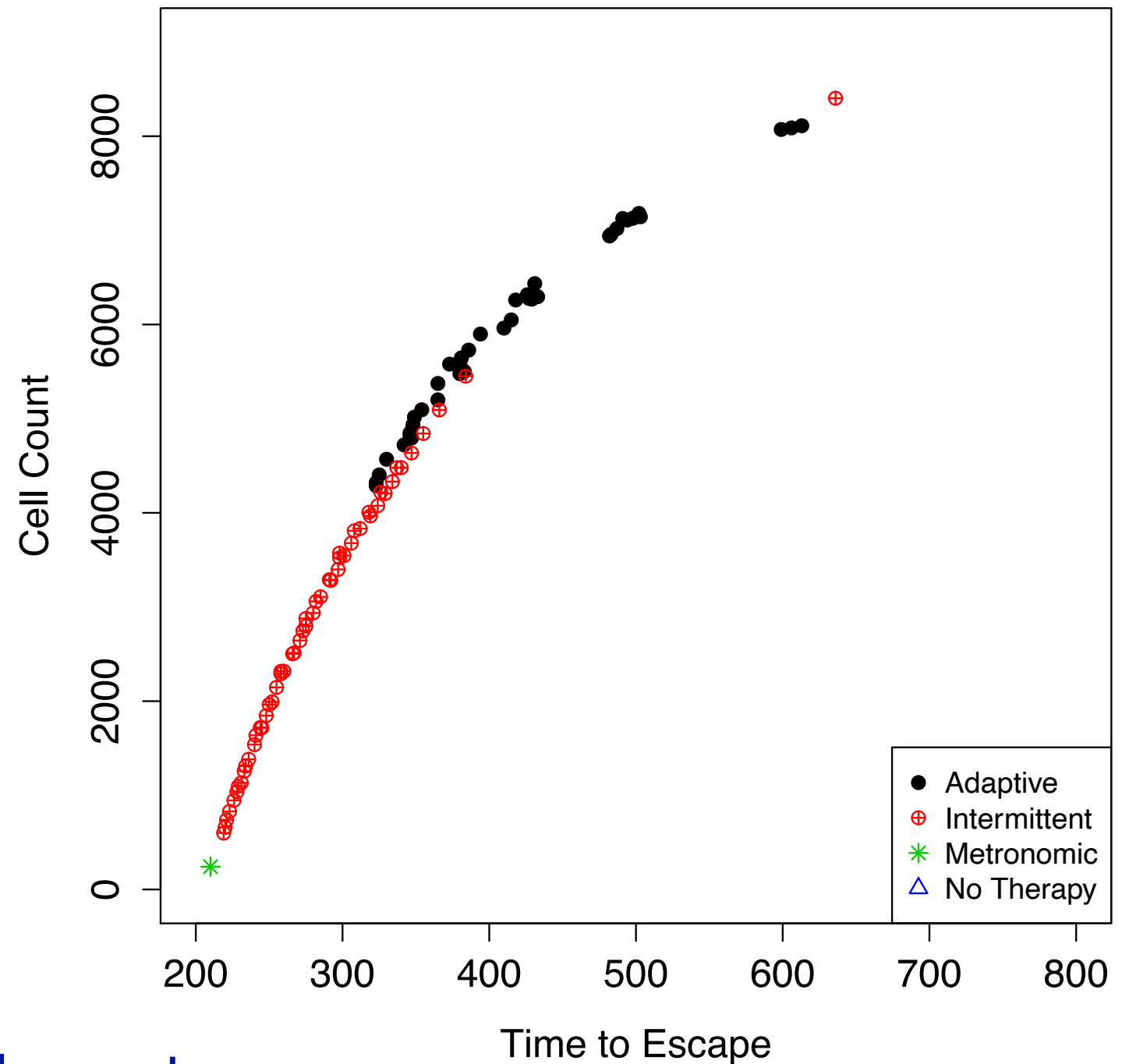- Two sources of androgen
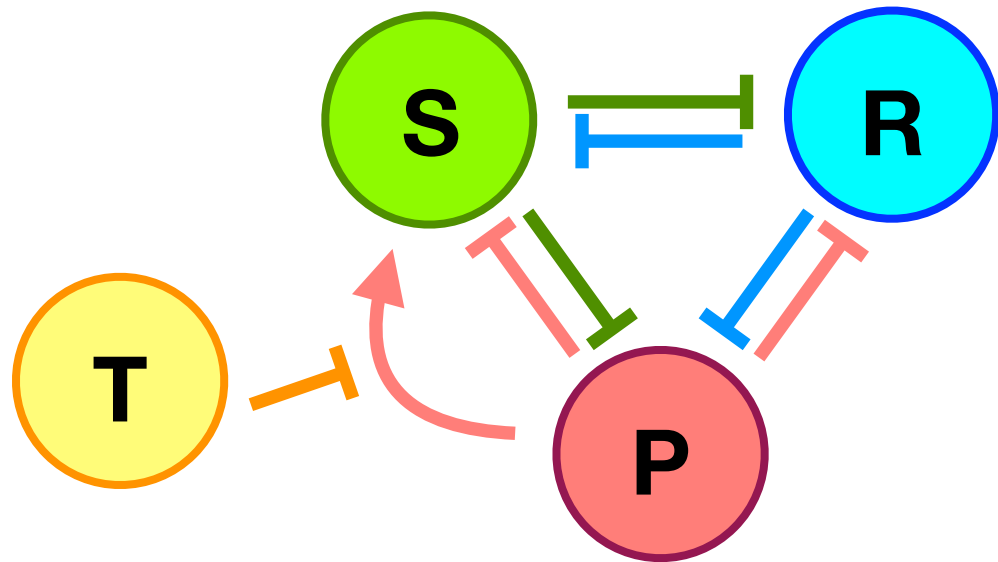- More realistic drug effects

Outline

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- Comparative results

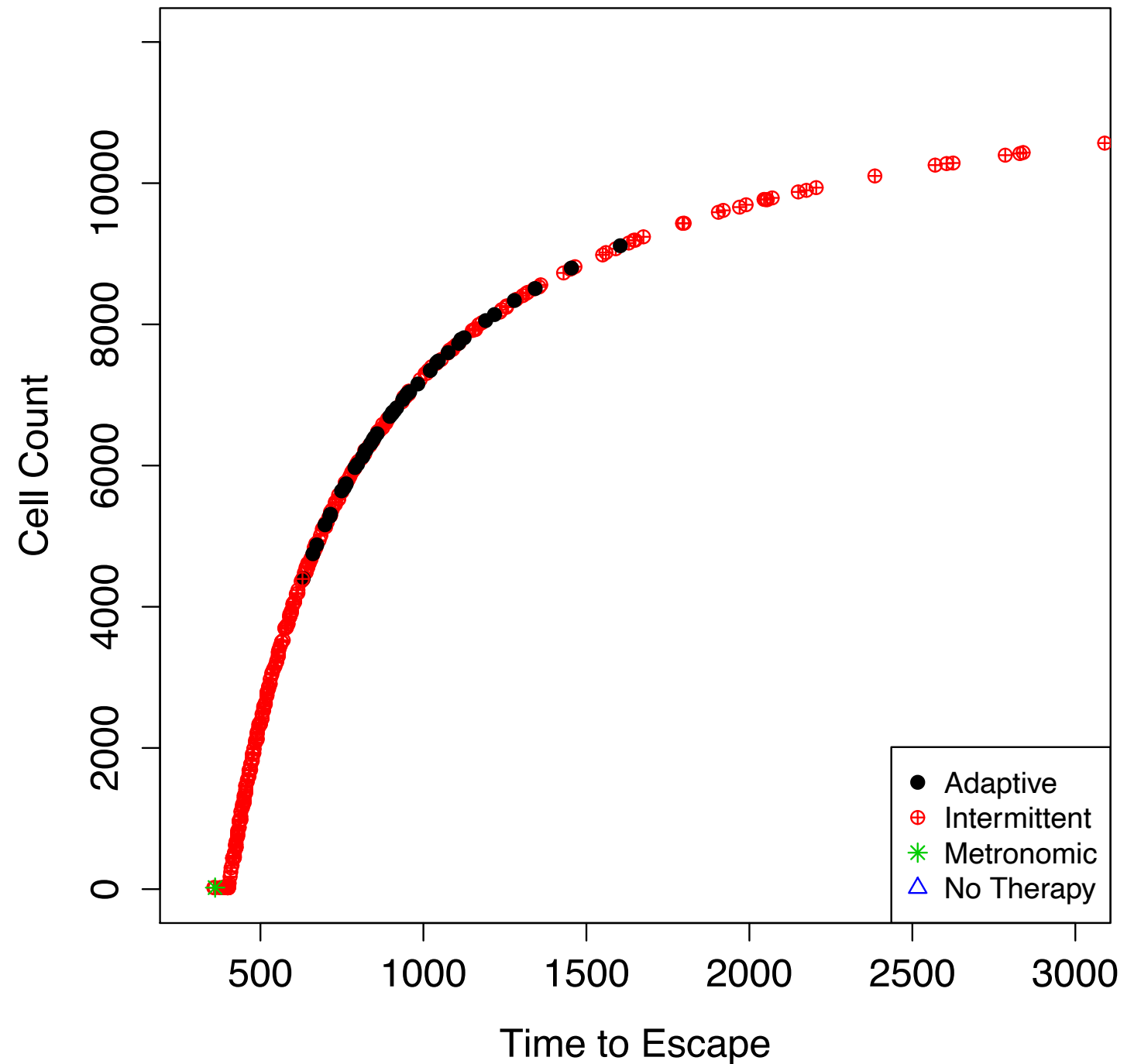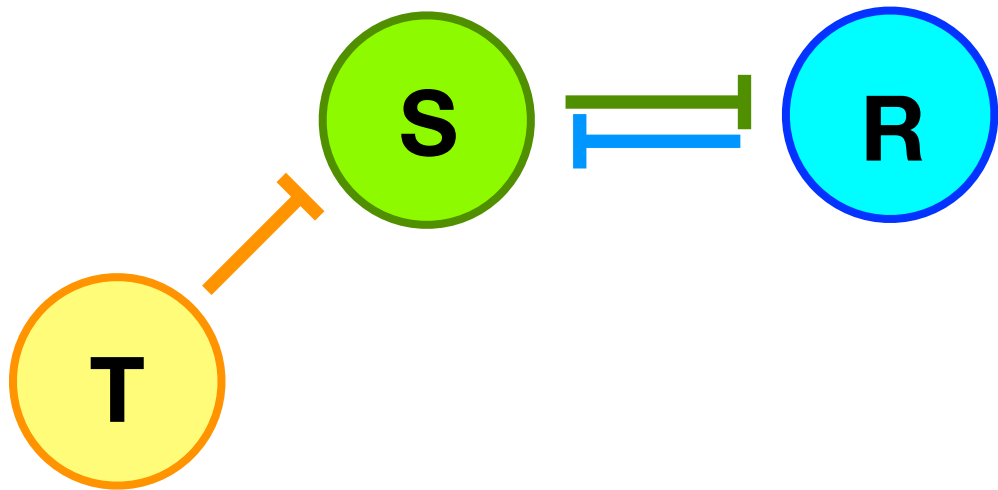- Ruminations on modeling and treatment
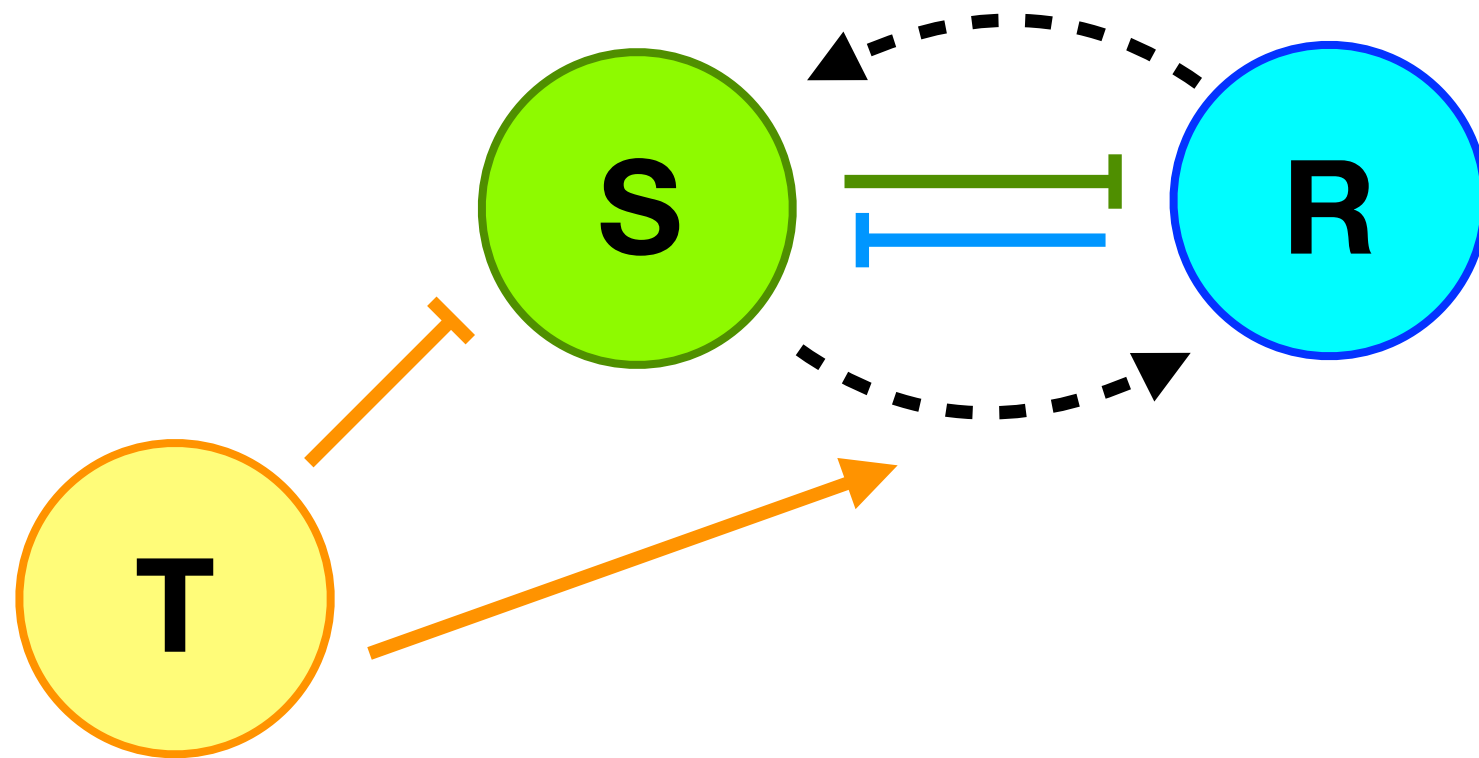
Zhang et al model

- Tight tradeoff between and cell count
- Adaptive and intermittent follow same tradeoff
- Resistance never emerges without therapy

Vanilla Lotka-Volterra model

- Similar tradeoff
- Results more extreme with these parameters
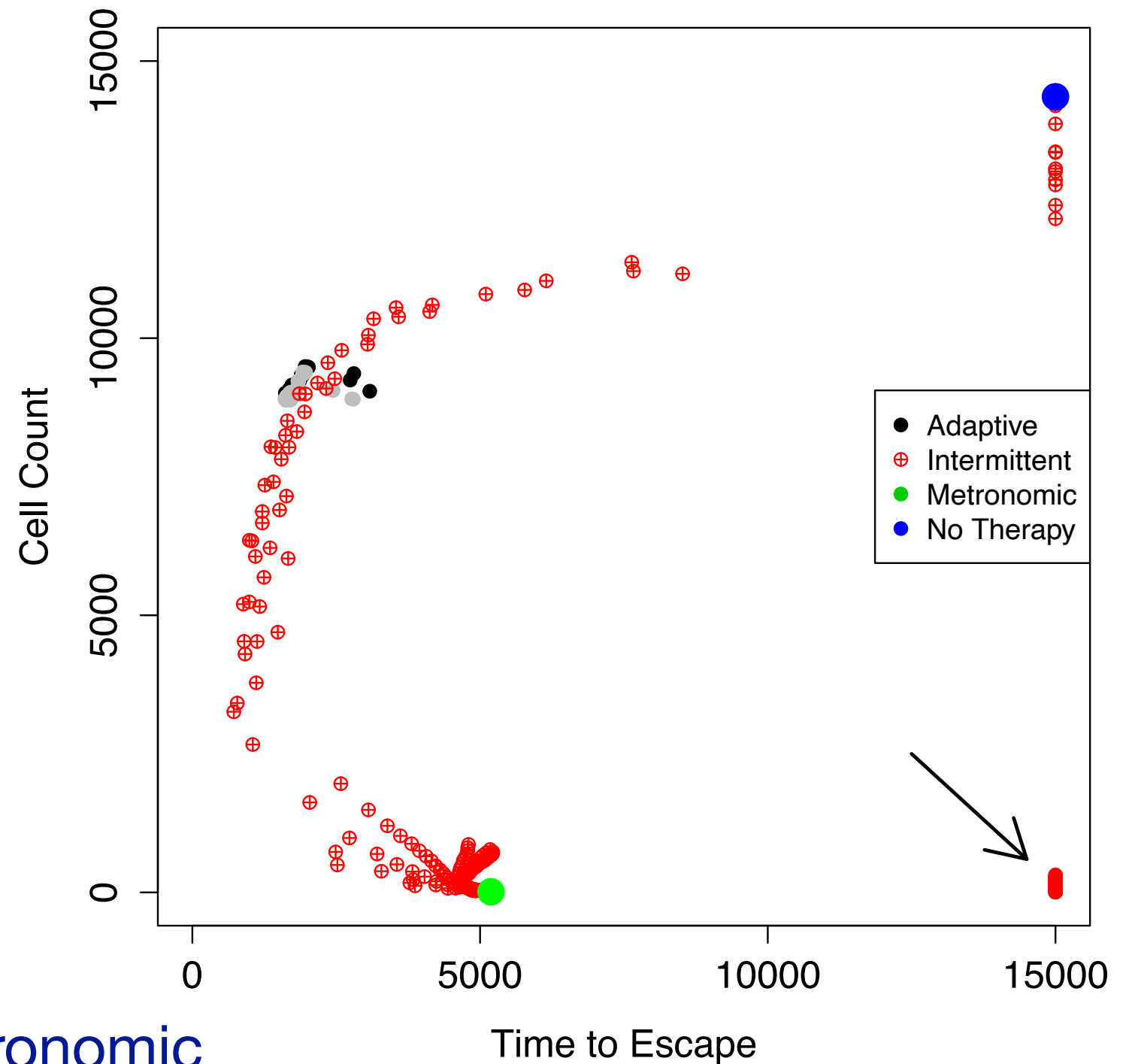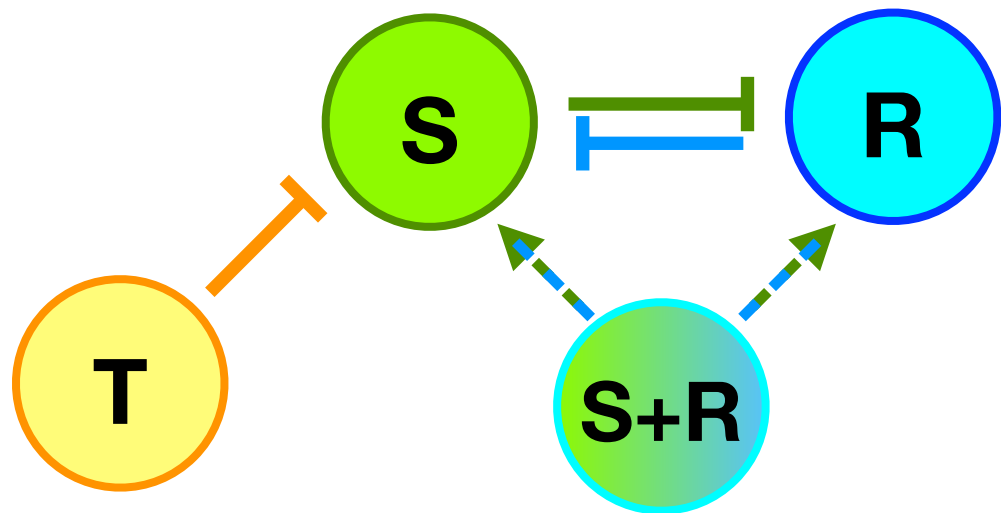- Resistance never emerges without therapy

Lotka-Volterra model with plasticity

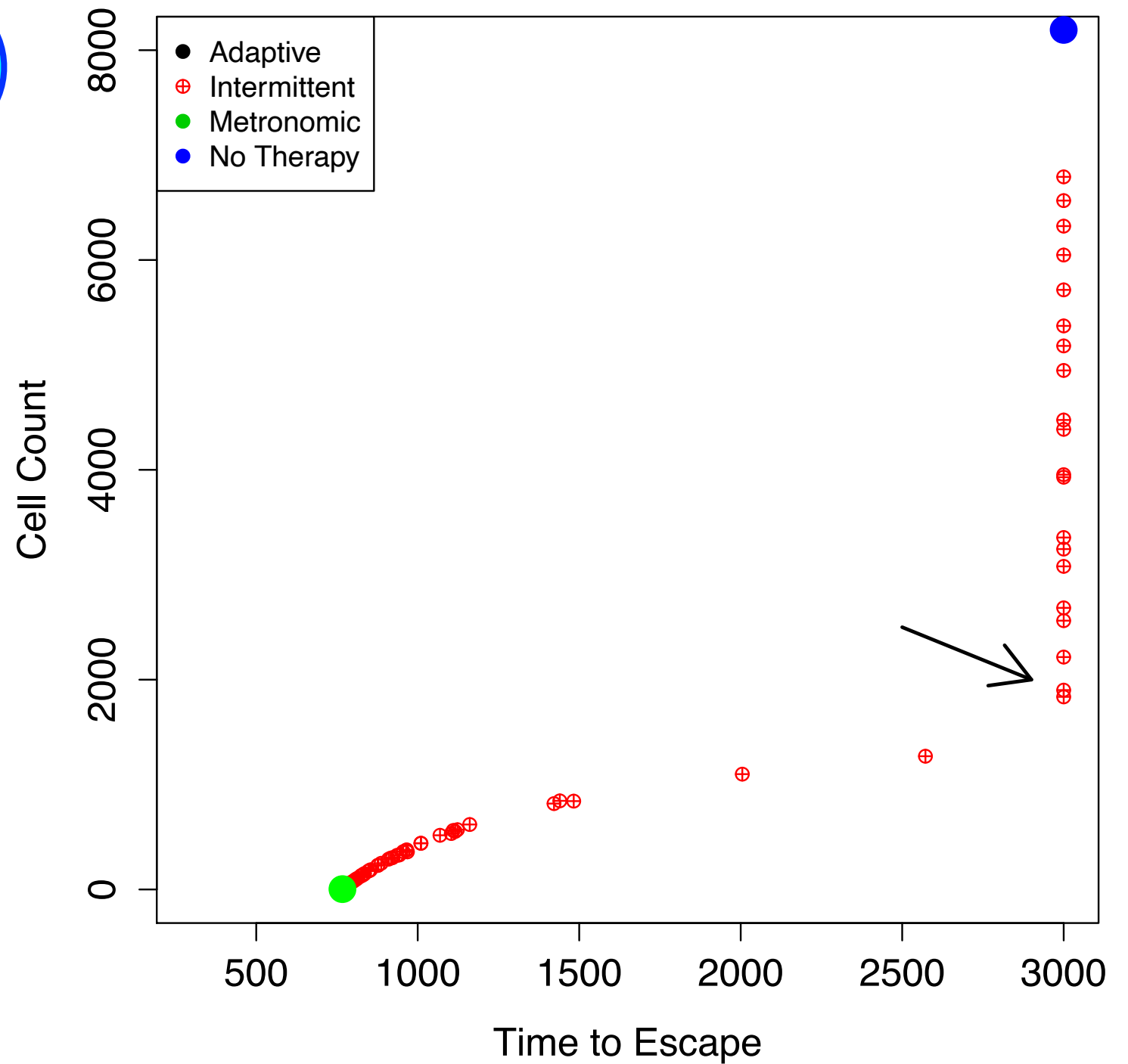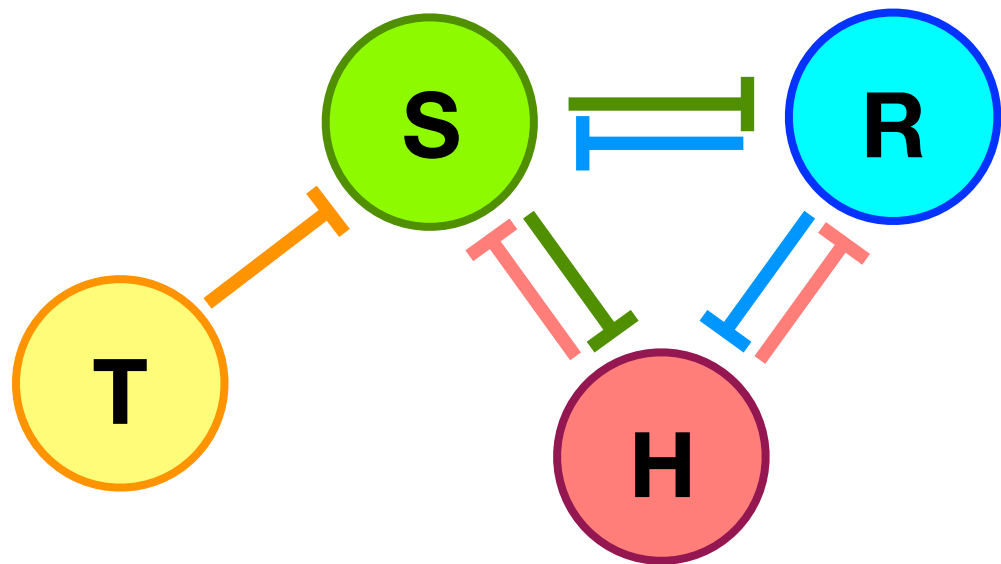- S: Sensitive cells
- R: Resistant cells
- T: Therapy

- Nothing to show: escape is instantaneous
- Managing behavior is harder than managing population dynamics
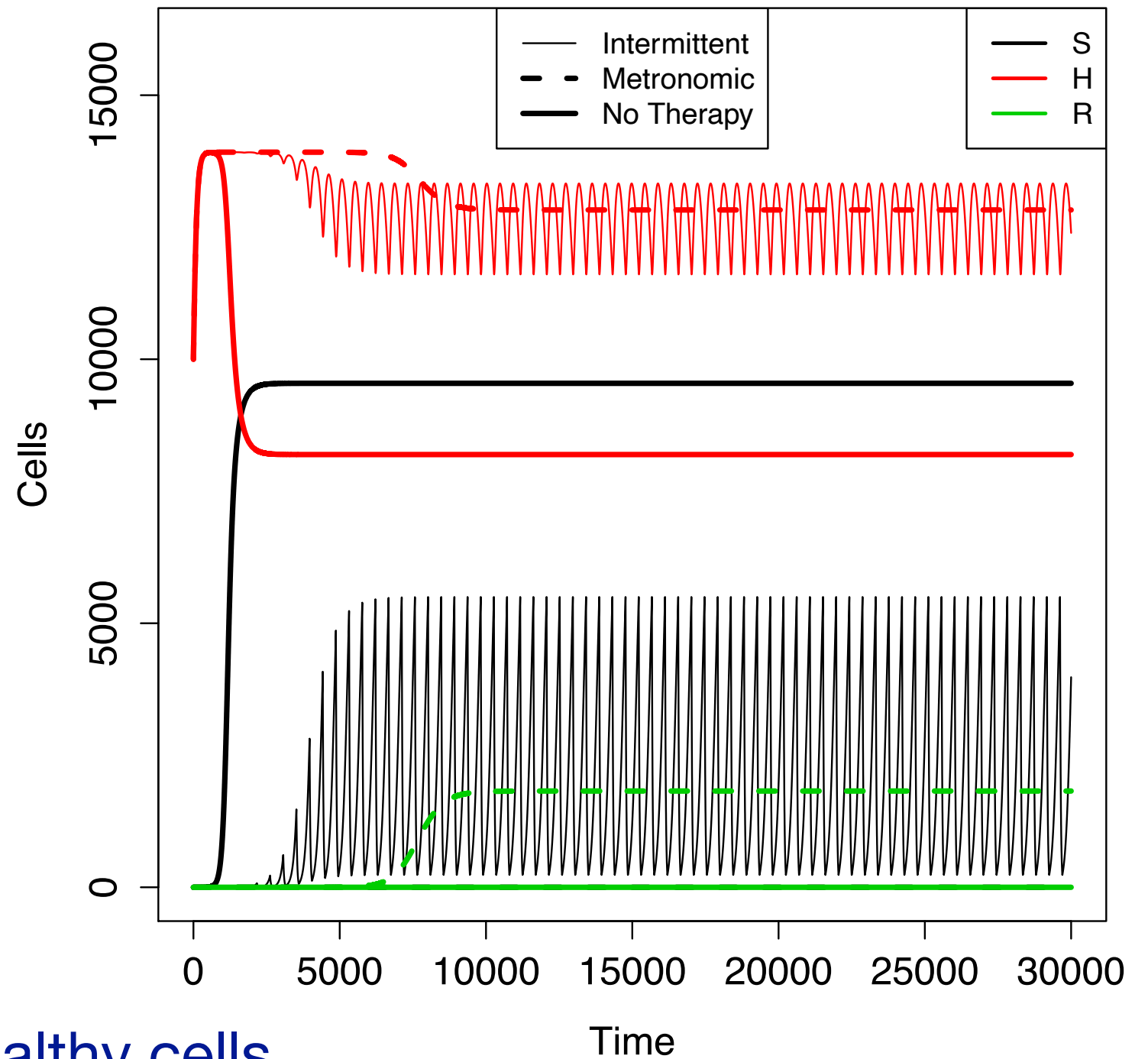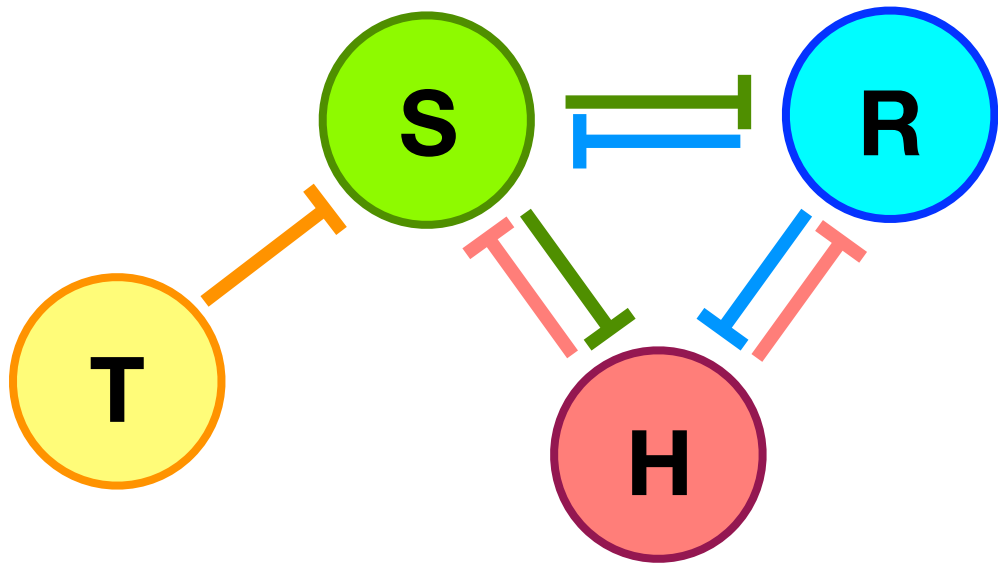
Lotka-Volterra model with Allee effect

- Enough therapy acts like metronomic
- With our parameters, Allee effect can prevent escape
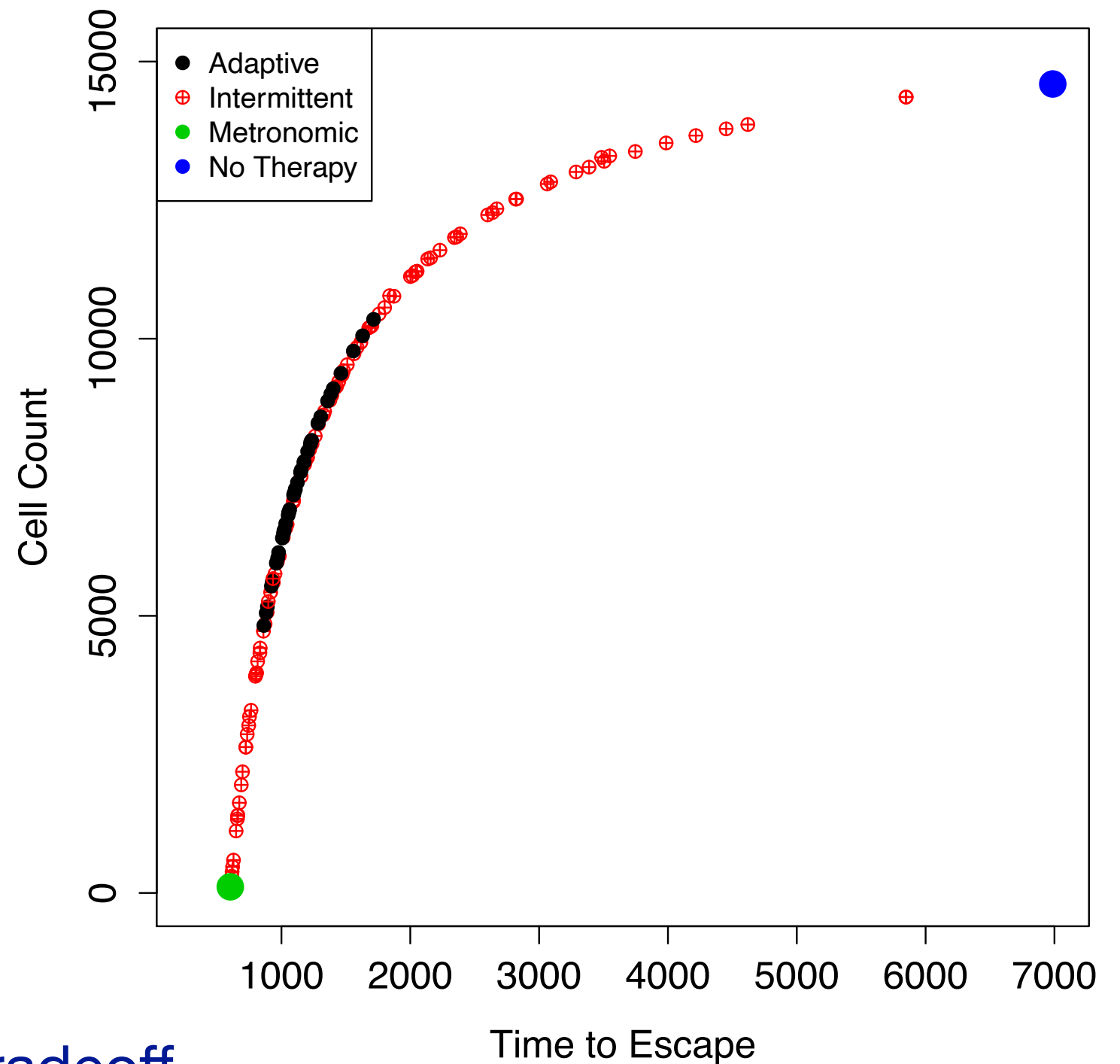- Resistance never emerges without therapy
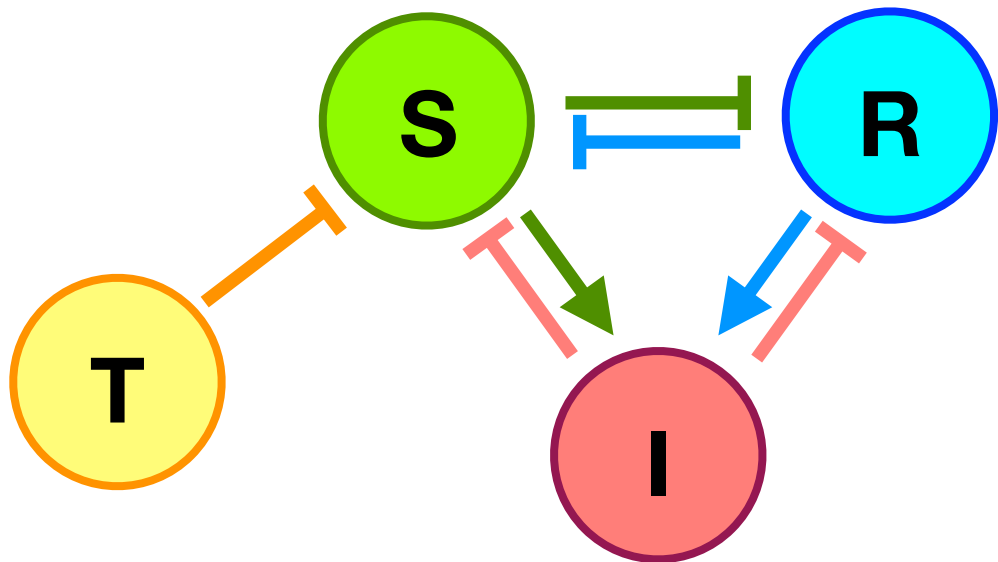
Healthy cells model

- Tradeoff still apparent
- Appropriate intermittent strategies maintain healthy cell population
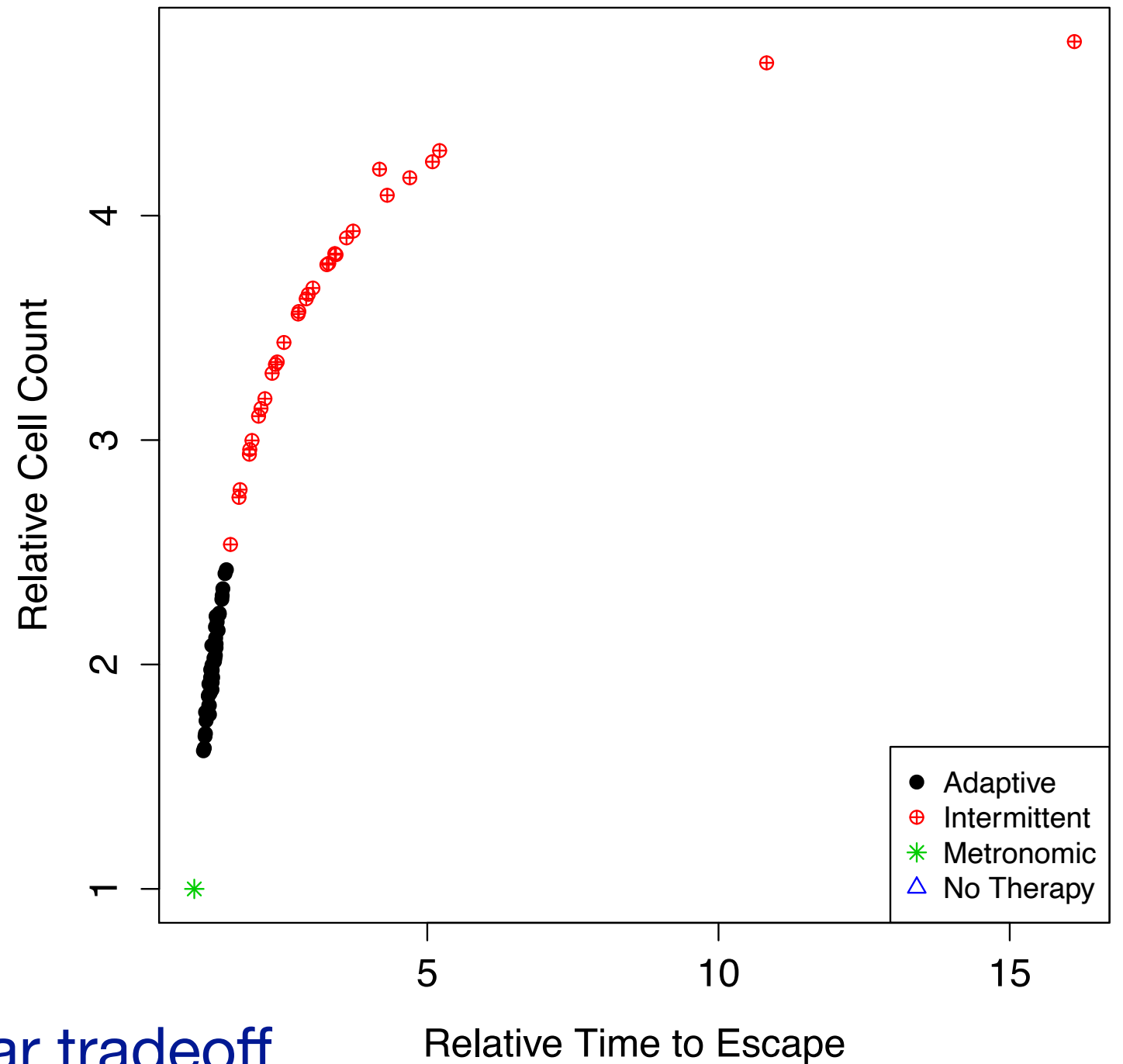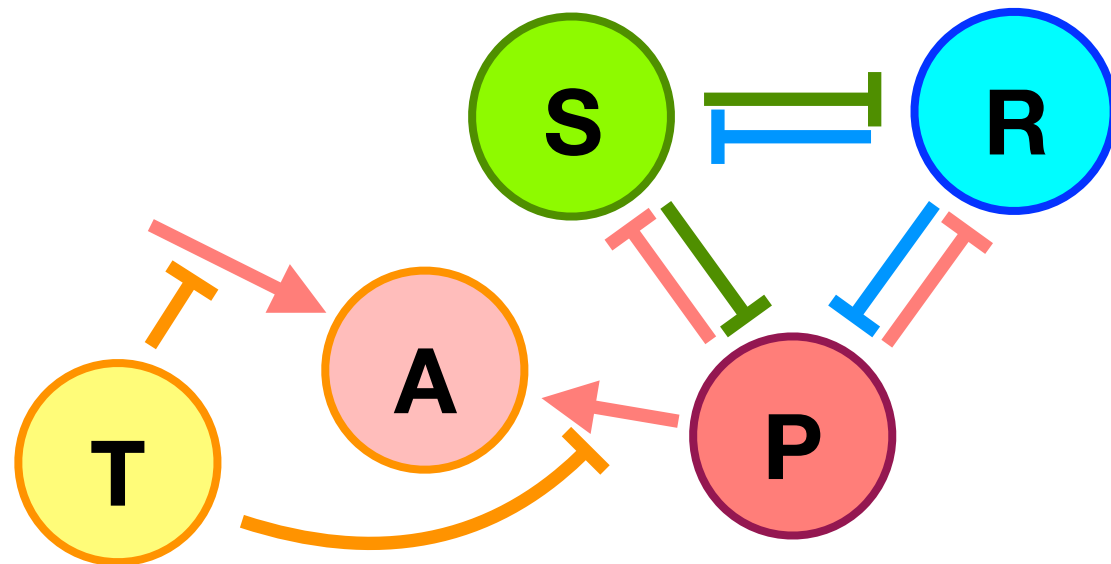
Healthy cells model

- Optimal strategy maintains healthy cells
- Excessive treatment releases resistant cells

Immune cells model

- Therapies follow the familiar tradeoff
- Resistance never emerges without therapy

Mechanistic androgen model

- Both therapies follow the familiar tradeoff
- Order switched from Lotka-Volterra family models
- Resistance never emerges without therapy

What does this have to do with COVID?

- Ecology: The study of population regulation: Where's the density dependence?
- Evolution: Driven by that density dependence
- SARS-CoV2: Minimal density dependence and currently rather little evolution
- Cancer: Different mechanisms of density dependence demand different treatments, and rapidly growing metastases may not be

gethealthystayhealthy.com
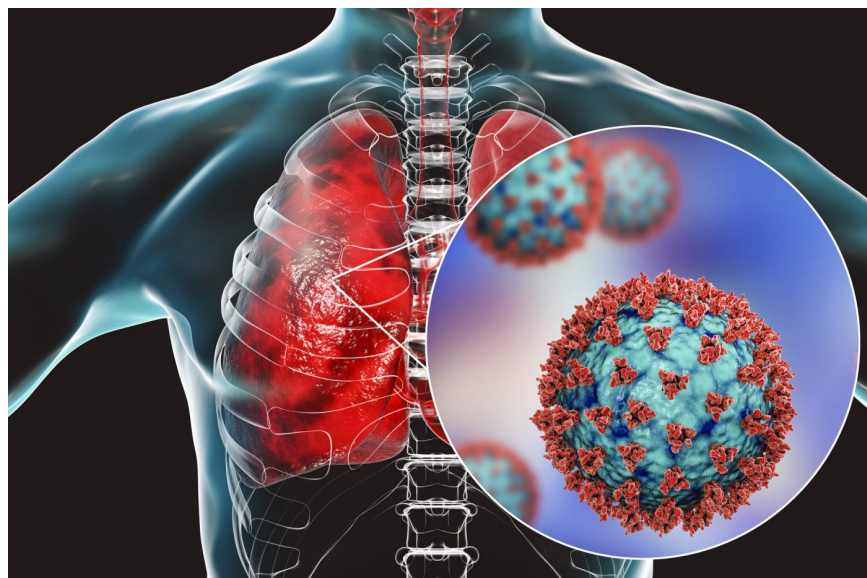
clinicalomics.com
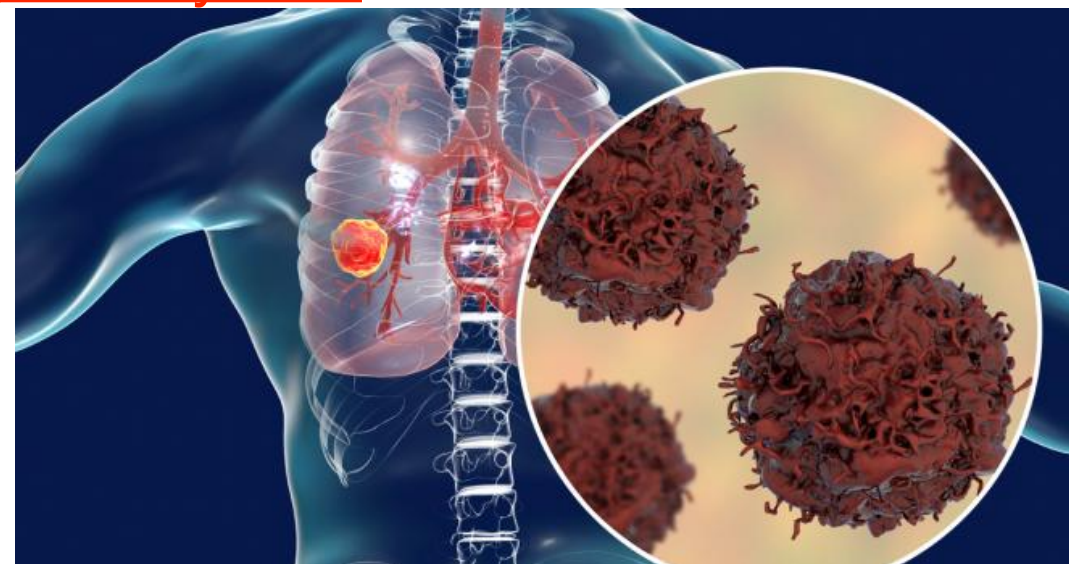
Models and treatment

- For models of this class
  a. Adaptive therapy and intermittent therapy give the same results
  b. Optimal strategy depends on the structure of the system
- Why adaptive therapy might be better than this looks
  c. It naturally adjusts to patient parameters
  d. We need to understand mechanisms of interaction to find the right target therapy levels
  e. Integrating models with in vivo and in vitro data is key