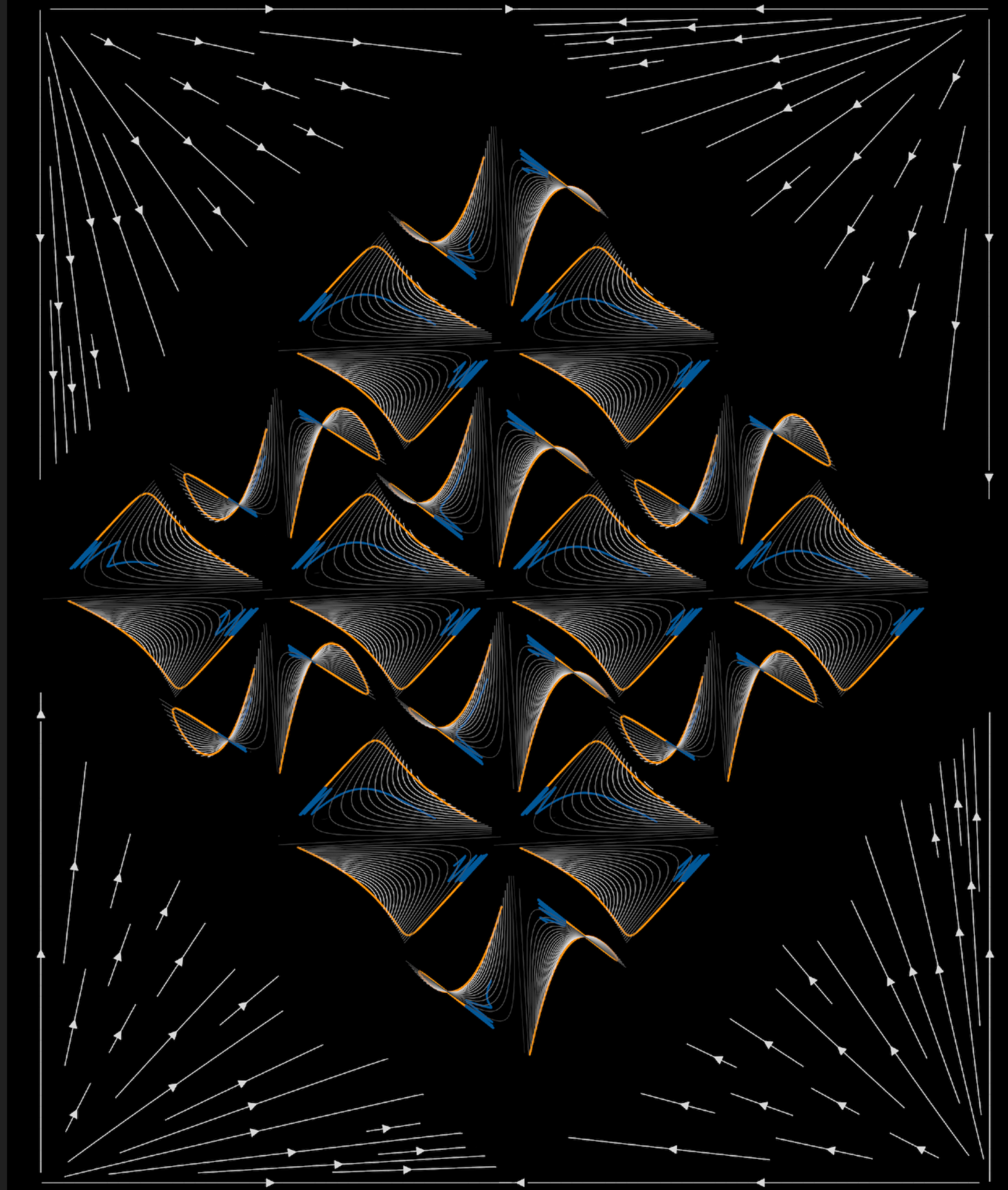
Spatial structure impacts adaptive therapy by shaping intra-tumoral competition

Maximilian Strobl



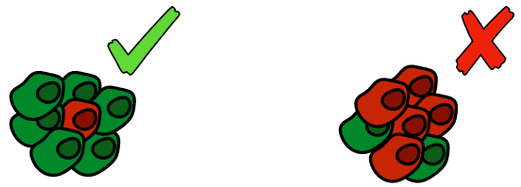
@StroblMAR

UNIVERSITY OF OXFORD

MOFFITT CANCER CENTER

AT Selection Criteria

Important Factors in AT

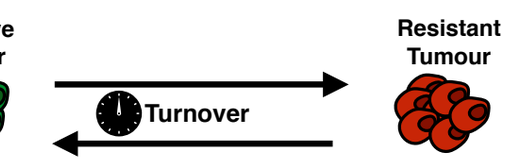


1. Initial resistance fraction

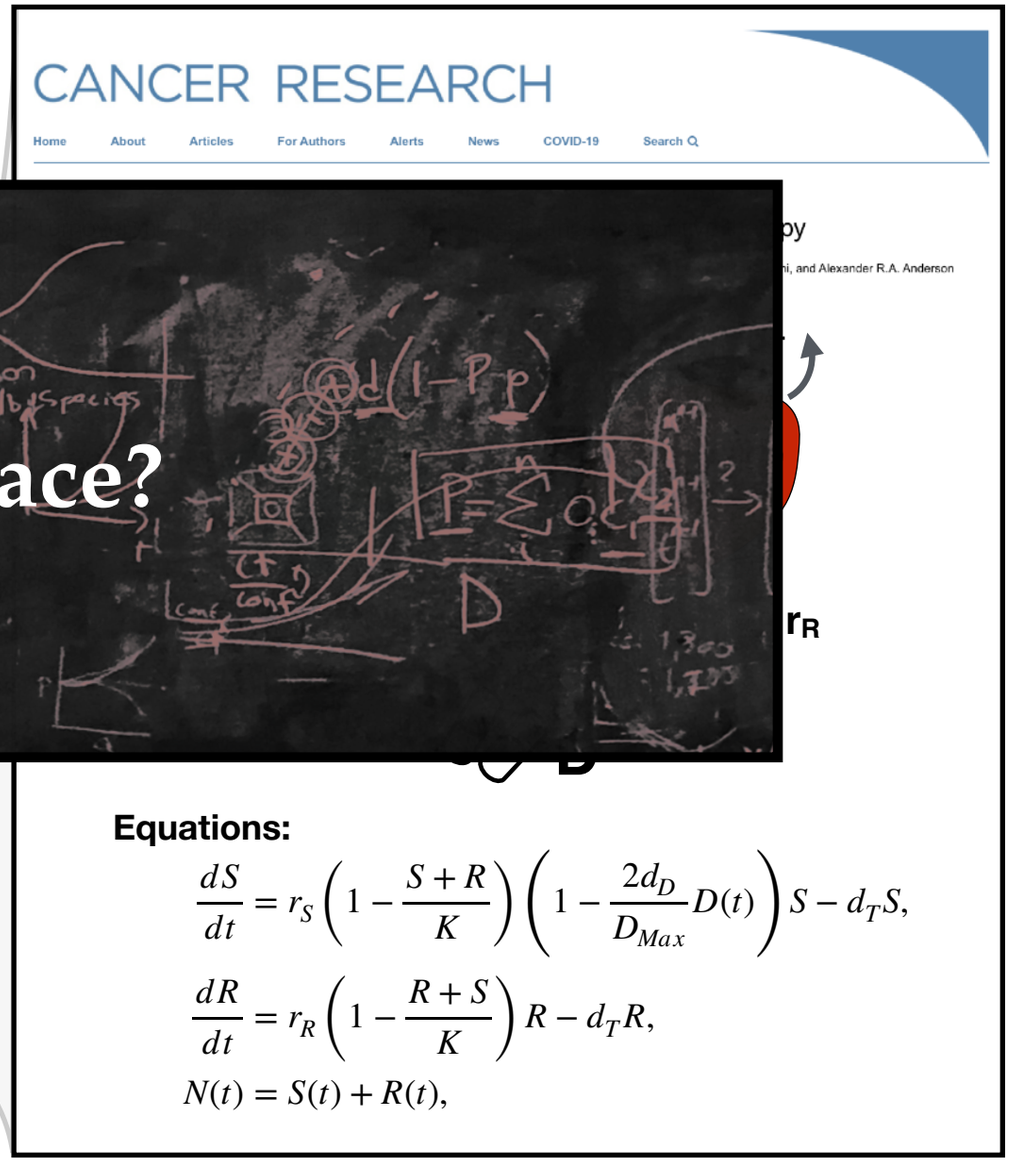
2. Vicinity to ca

3. Resistant

4. Turnover

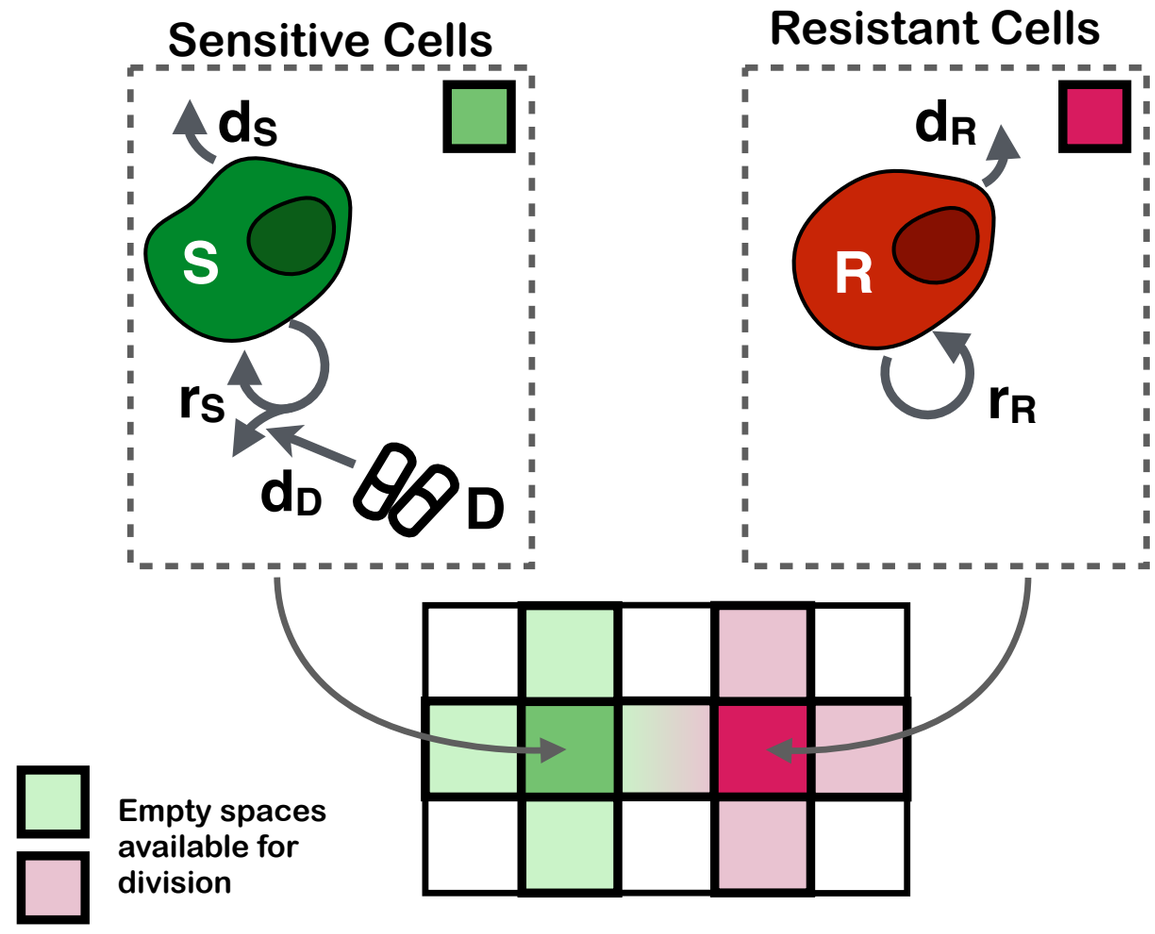


What about space?

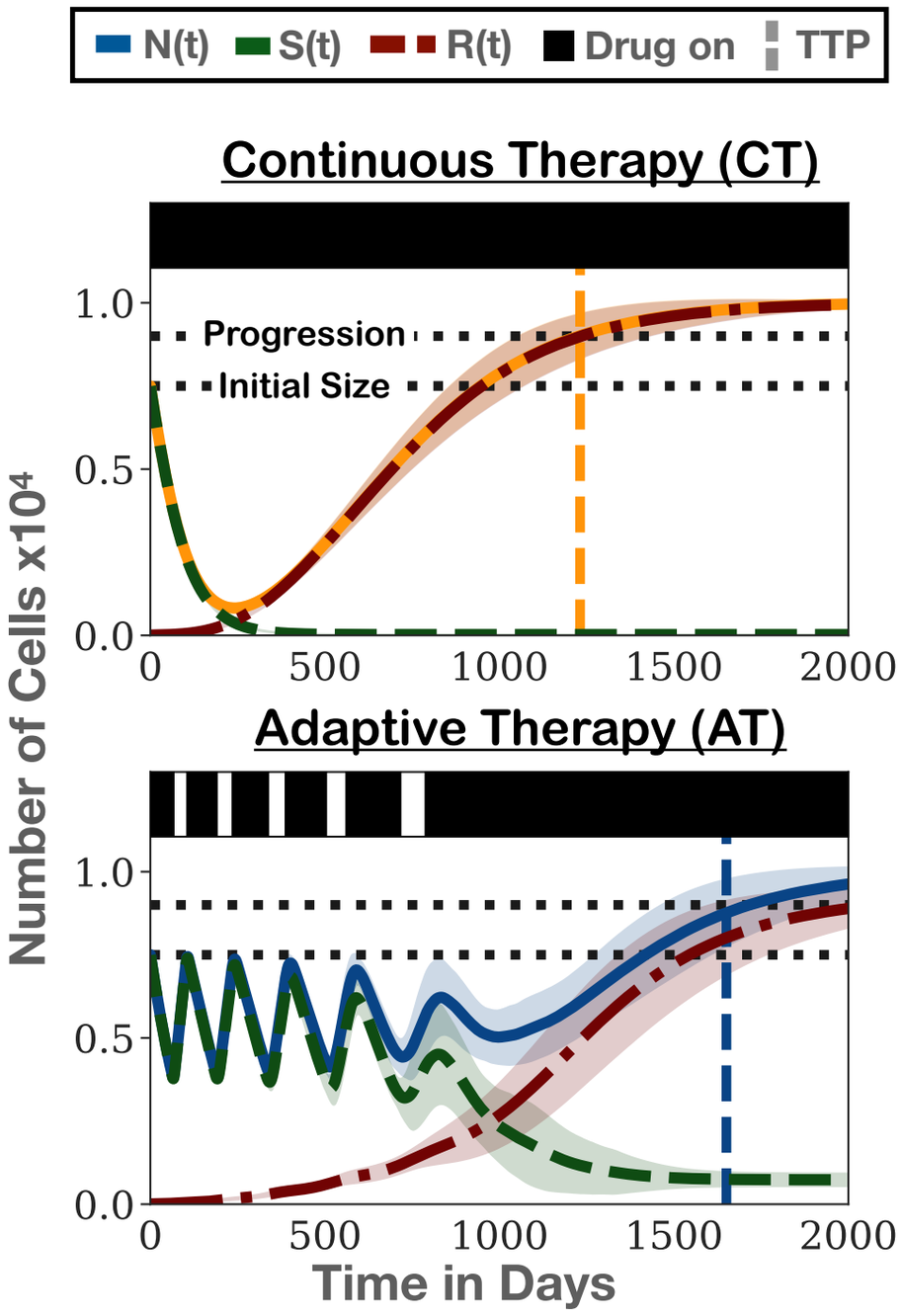


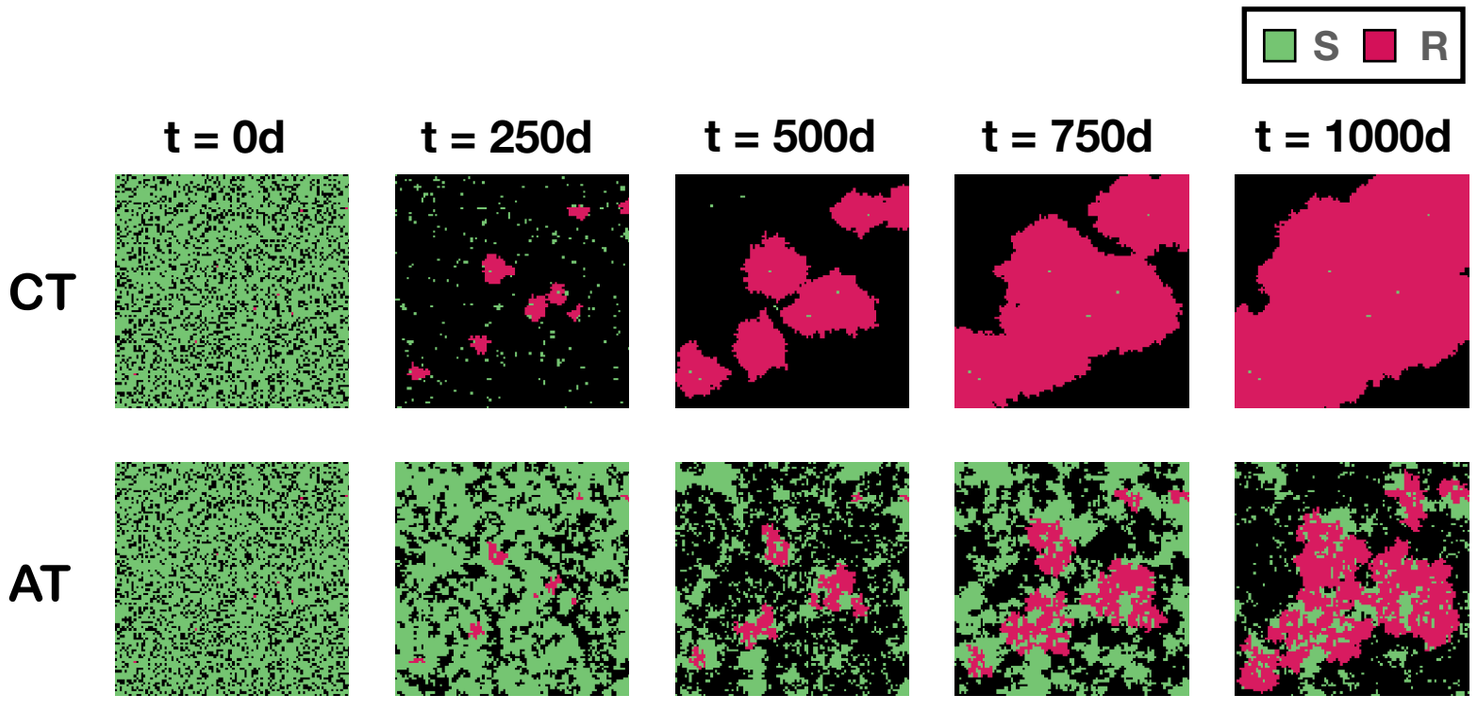
The Model

- **Assumptions:**
  - 2-D, on-lattice ABM.
  - Sensitive and resistant cells.
  - Drug kills dividing cells.
- **Drug Schedules:**
  - Continuous Tx: $D(t) = D_{Max}$
  - Adaptive Tx from trial.
- **Parameters:**
  - Previous AT modelling studies in prostate cancer.



Can AT improve over CT?



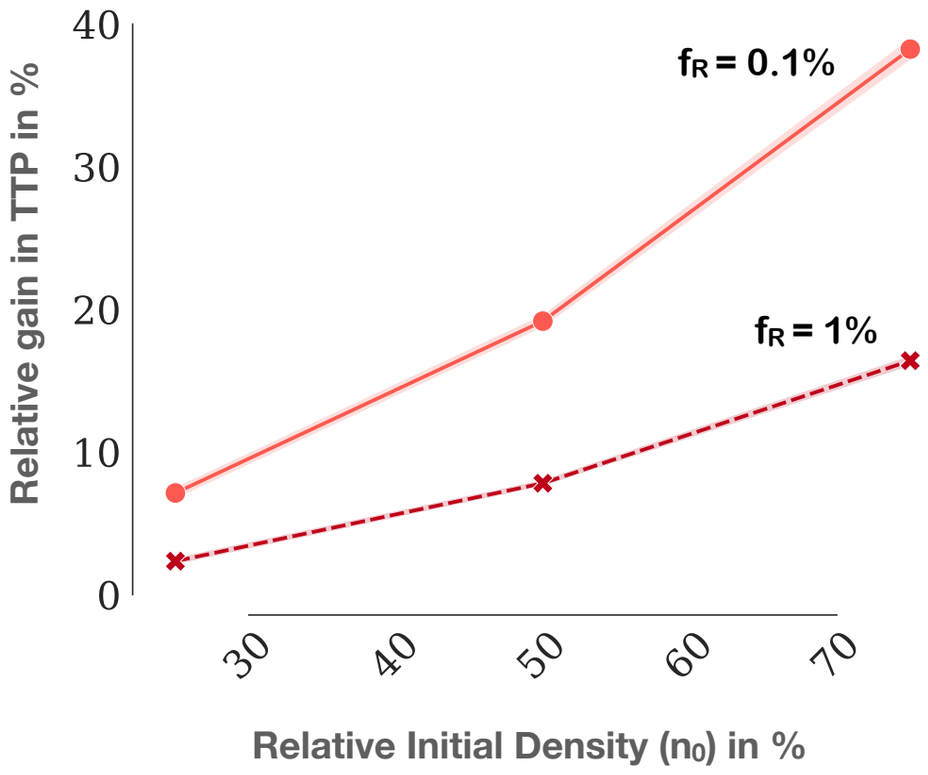


- Random ICs as a "worst case".
- AT can still be beneficial.

Parameters: n_0 = 75%, f_R = 0.1%

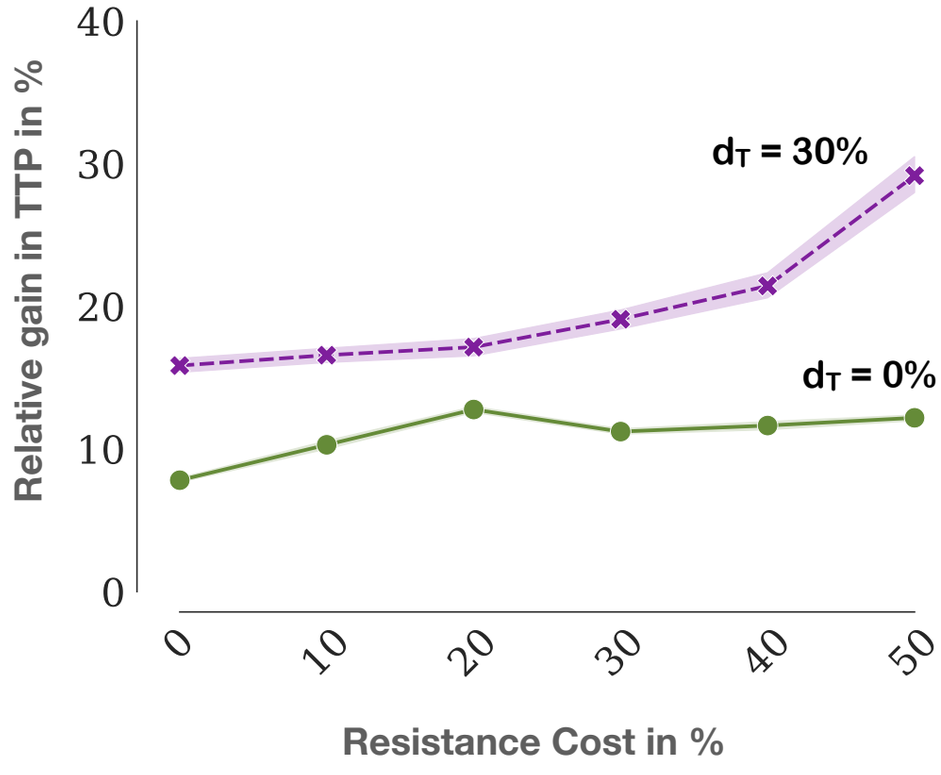
The models agree qualitatively

Impact of Initial Conditions



- Crowding and low resistance fraction benefit AT.

Impact of Cost and Turnover



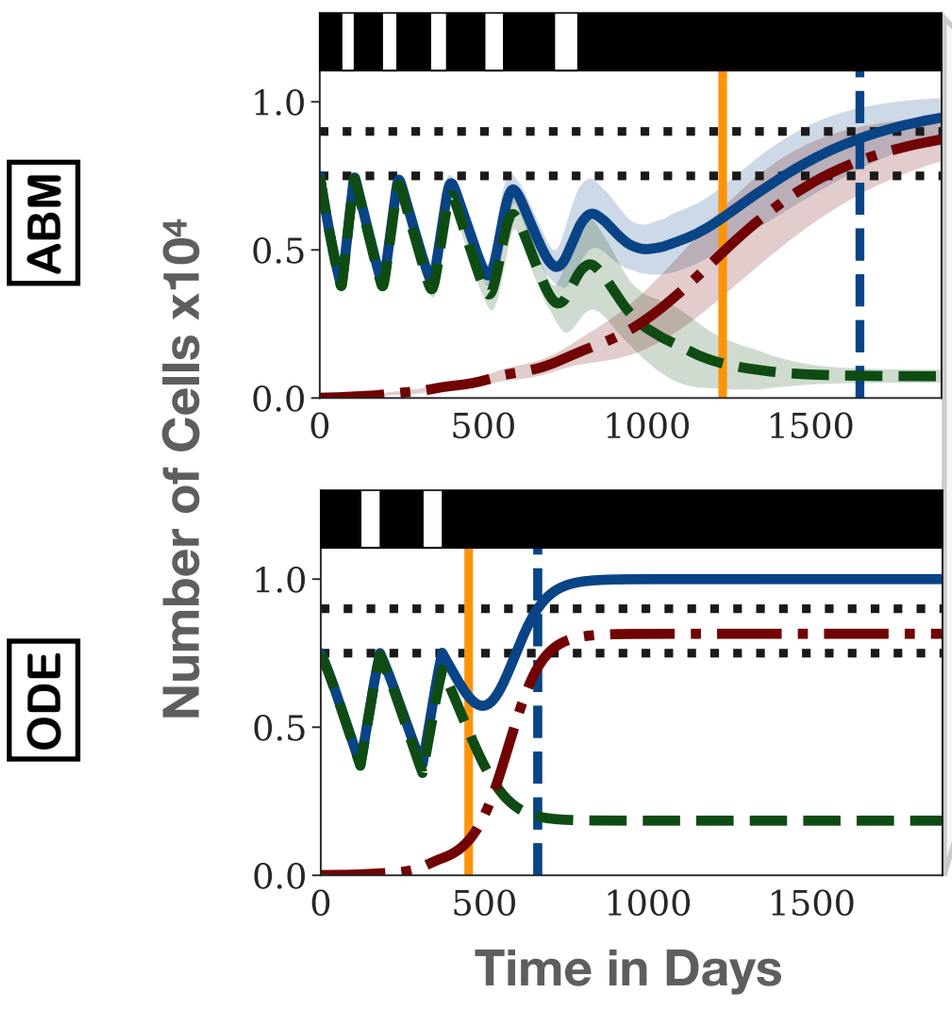
- Turnover aids AT and modifies the impact of resistance costs.

But quantitative dynamics quite different

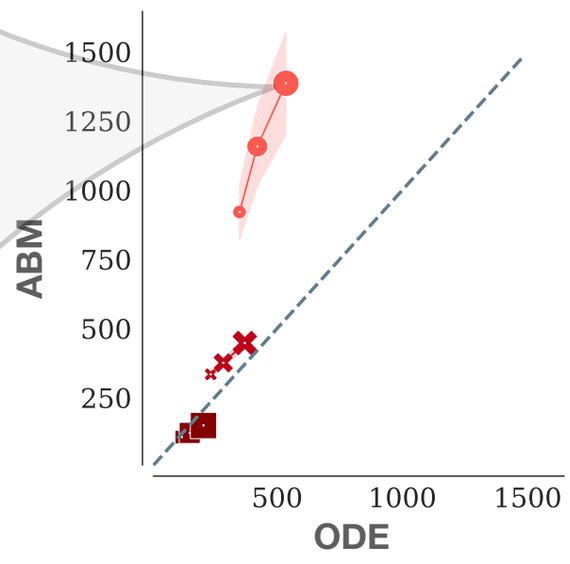
N(t) under AT | S(t) | R(t) | Drug on | TTP_{CT} | TTP_{AT}

Initial Resistance (f_R): 0.1% 1% 10%
Initial Density (n_0): 35% 50% 65%

Simulations for the same parameters

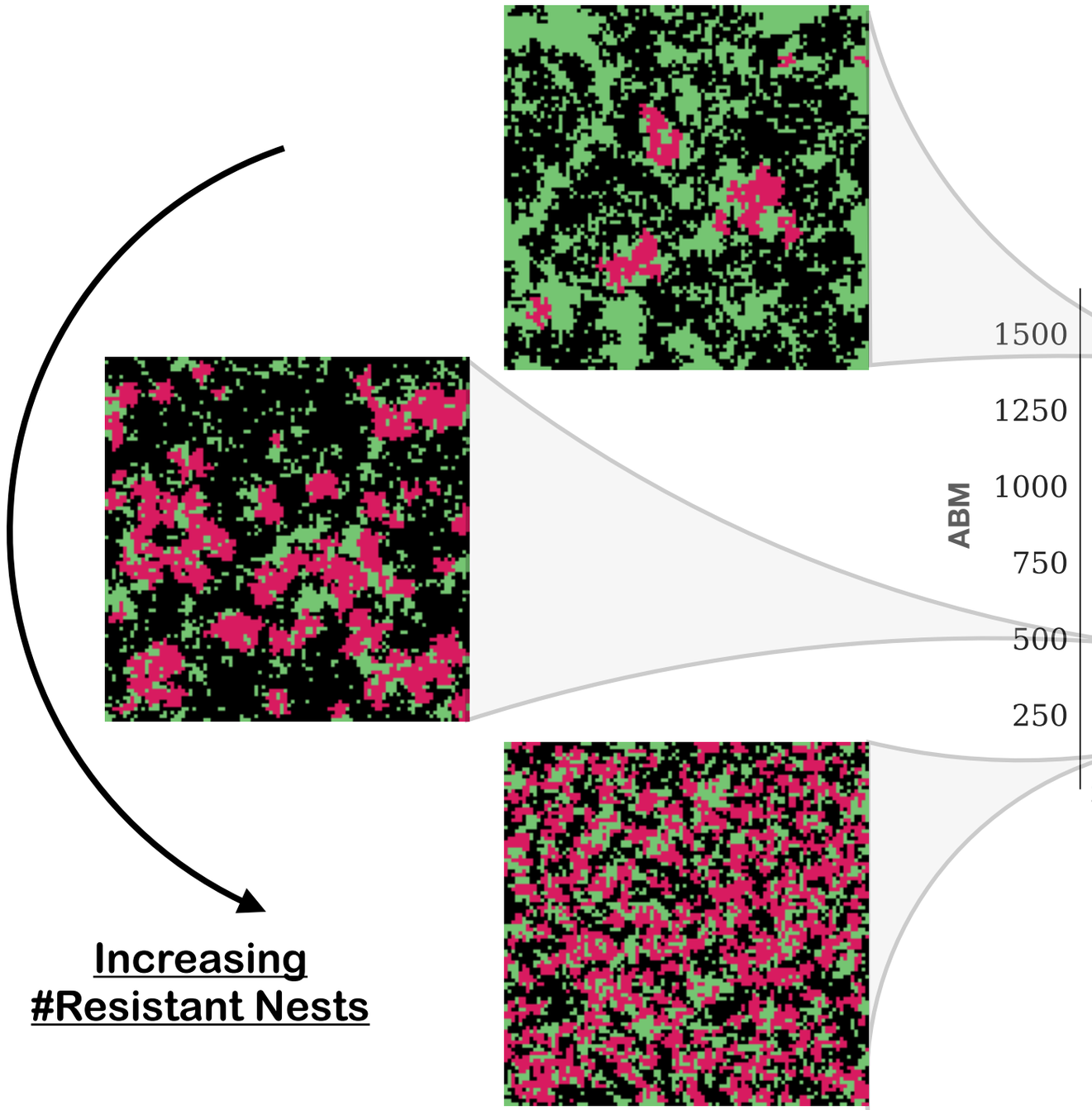


TTP_{AT} in Days



- The spatial model predicts different time dynamics, and generally **smaller** relative benefit.

Why do the models differ?



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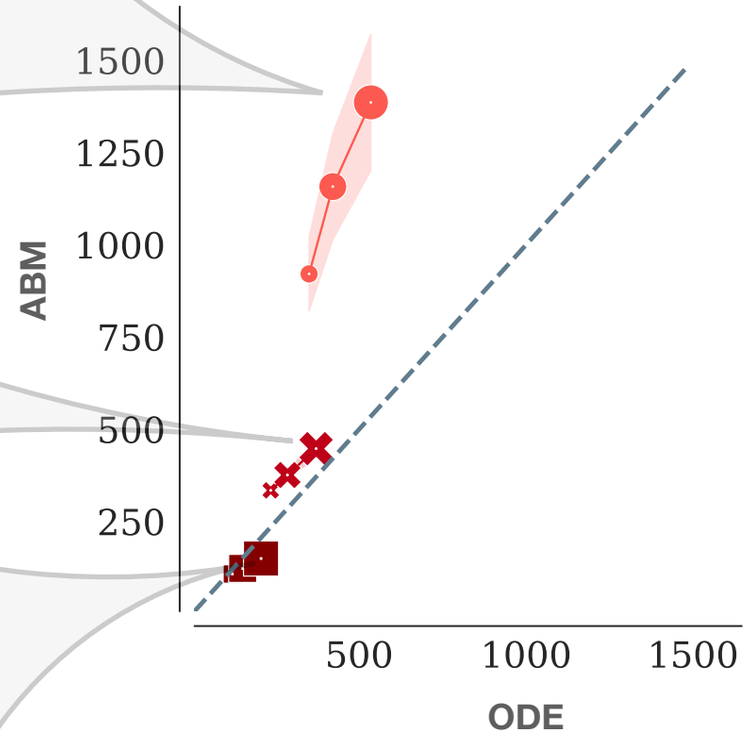
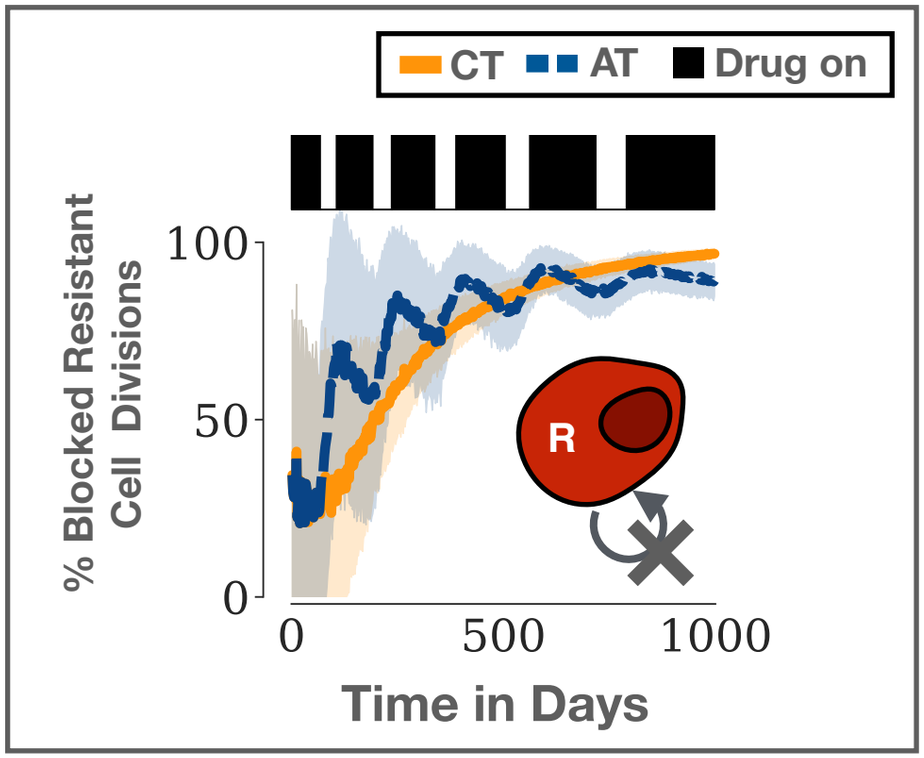
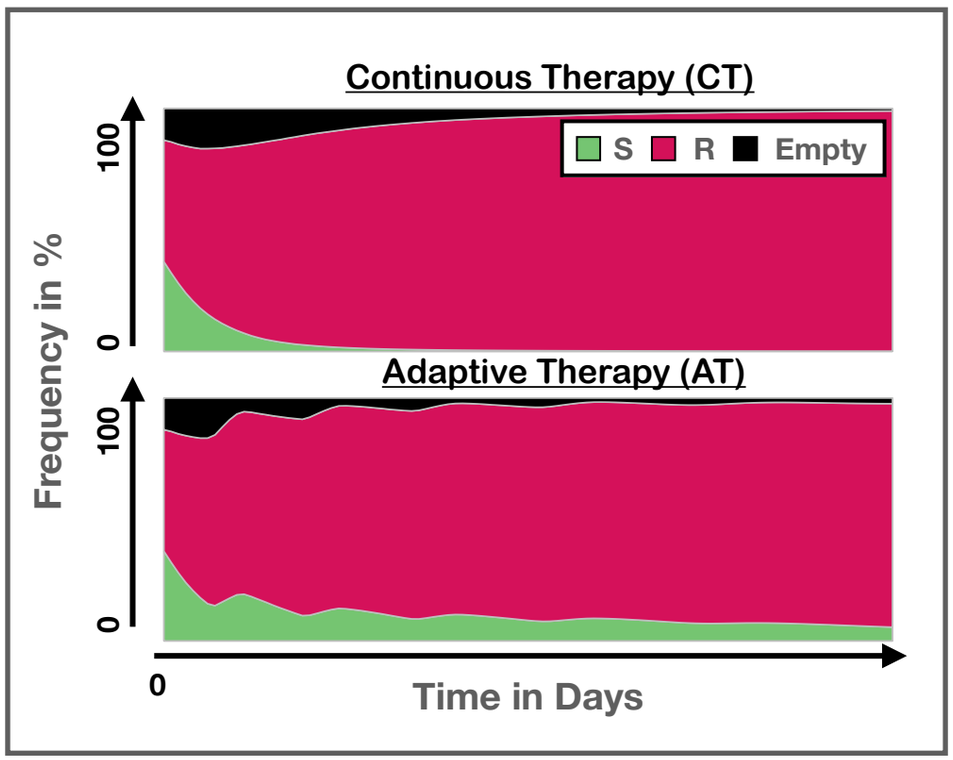


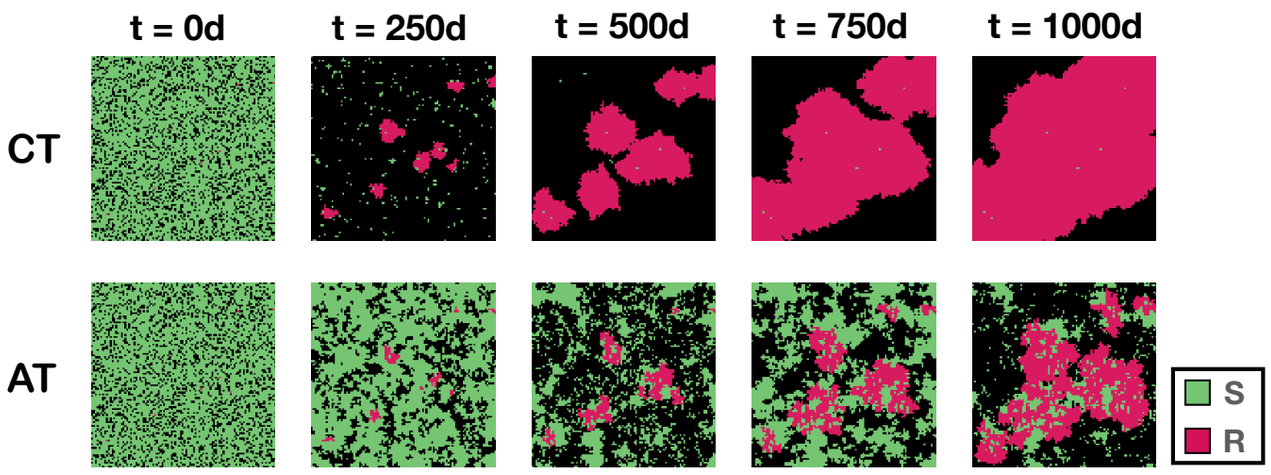
Quantifying competition

1) How much competition is there?



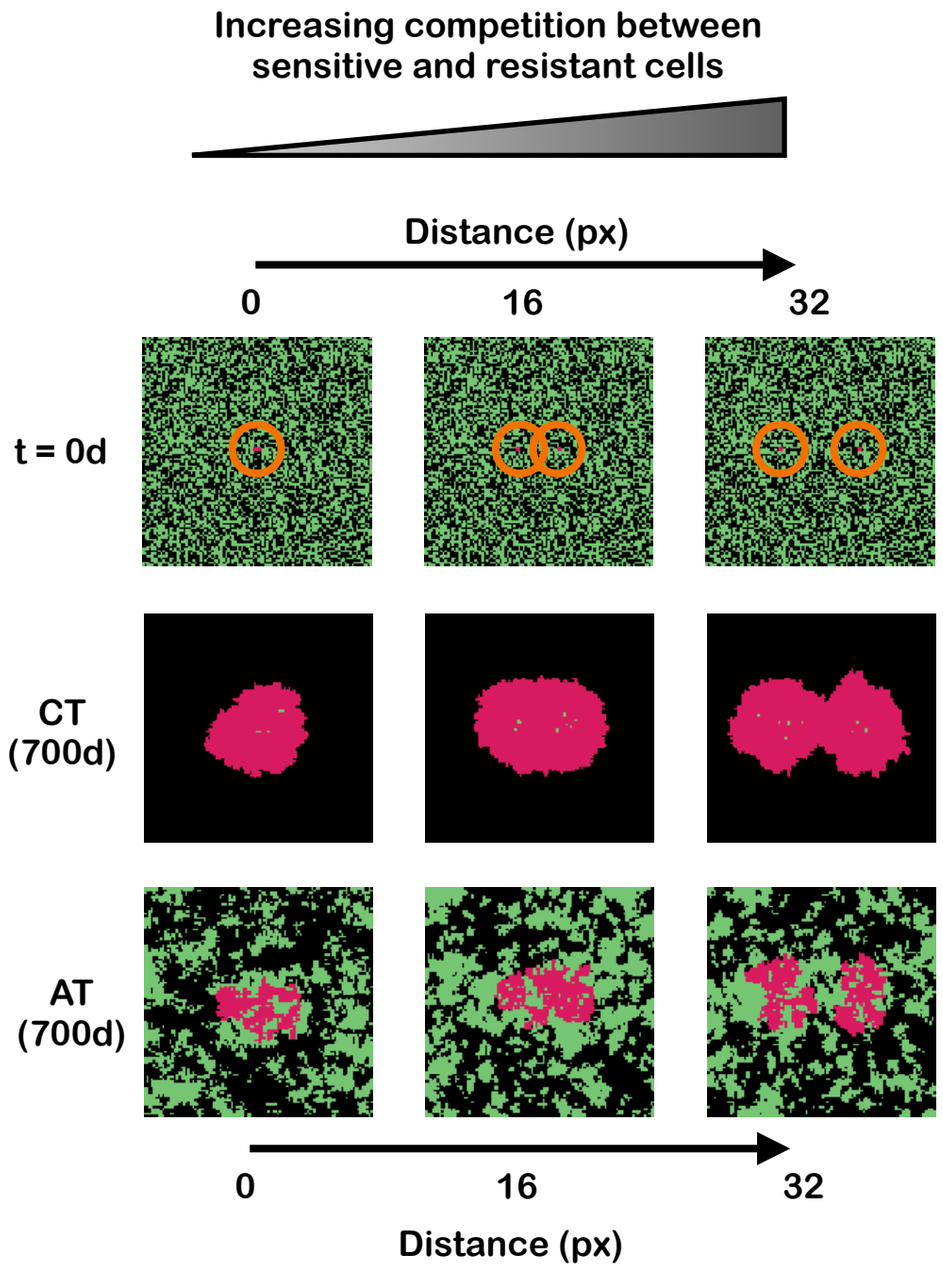
2) Who do resistant cells compete with?

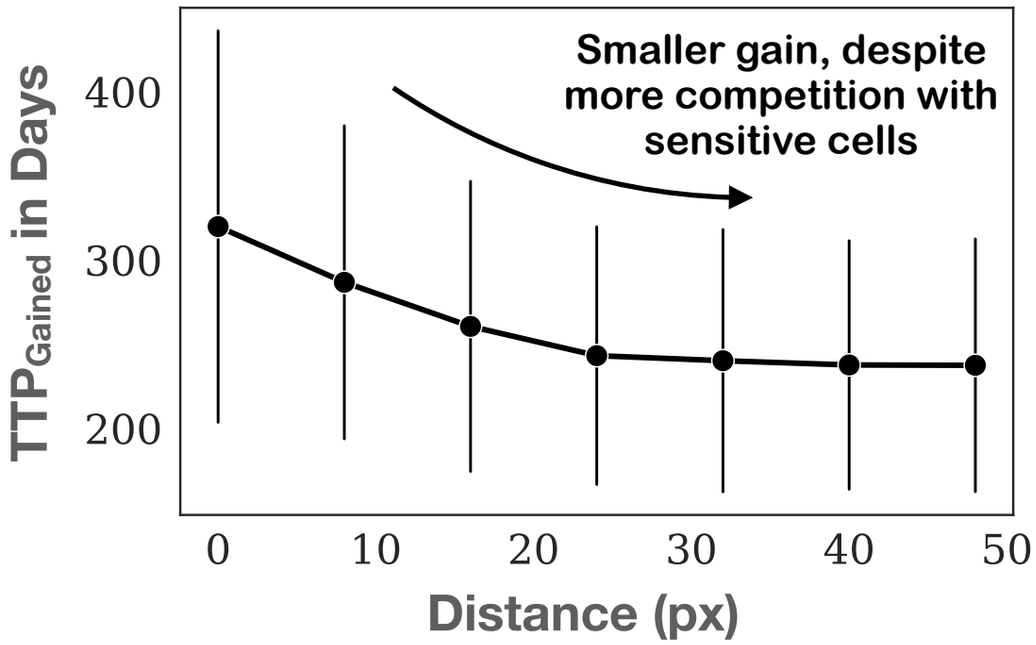




- **Conclusions:**
  - Competition increases under AT.
    - But also under CT…
  - Most resistant cells compete with other resistant cells!

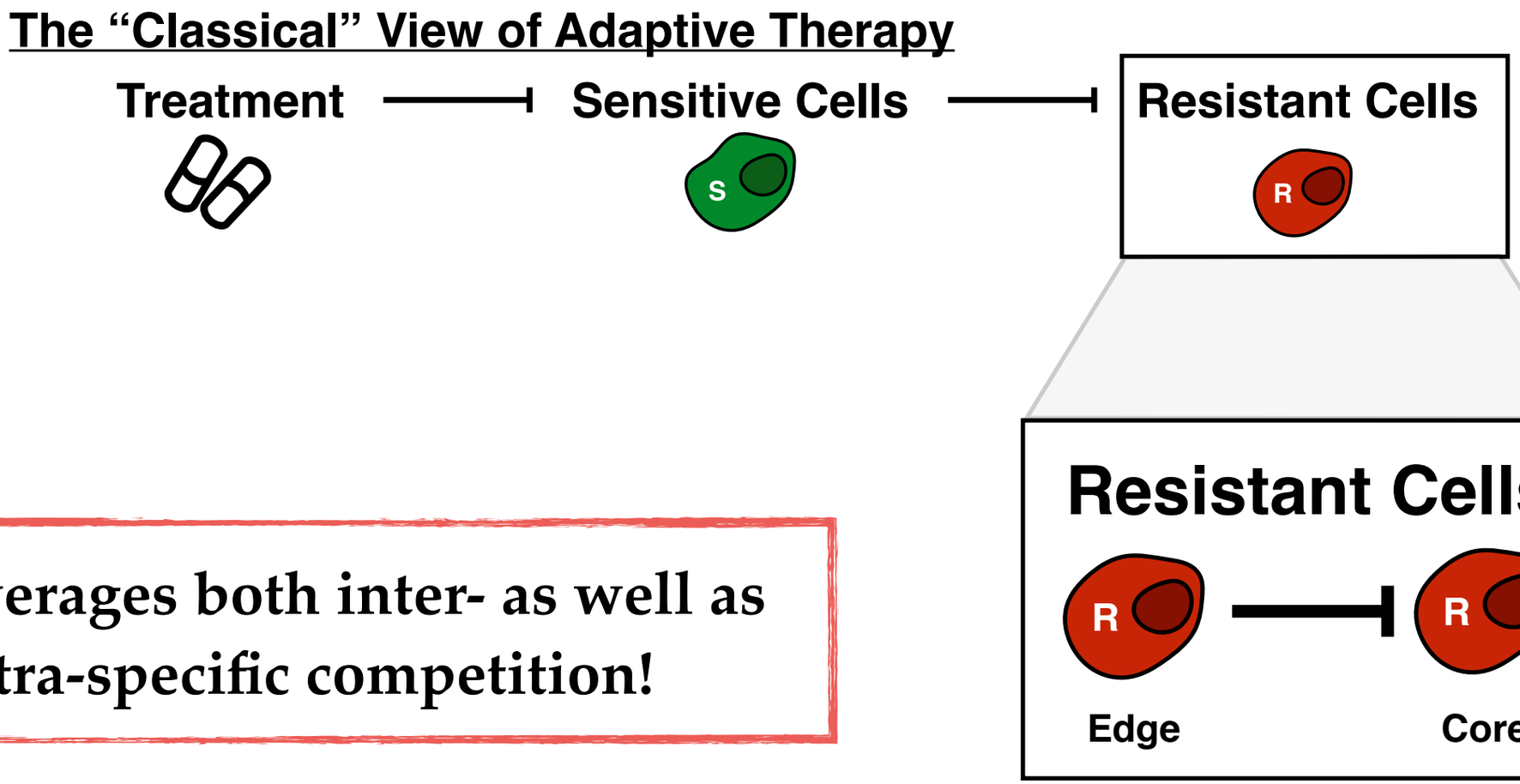
A double-edged sword





- Competition with sensitive cells is a double-edged sword.
- That's why intra-specific competition is important.

AT is not only about sensitive cells



→ **AT leverages both inter- as well as intra-specific competition!**

*Diagram adapted from Carlo Maley

The Bruchovsky (2006) et al data

Final Results of the Canadian Prospective Phase II Trial of Intermittent Androgen Suppression for Men in Biochemical Recurrence after Radiotherapy for Locally Advanced Prostate Cancer

Clinical Parameters

Nicholas Bruchovsky, MD, PhD[1]
Laurence Klotz, MD[2]
Juanita Crook, MD[3]
Shawn Malone, MD[4]
Charles Ludgate, MD[5]
W. James Morris, MD[5]
Martin E. Gleave, MD[1]
S. Larry Goldenberg, MD[1]

BACKGROUND. This prospective Phase II study was undertaken to evaluate intermittent androgen suppression as a form of therapy in men with localized prostate cancer who failed after they received external beam irradiation.

METHODS. Patients who demonstrated a rising serum prostate-specific antigen (PSA) level after they received radiotherapy and who were without evidence of distant metastasis were accepted into the study. Treatment in each cycle consisted of cyproterone acetate given as lead-in therapy for 4 weeks, followed by a combination of leuprolide acetate and cyproterone acetate, which ended after a total of 36 weeks.

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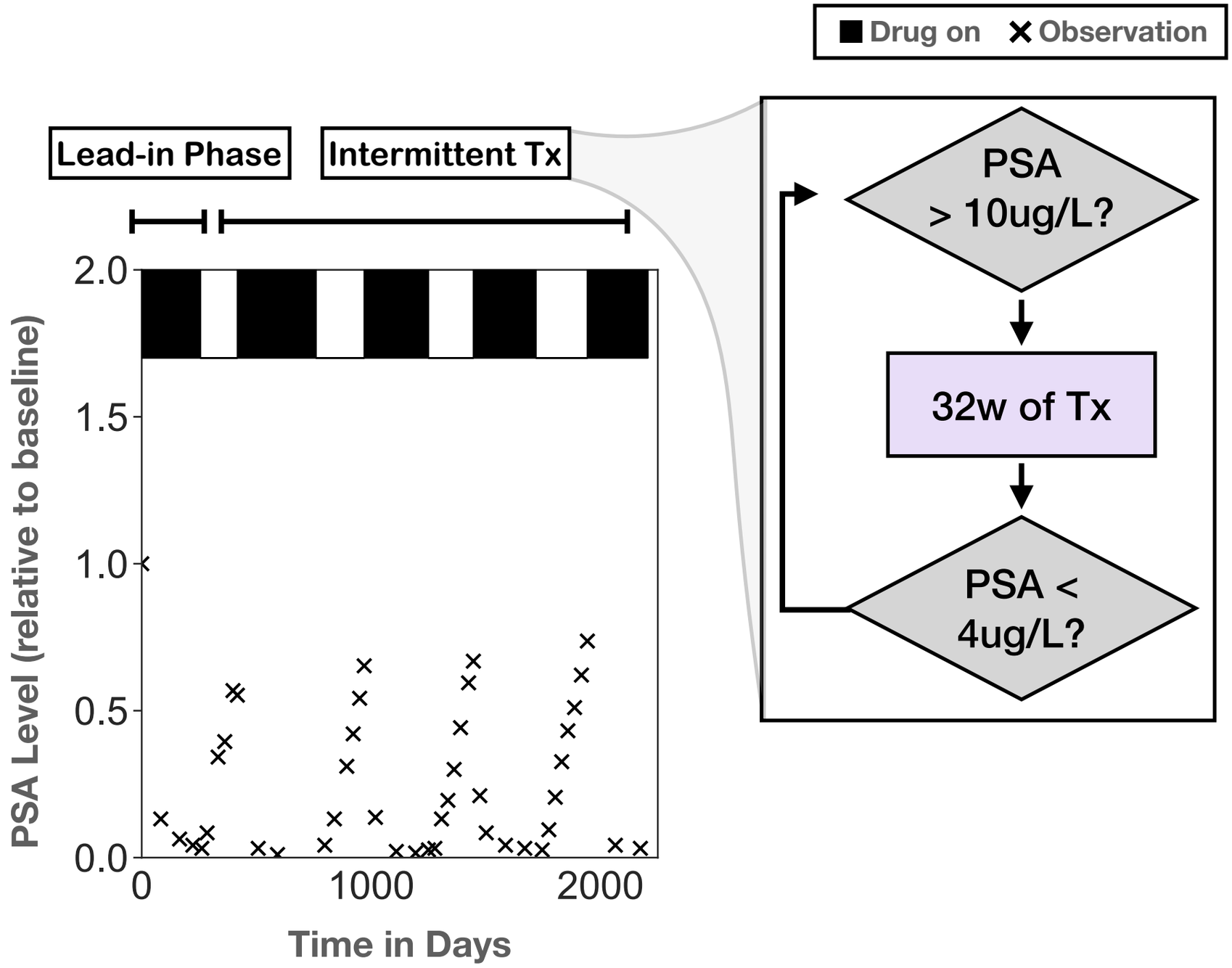
- Data from 67 patients undergoing intermittent androgen deprivation therapy.



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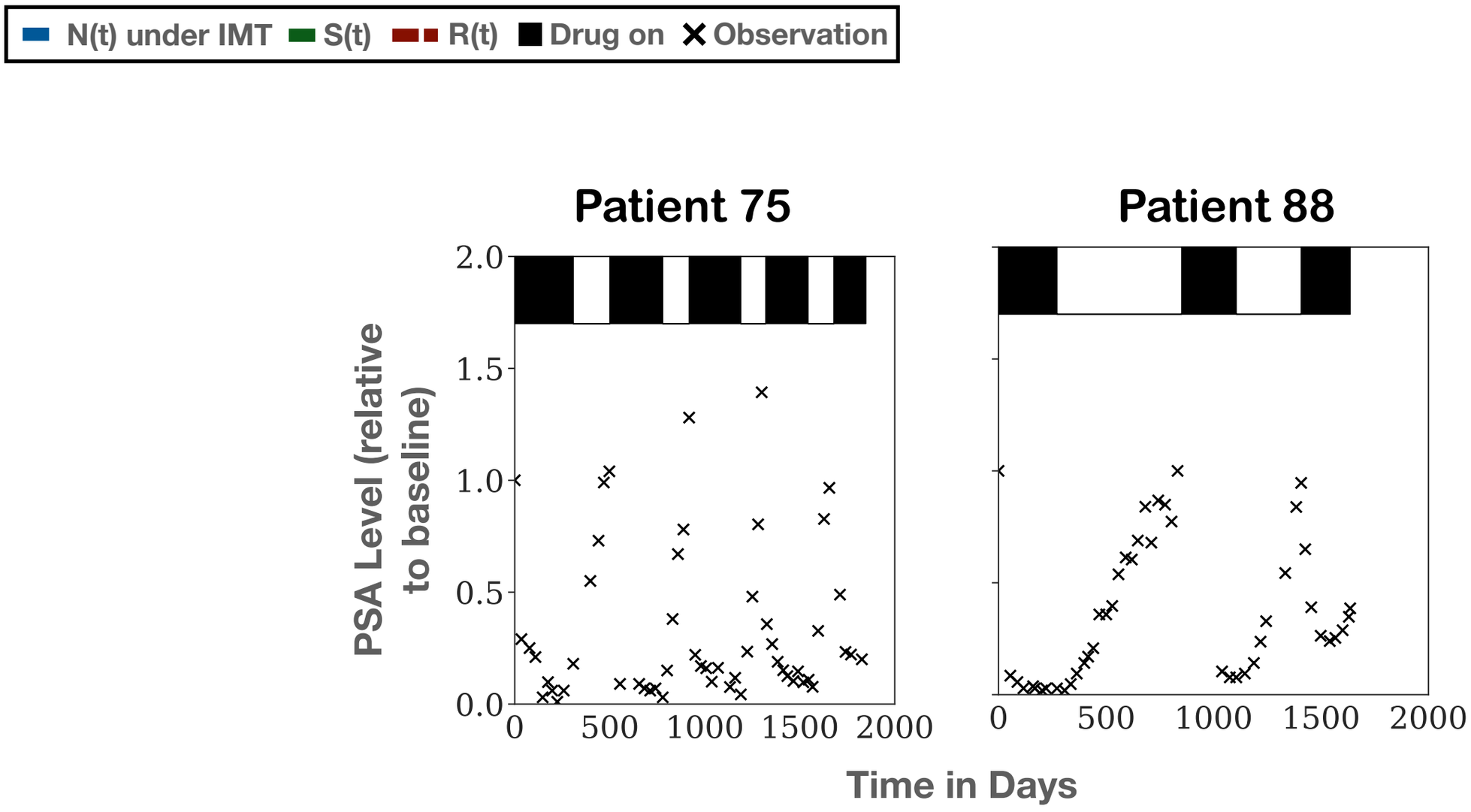
Fast and slow cyclers display different spatial organisation



- The ABM can fit the data.

Free parameters: n0, fR, cost, turnover.

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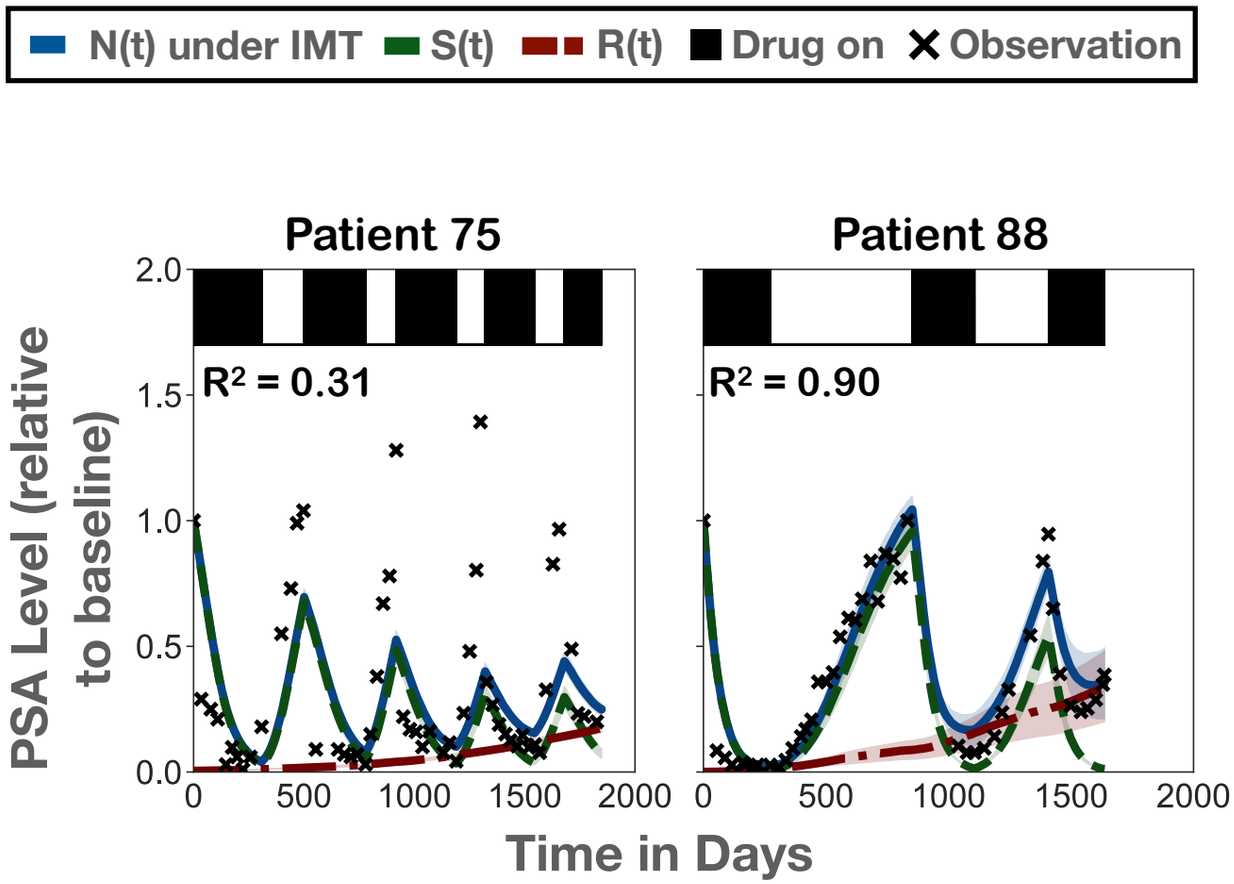
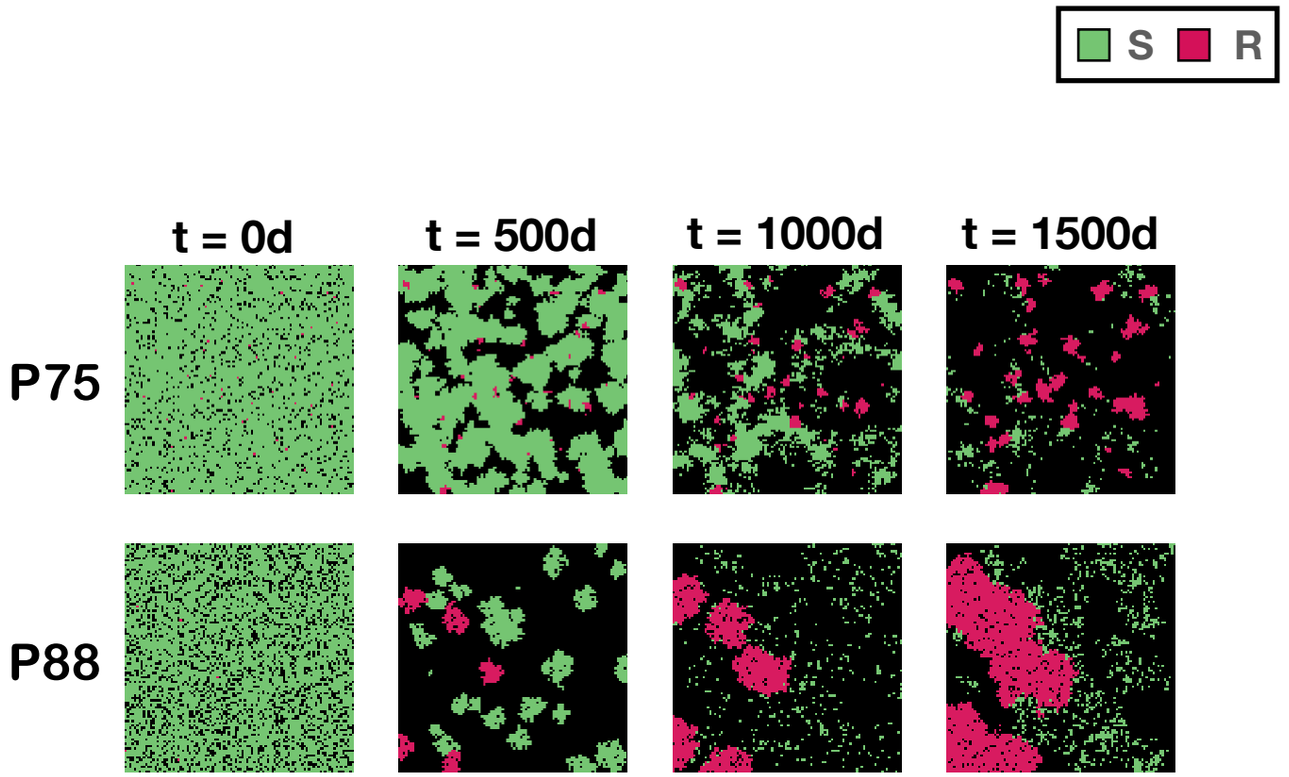
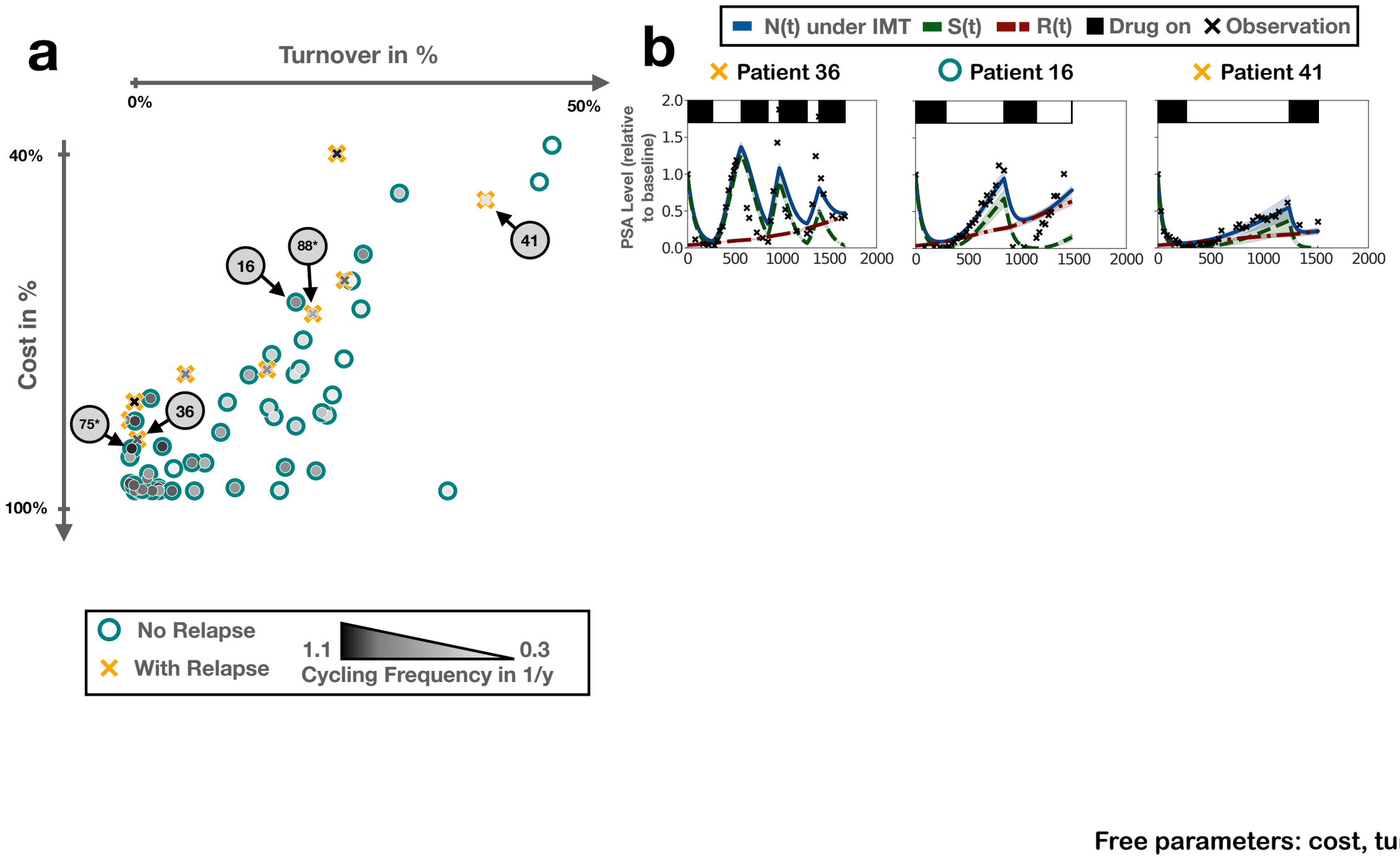




- The ABM can fit the data.
- Spatial organisation differs between fast and slow cyclers.

Free parameters: n0, fR, cost, turnover.

The Carpet-Patch Hypothesis



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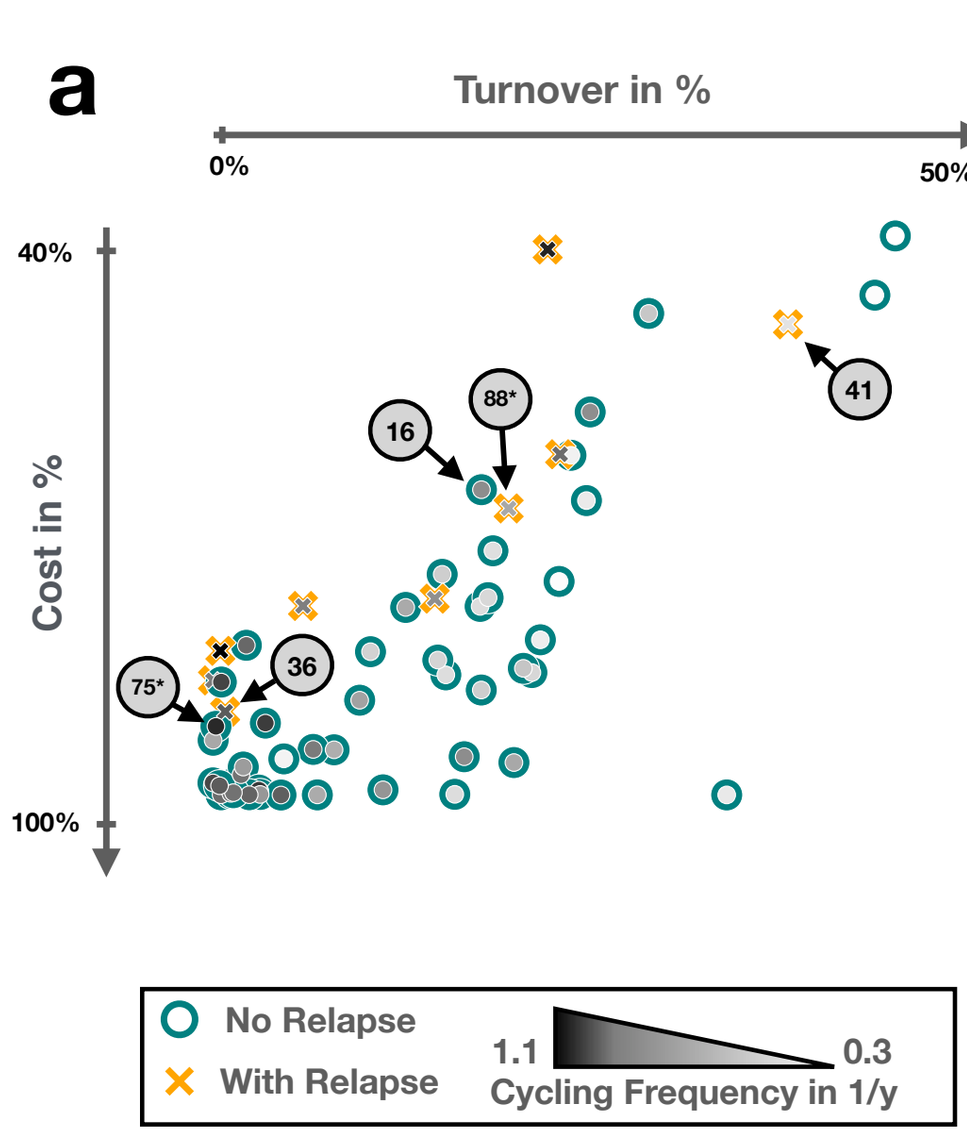
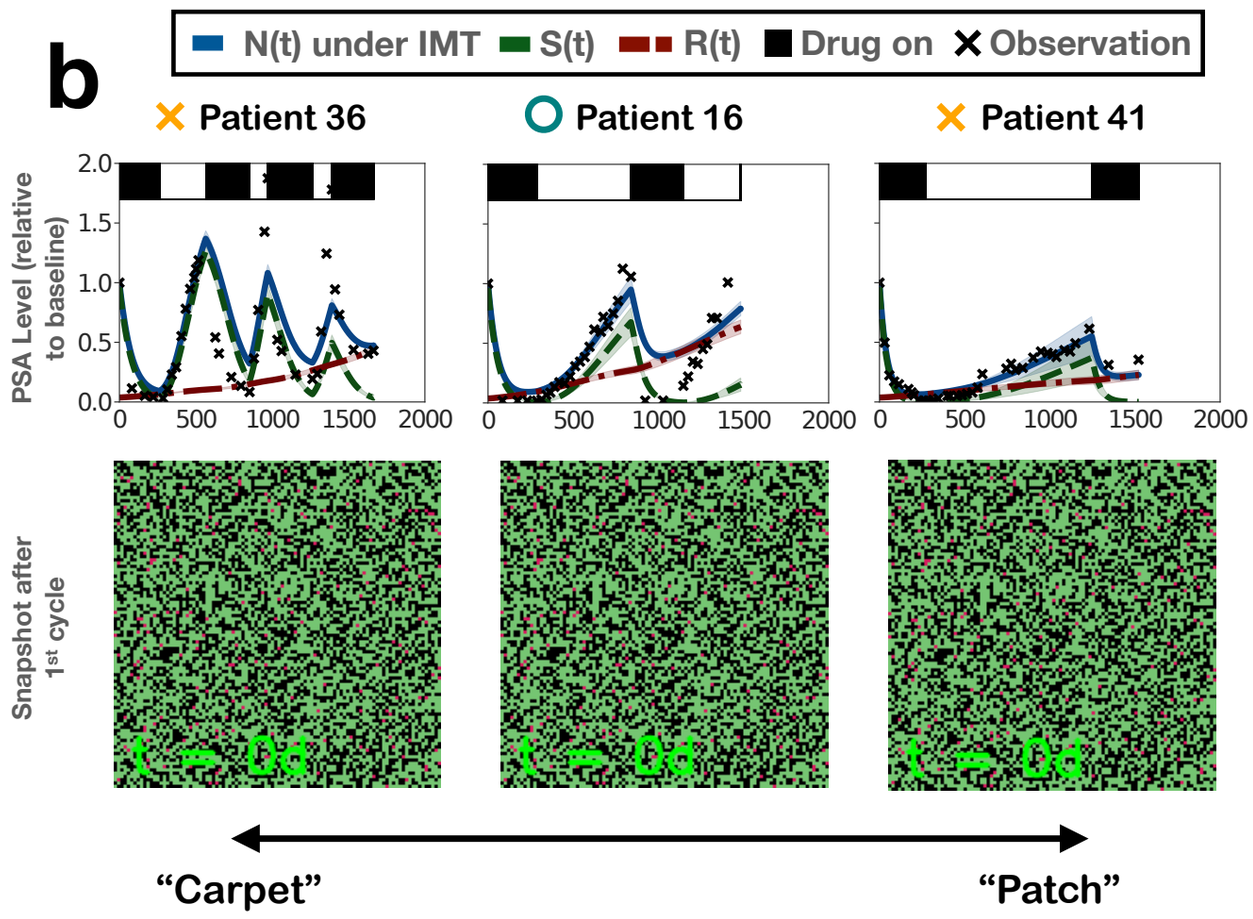
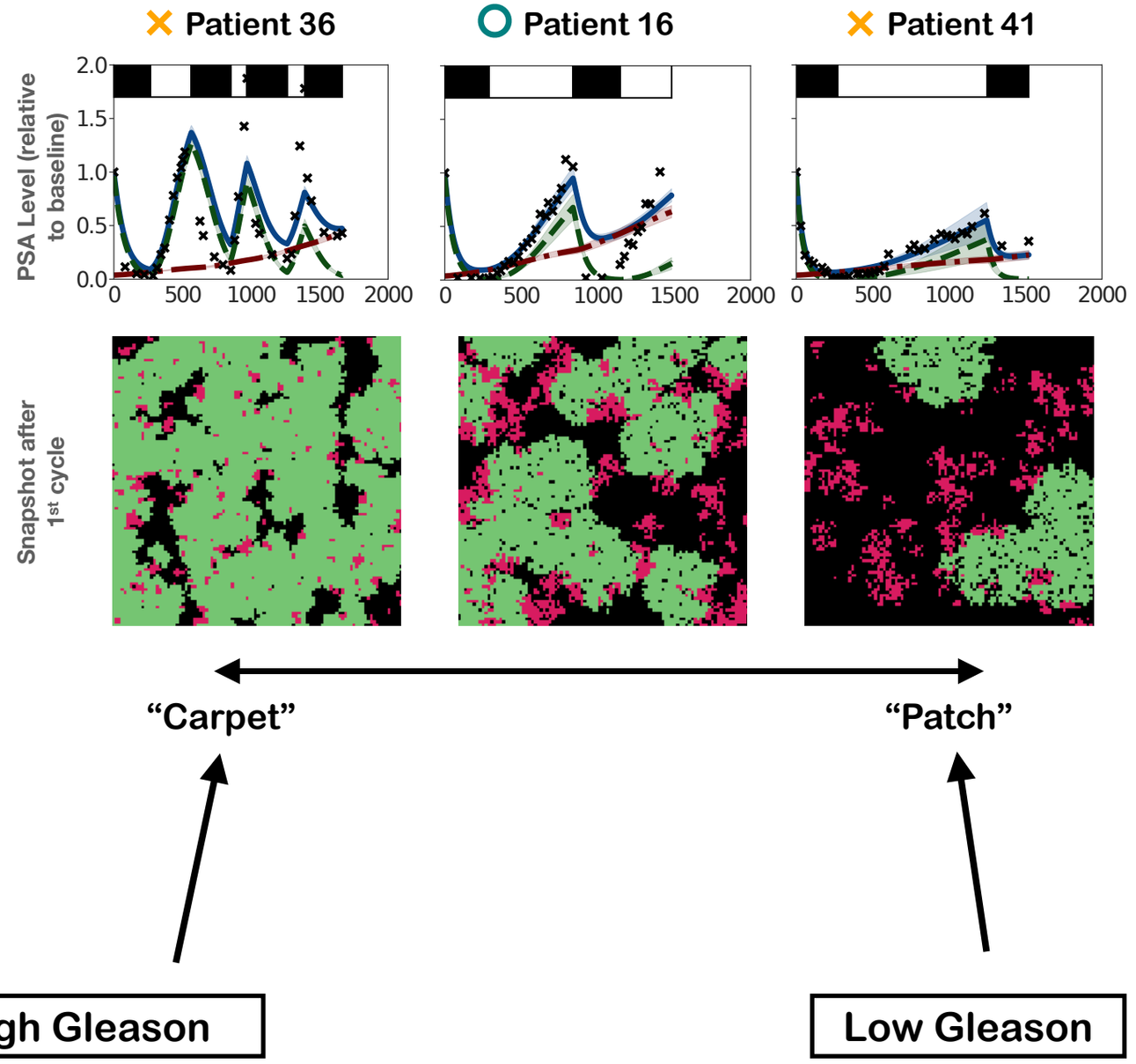




Free parameters: cost, turnover.

Is this idea plausible?

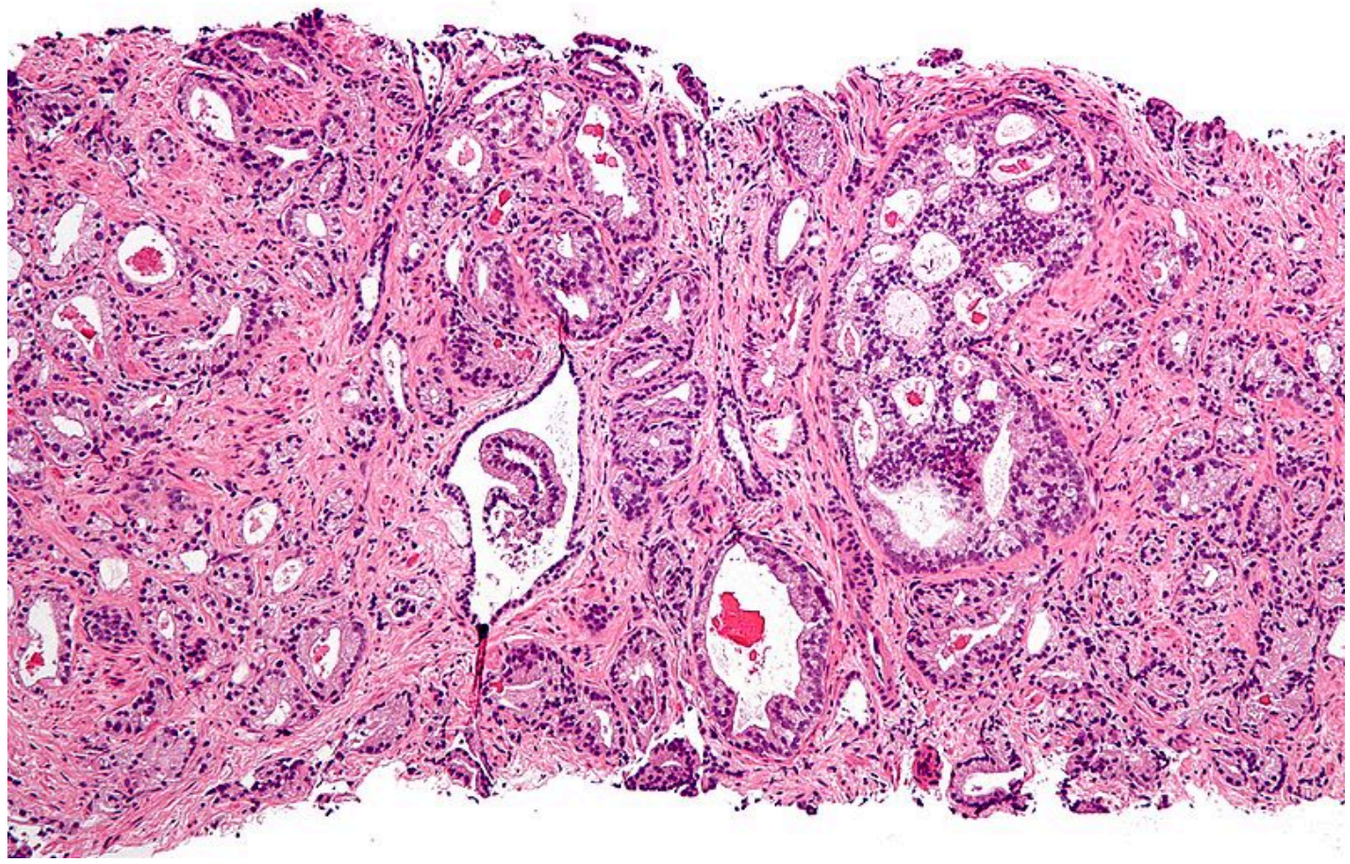
- Bruchovsky et al:
  "suggestive trend that a Gleason score <6 may be associated with a slightly longer time off treatment in the initial 2 cycles."



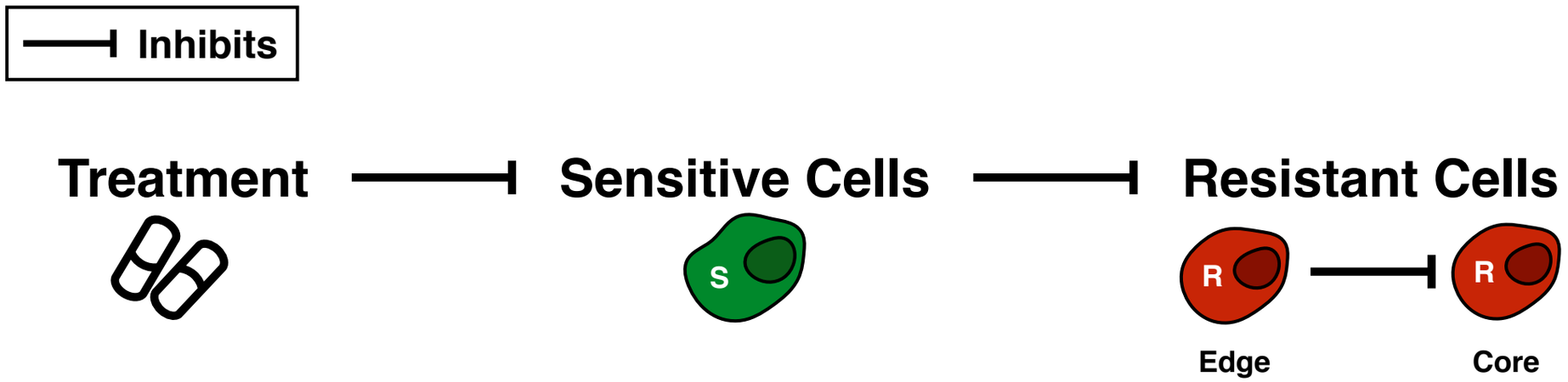
Free parameters: cost, turnover.

Where next?

- Look beyond Lotka-Volterra:
  - Spatial structure
  - Resource competition
- The role of normal tissue.
- Role of stochasticity?



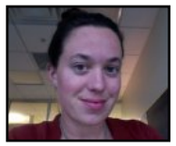
Summary



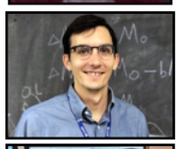
- **Intra-specific competition** is an important factor in AT.
- Need to incorporate **where** and **how often** resistance arises to judge benefit of AT.
- Patient **cycling dynamics** may tell us about spatial structure, and how we should adapt therapy.

Acknowledgements

Collaborators/Mentors



- Jill Gallaher



- Jeffrey West

- Mark Robertson-Tessi

- Mehdi Damaghi

- Yannick Viossat

- Joel Brown

- Robert Gatenby

- Philip Maini

- Sandy Anderson

For more details:

Strobl et al (2020). Spatial structure impacts adaptive therapy by shaping intra-tumoral competition. bioRxiv

Strobl et al (2020). Turnover modulates the need for a cost of resistance in adaptive therapy. Cancer Research.

Mathonco Blog post: K for carrying capacity.

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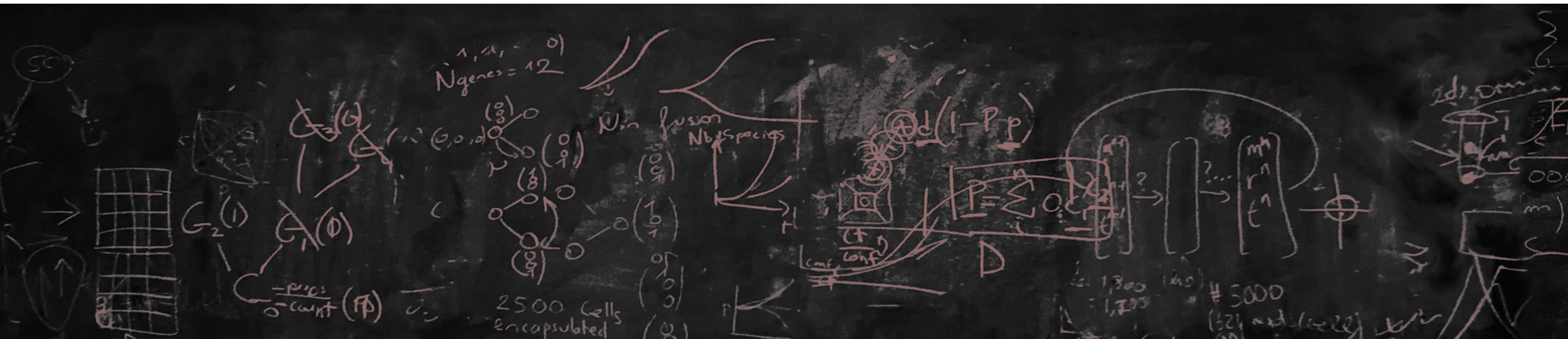
Systems Approaches to Biomedical Science IDC

IMO

MOFFITT CANCER CENTER


Ngenes = 12
Num fusion
Nb Spacings
2500 cells
encapsulated
5000

Appendix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