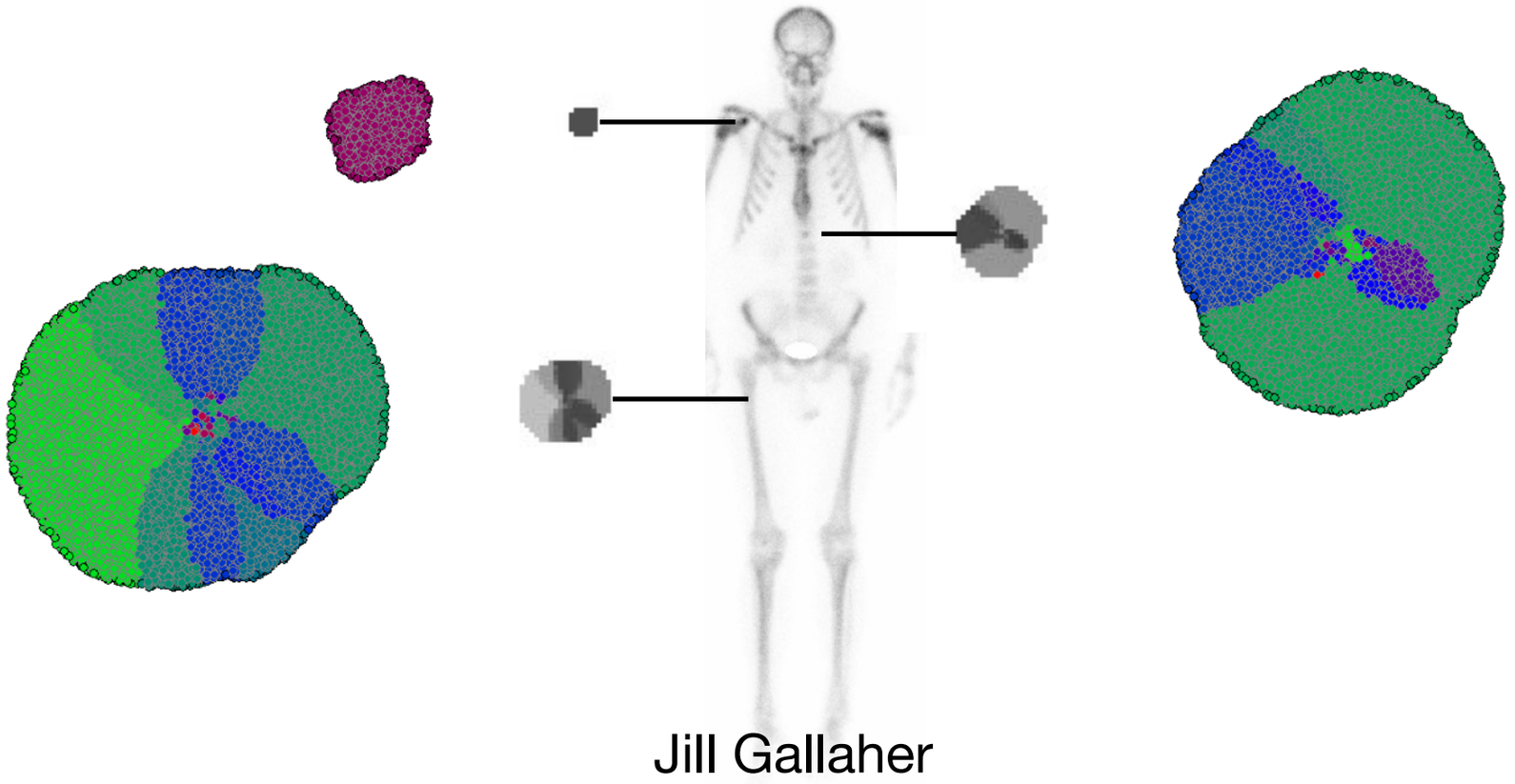
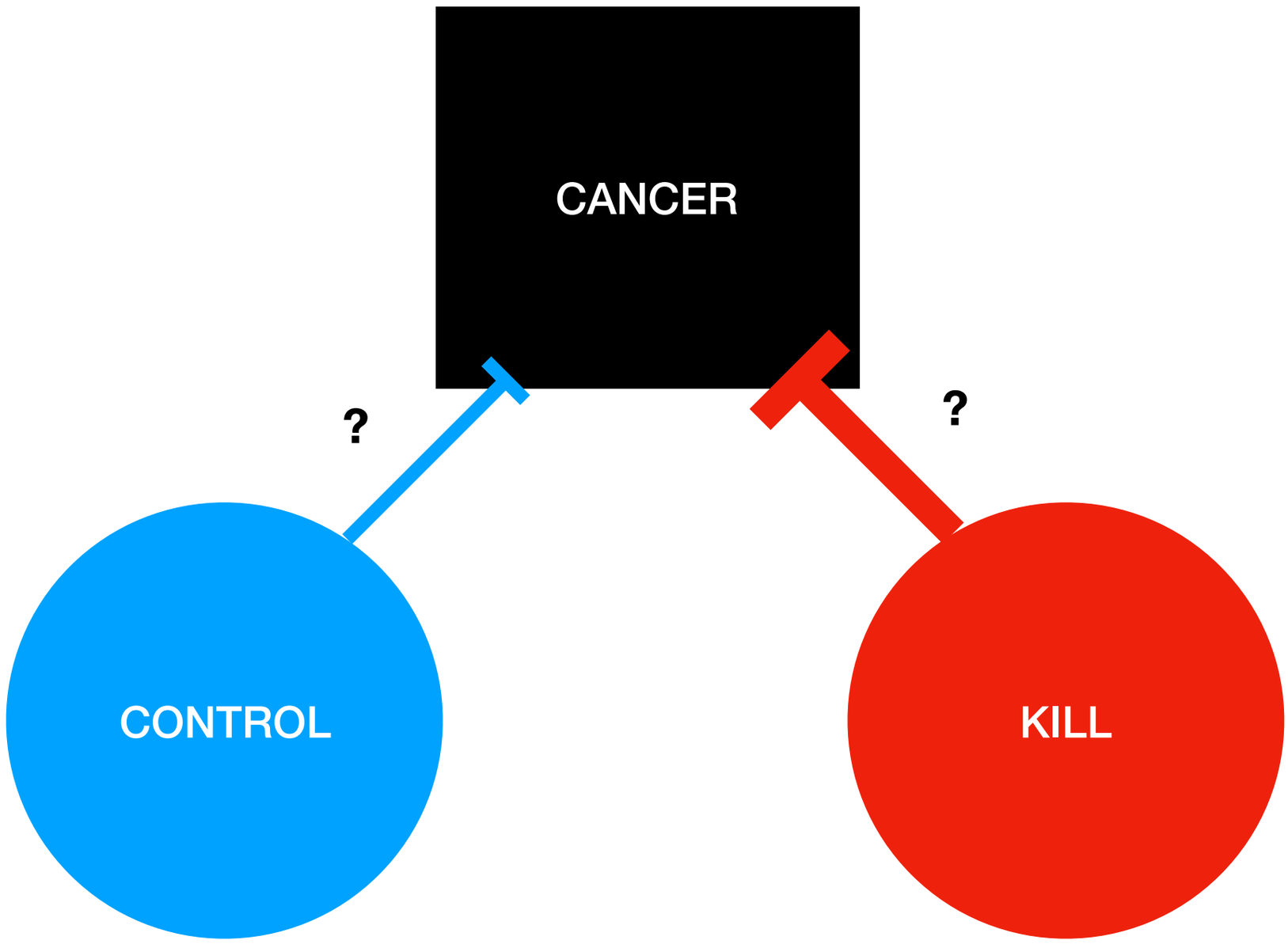
Dynamics of spatial metastatic systems during adaptive therapy



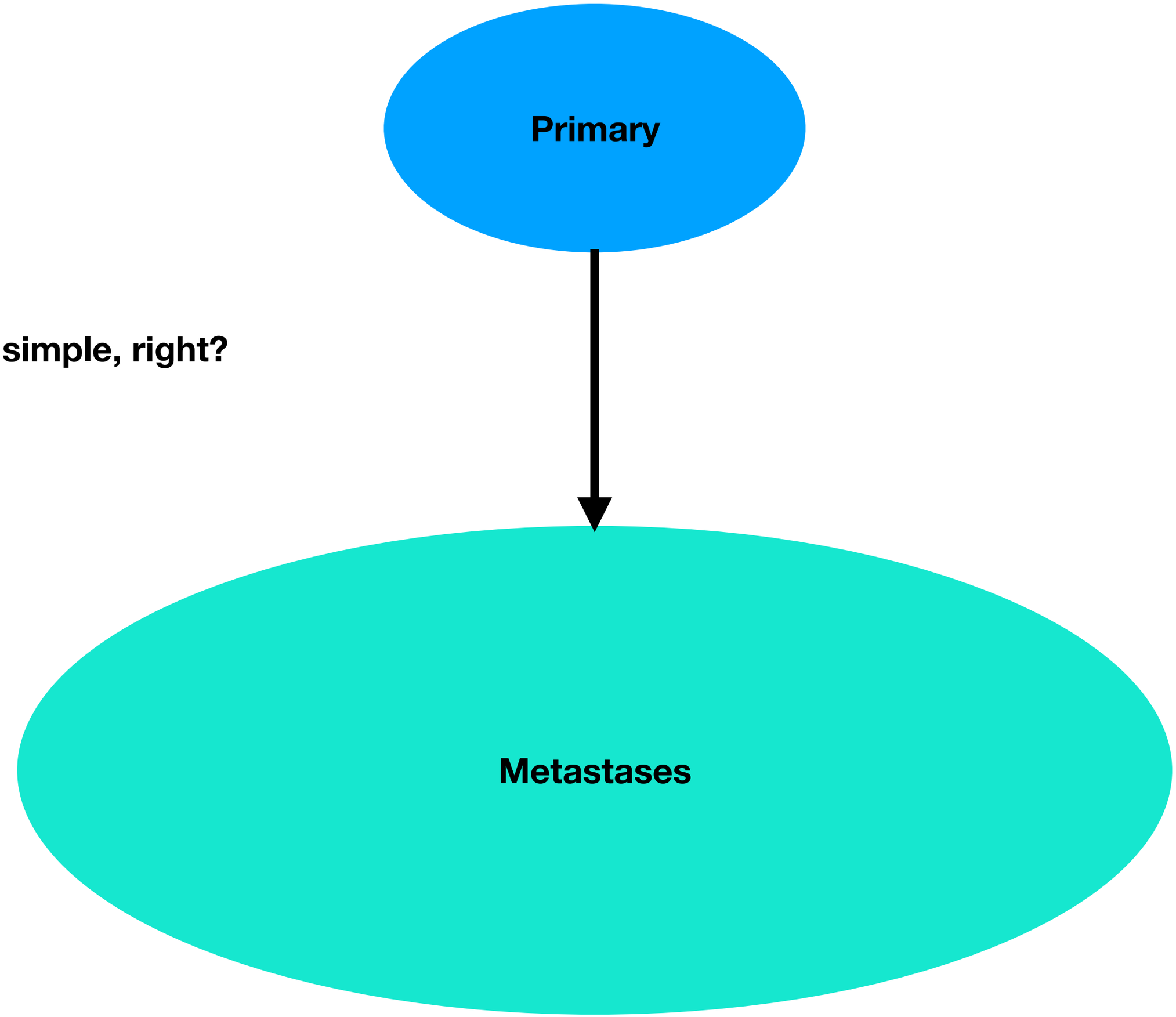
Jill Gallaher
Moffitt Cancer Center
CATMO 2020

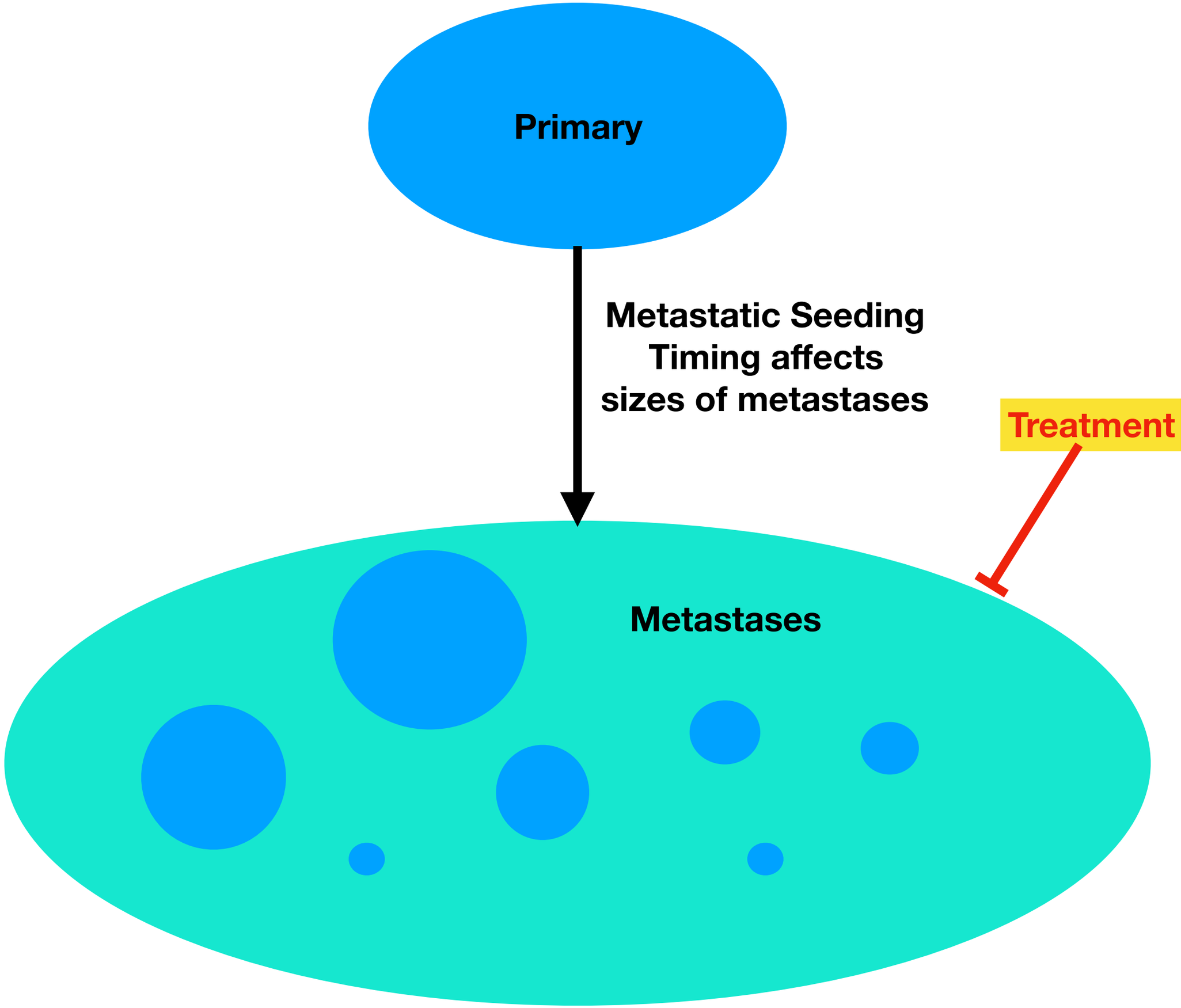
To kill or control?



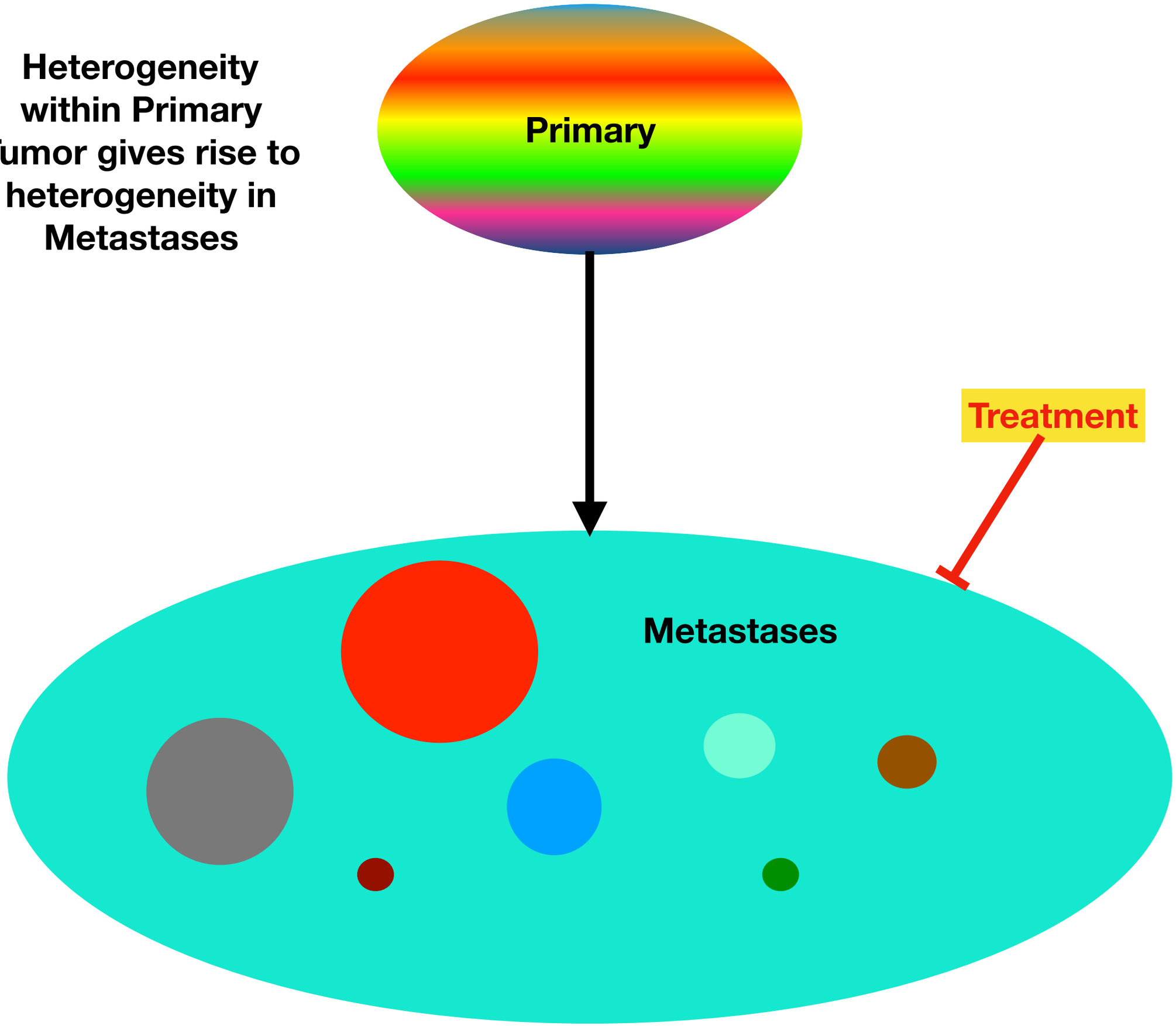
… BUT adaptive therapy can also be about characterization of the disease state

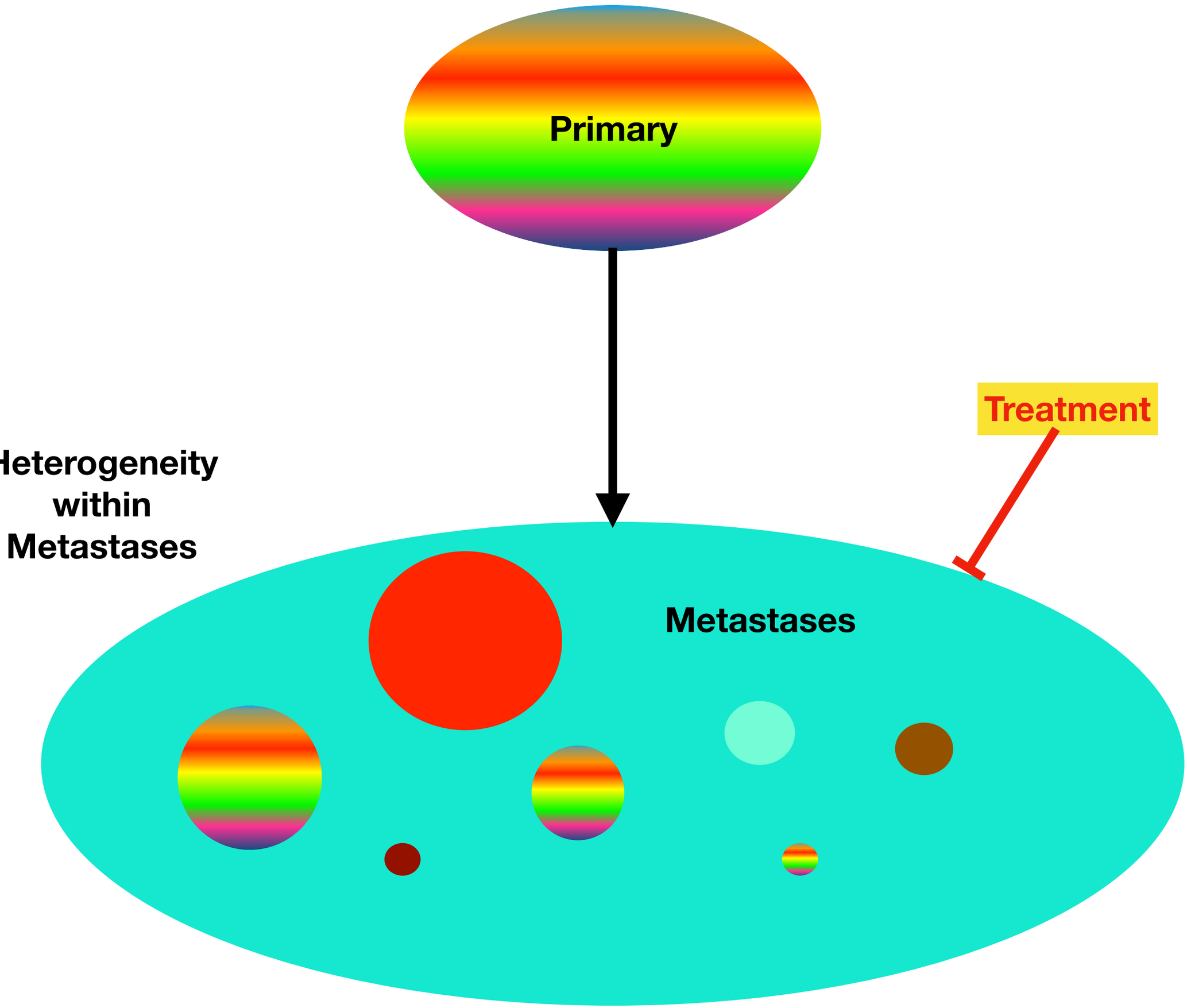
simple, right?



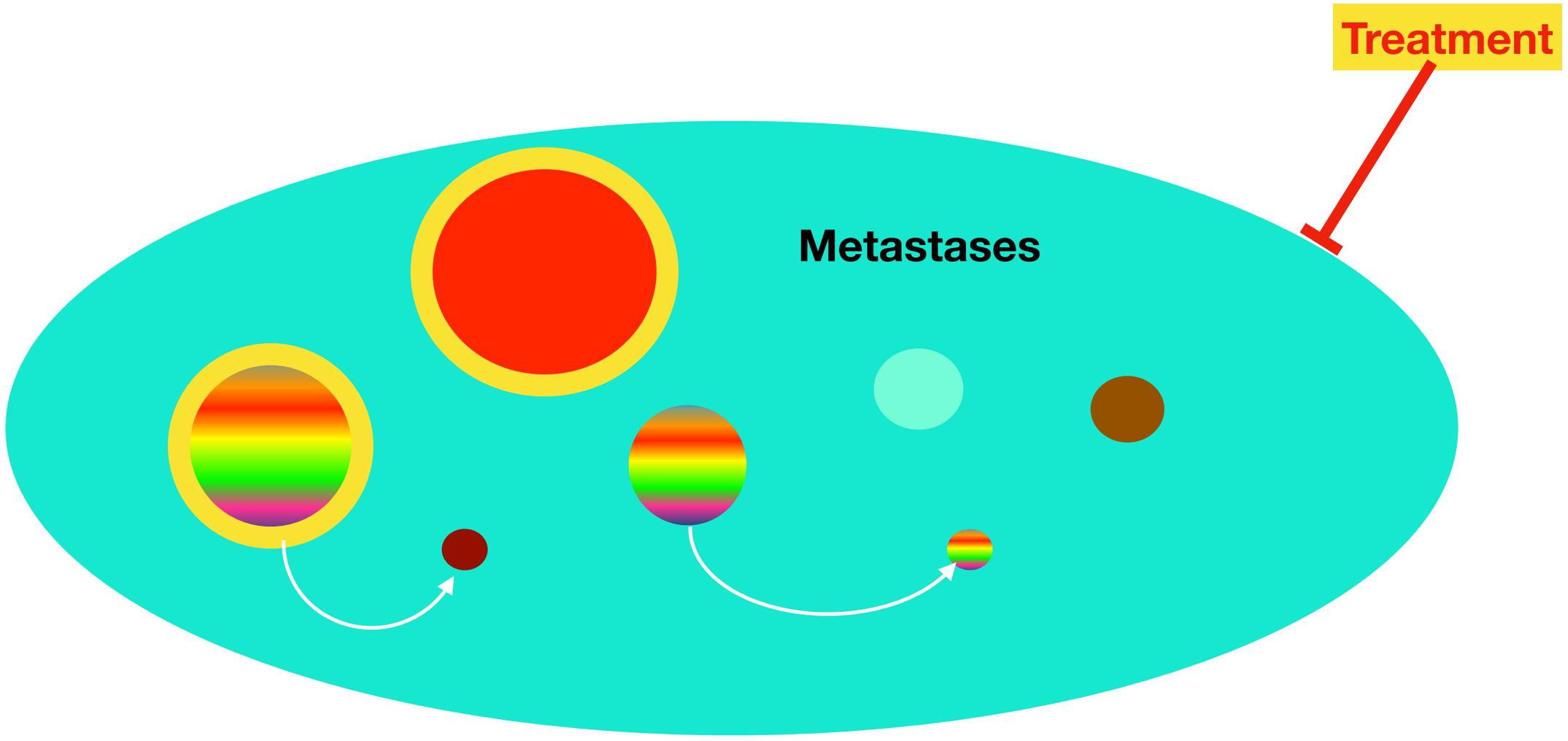

Primary
Metastatic Seeding
Timing affects
sizes of metastases
Treatment
Metastases

Heterogeneity within Primary Tumor gives rise to heterogeneity in Metastases




Primary
Treatment
Heterogeneity within Metastases
Metastases

There could be seeding from mets to mets



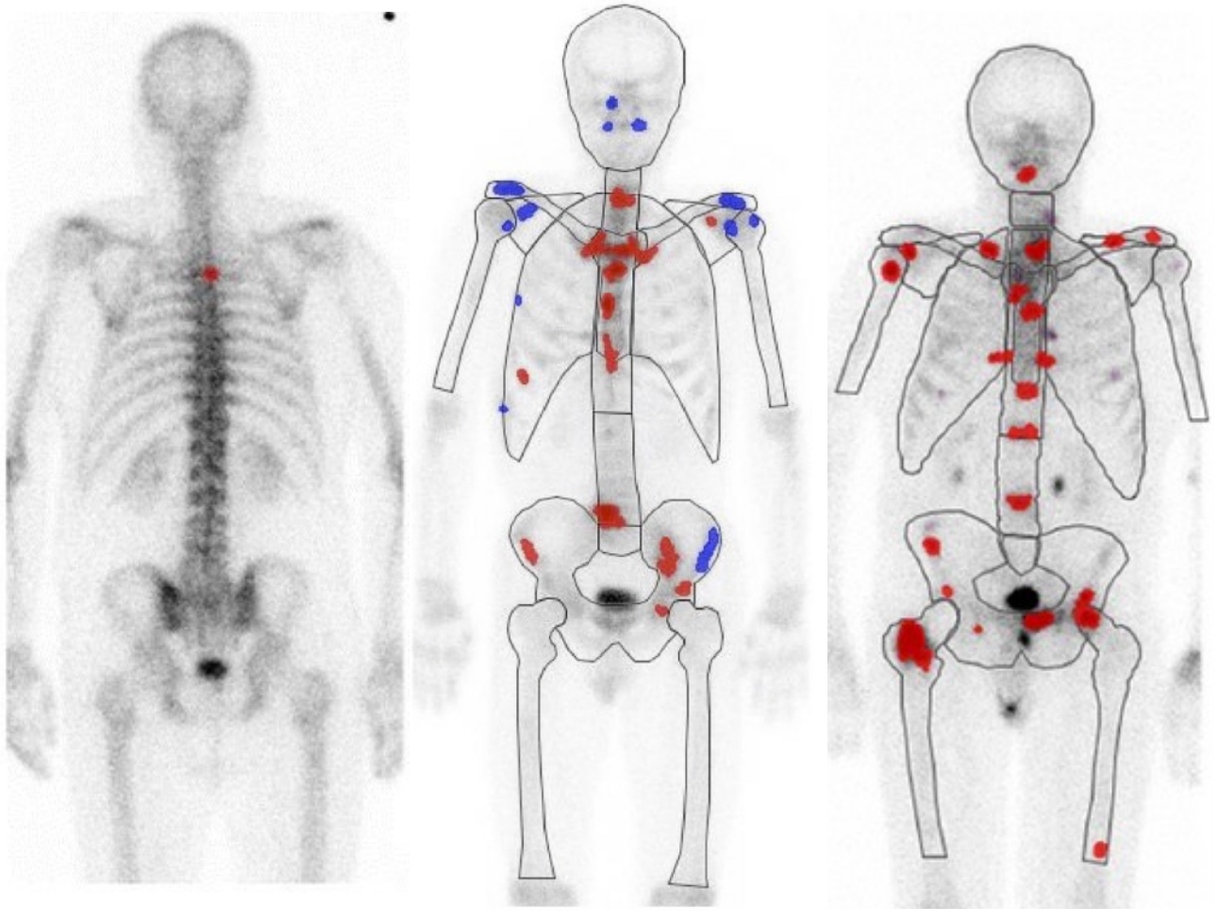
Metastases are not binary.

"One of the reasons metastasis is so difficult to define is that the same word describes the process and the outcome."

Do we need to redefine a cancer metastasis and staging definitions?

Danny R. Welch, Ph.D.

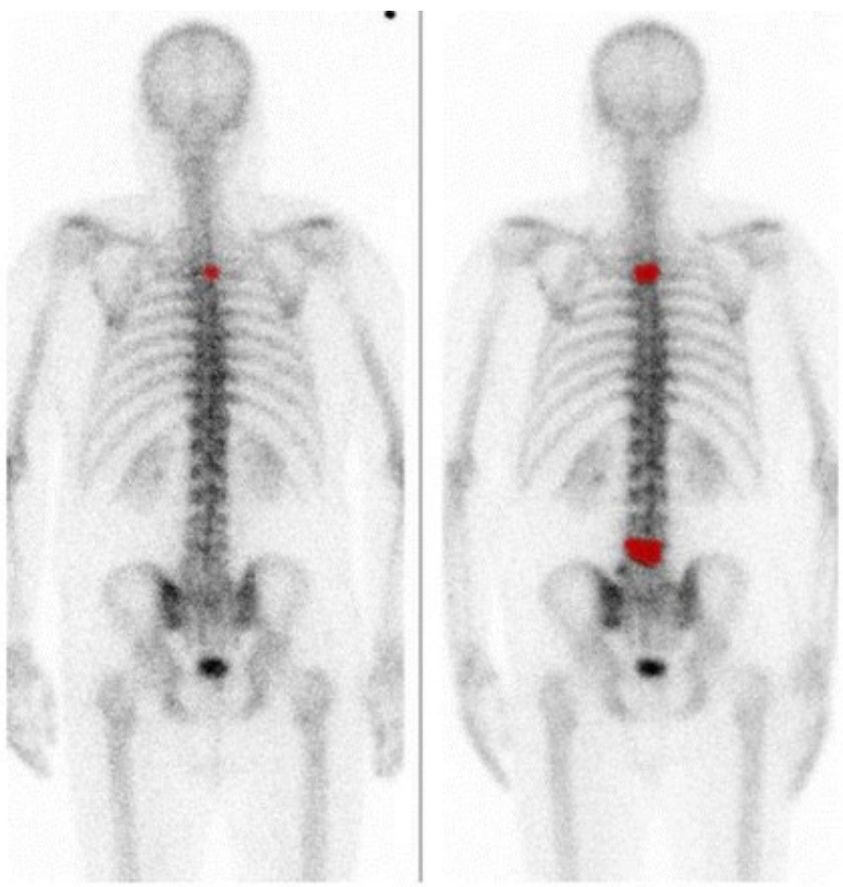
Breast Dis. 2006; 26: 3–12.



Different distributions of mets

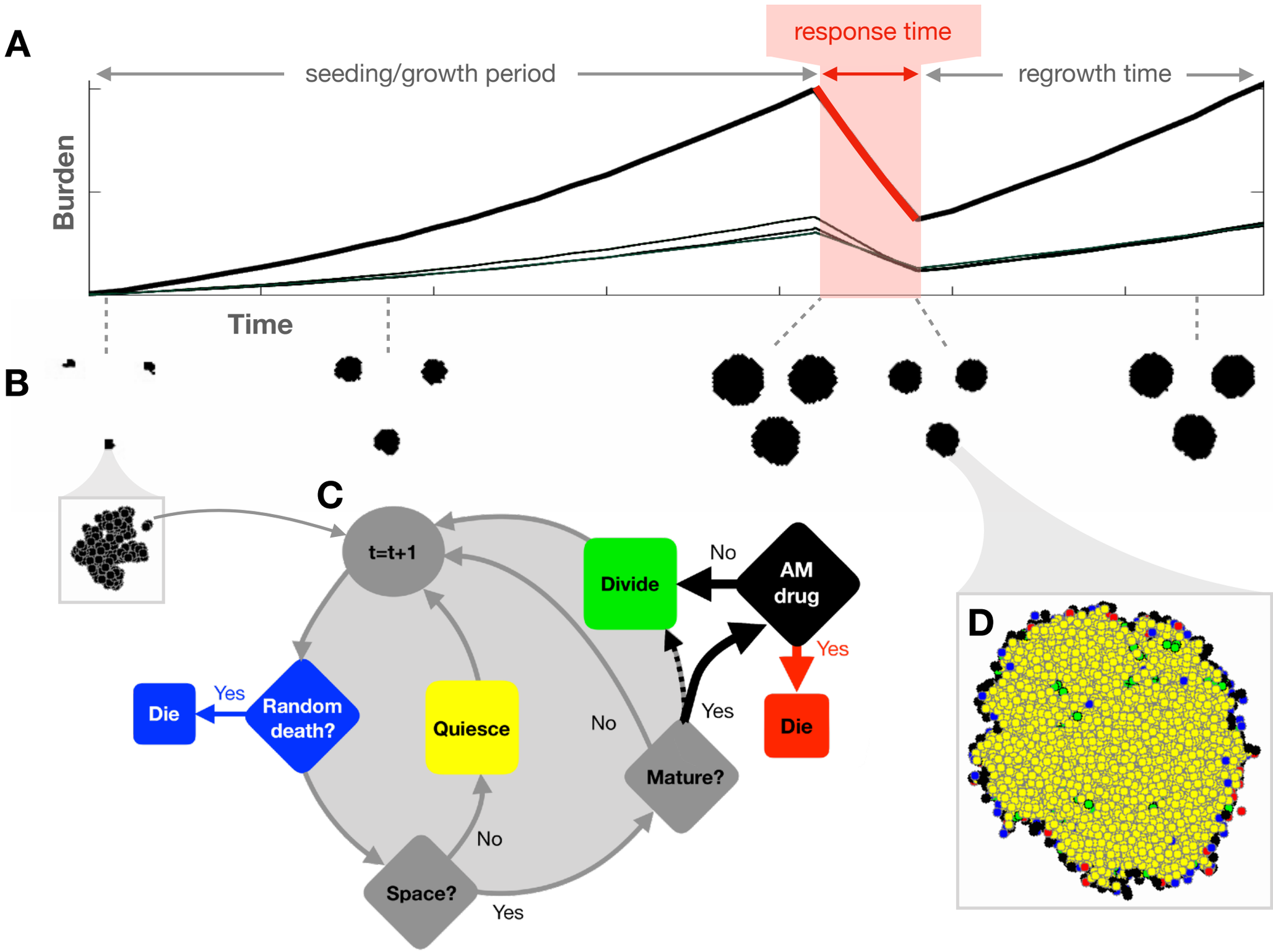
"To me, cancer is a verb, not a noun. 'You're cancering.' It's not something the body gets, it's something the body does."
-David Agus

Pre-Tx **Post-Tx**



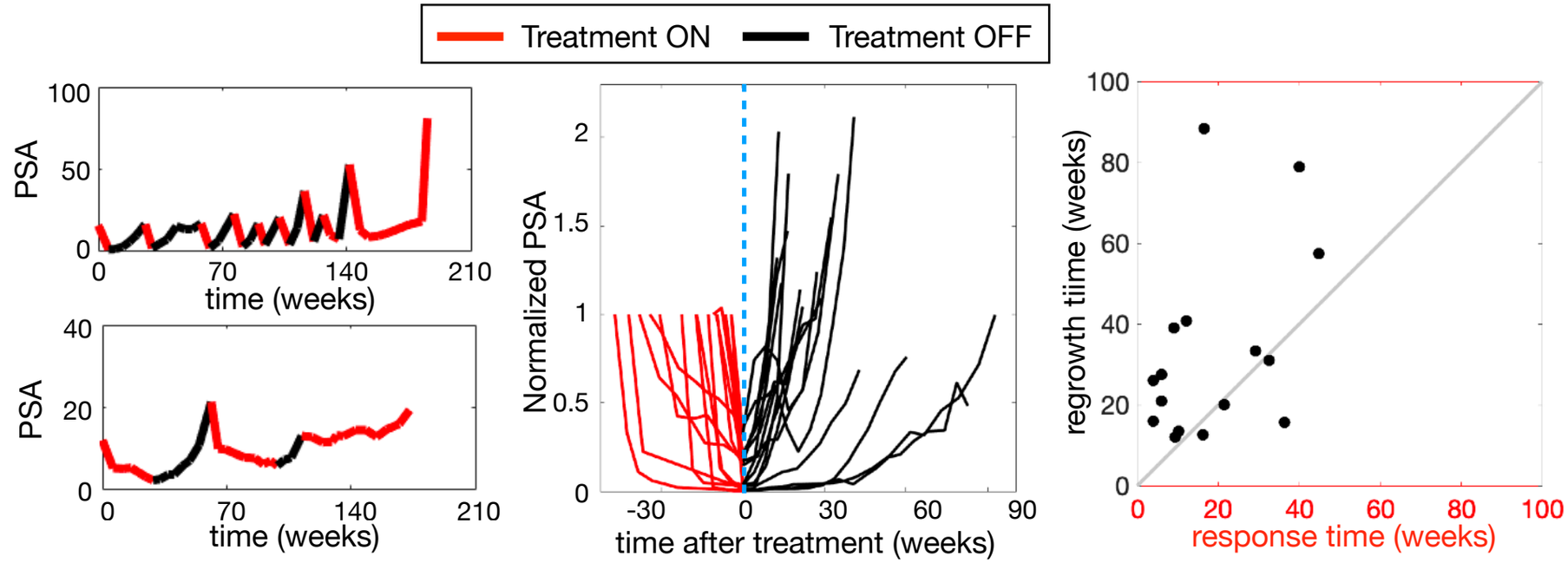
Change in mets over time

Model framework

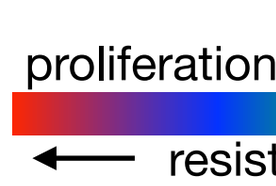


What affects adaptive therapy cycle dynamics?

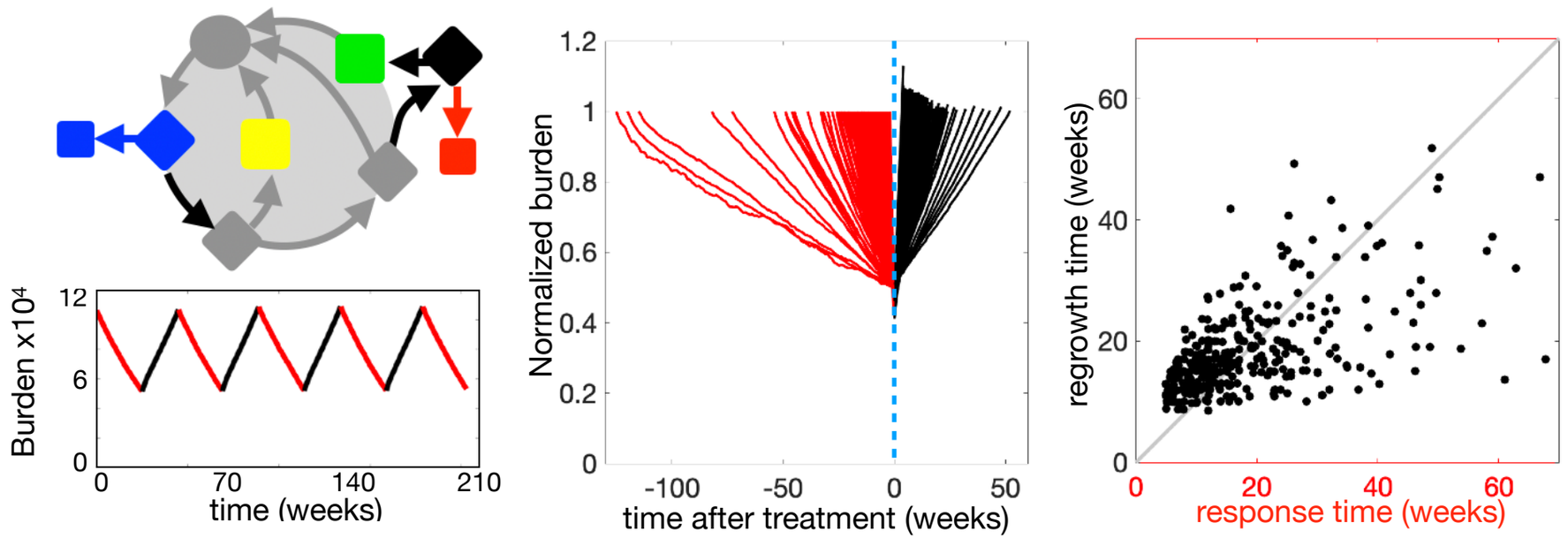
AT trial data



Parameter	Meaning	Value	Units
b	total cell burden	20,000-150,000	cells
m	metastases count	1-10	mets
s	sensitivity	60-100	%
d	cell turnover	0-0.06	day^{-1}
σ_{S1}	Intertumor heterogeneity	0	%
σ_{S2}	Intratumor heterogeneity	0	%



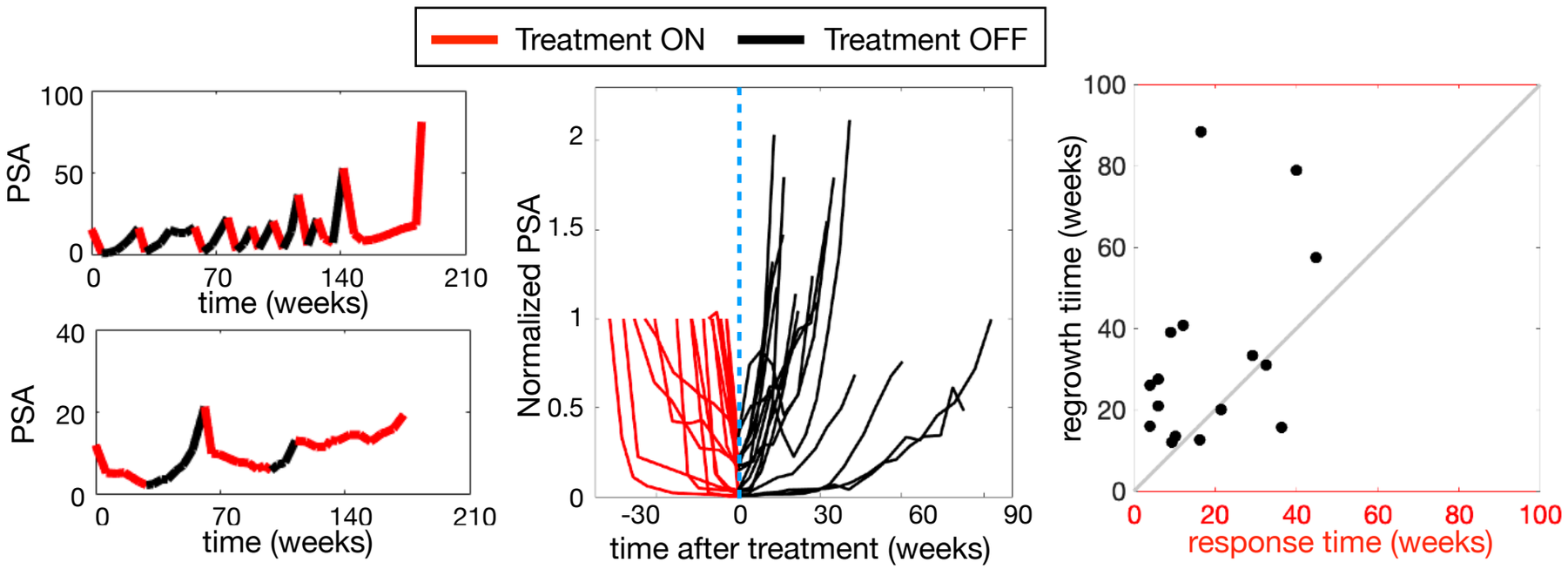
model: cell cycle dependent drug



Cell cycle independent drug shifts toward quicker response times and longer regrowth times

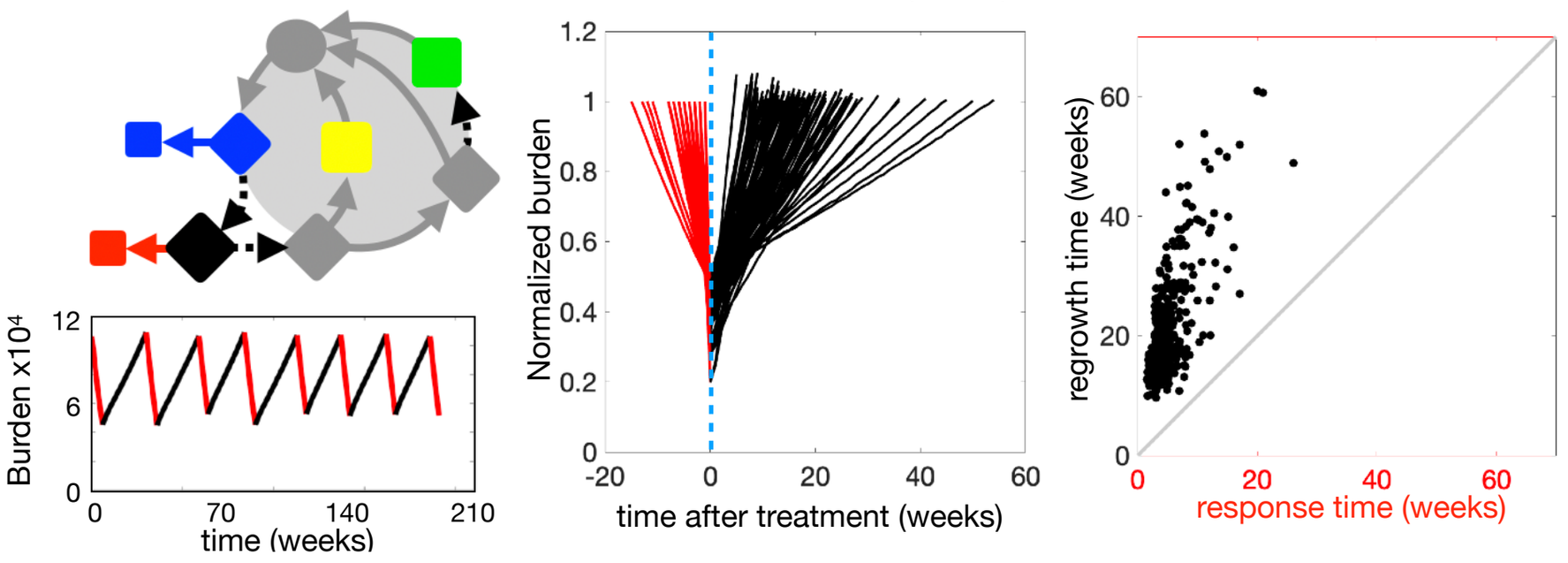
AT trial data

A



model: cell cycle independent drug

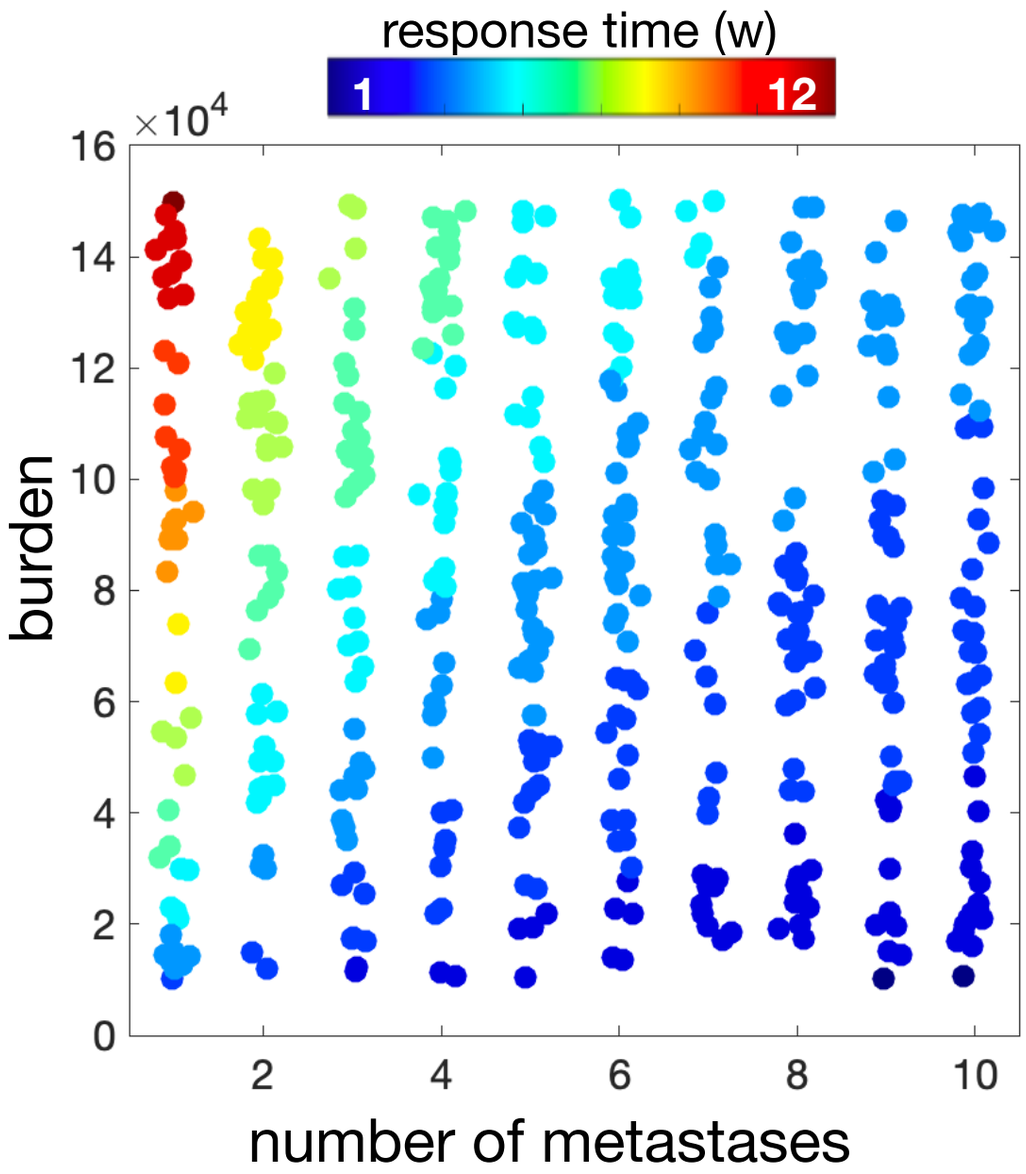
C

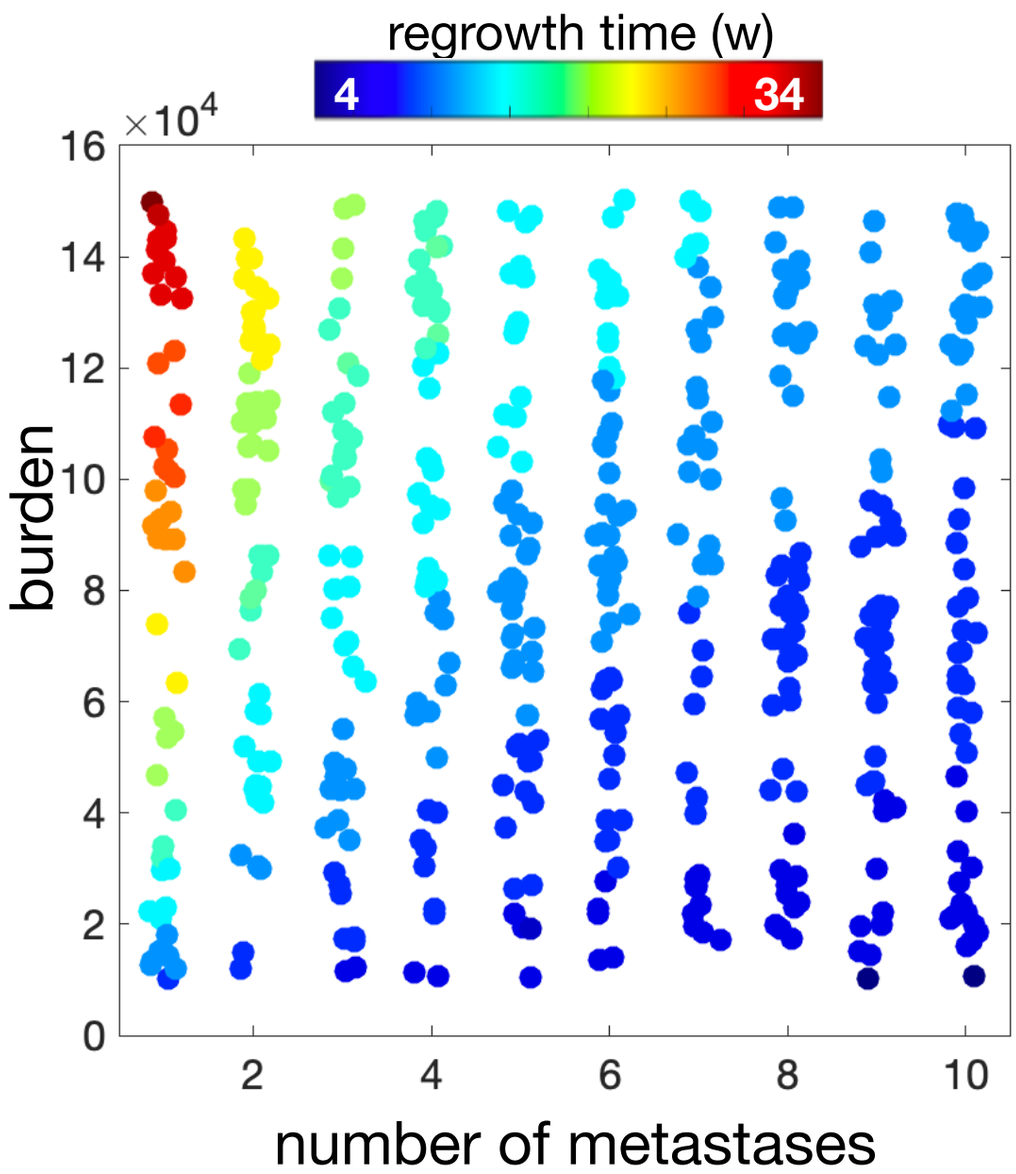


How does *burden* and *number of metastases* affect adaptive therapy cycling?

Longer cycles for few mets with high burden
Shorter cycles for many mets with low burden

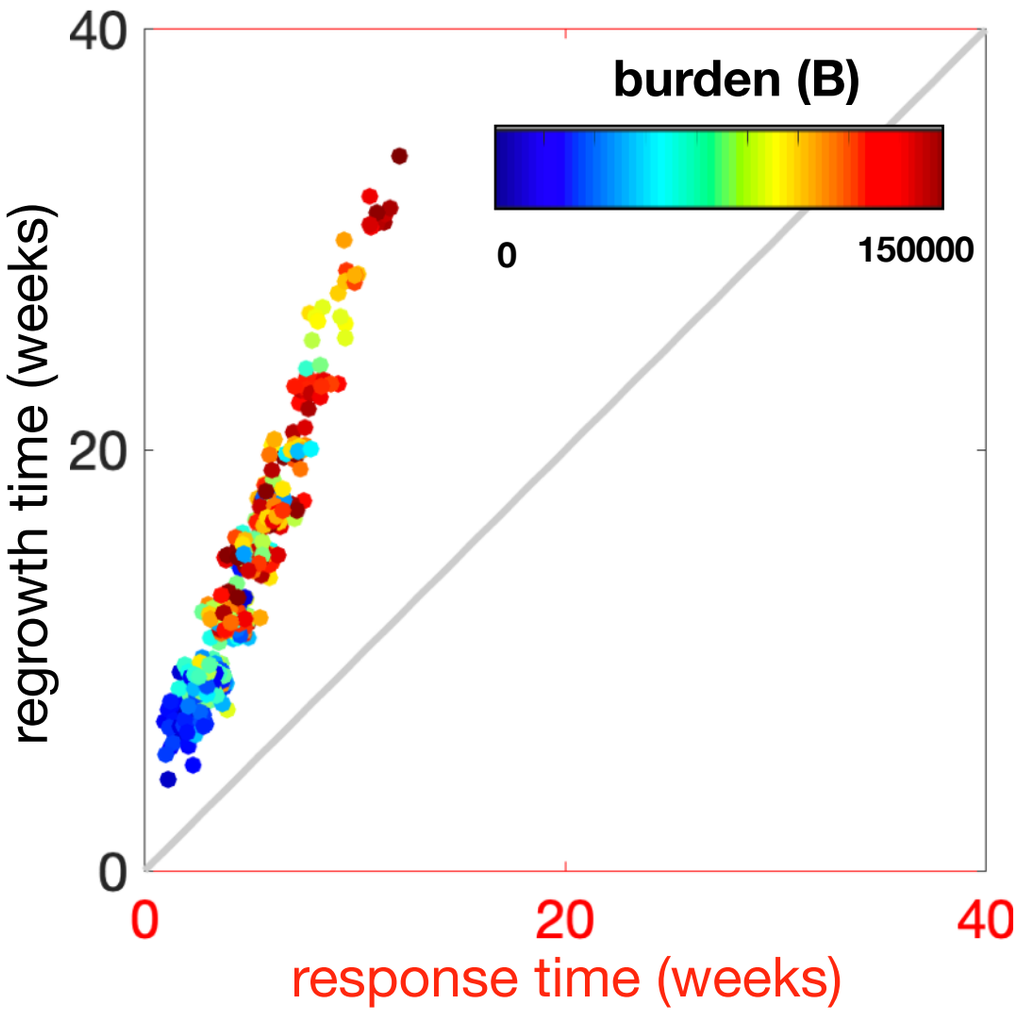
Parameter	Value
b	20,000-150,000
m	1-10
s	100
d	0
σ_{S1}	0
σ_{S2}	0

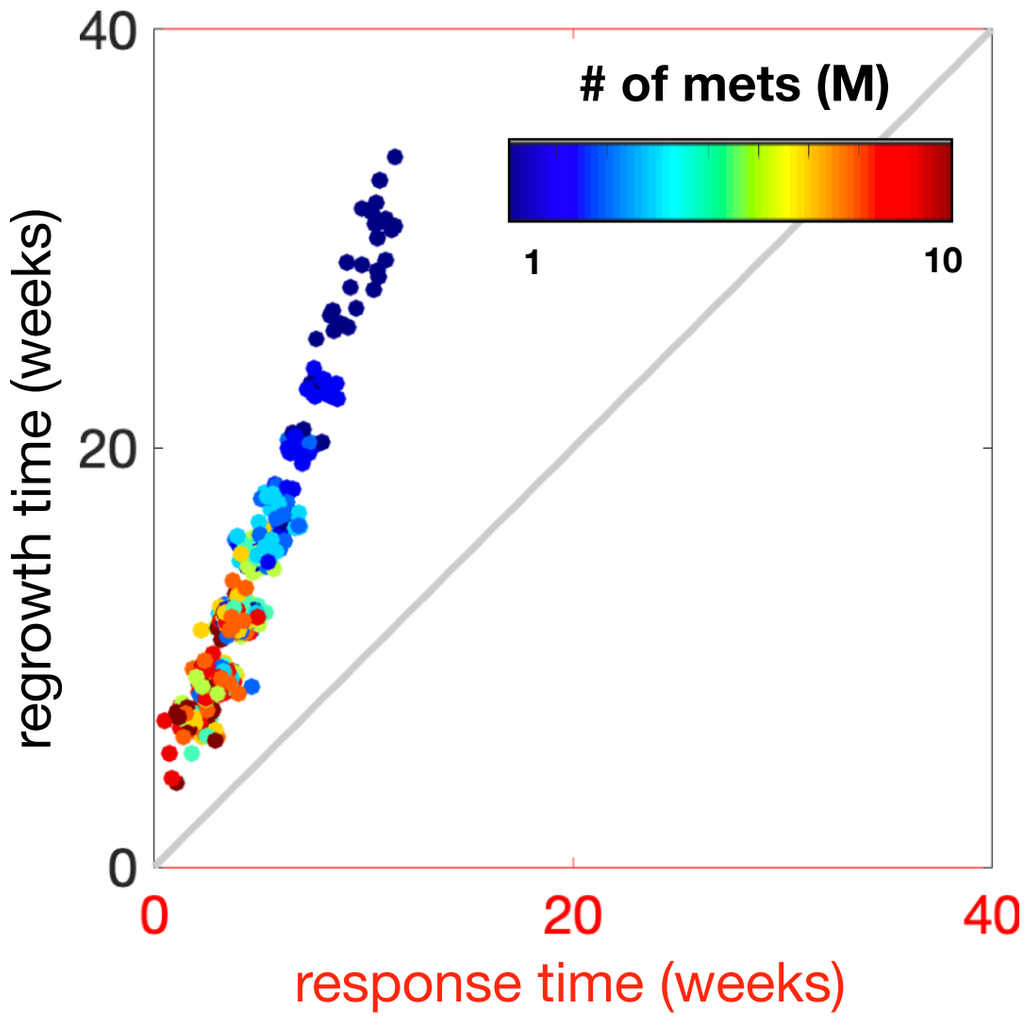


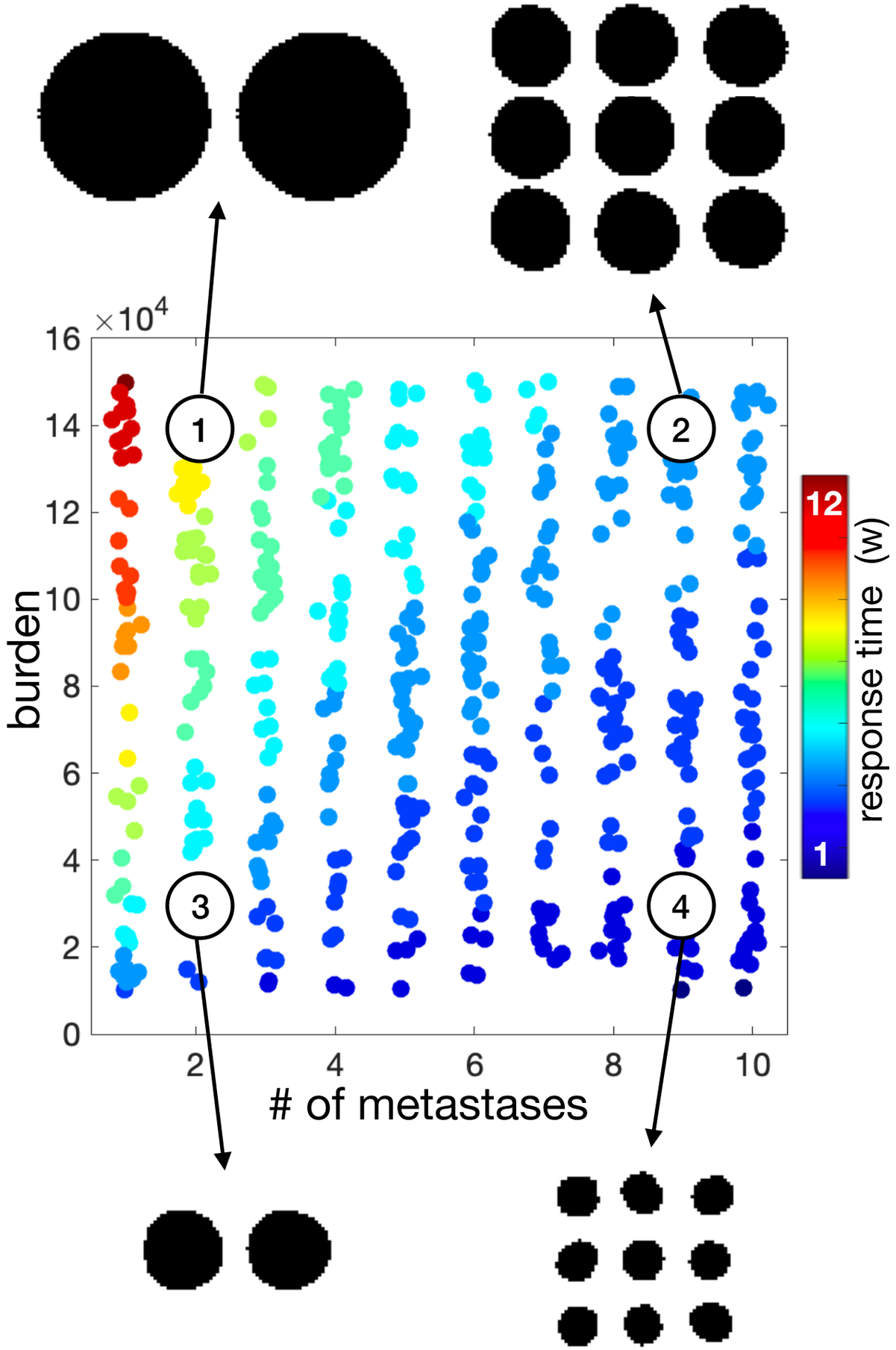


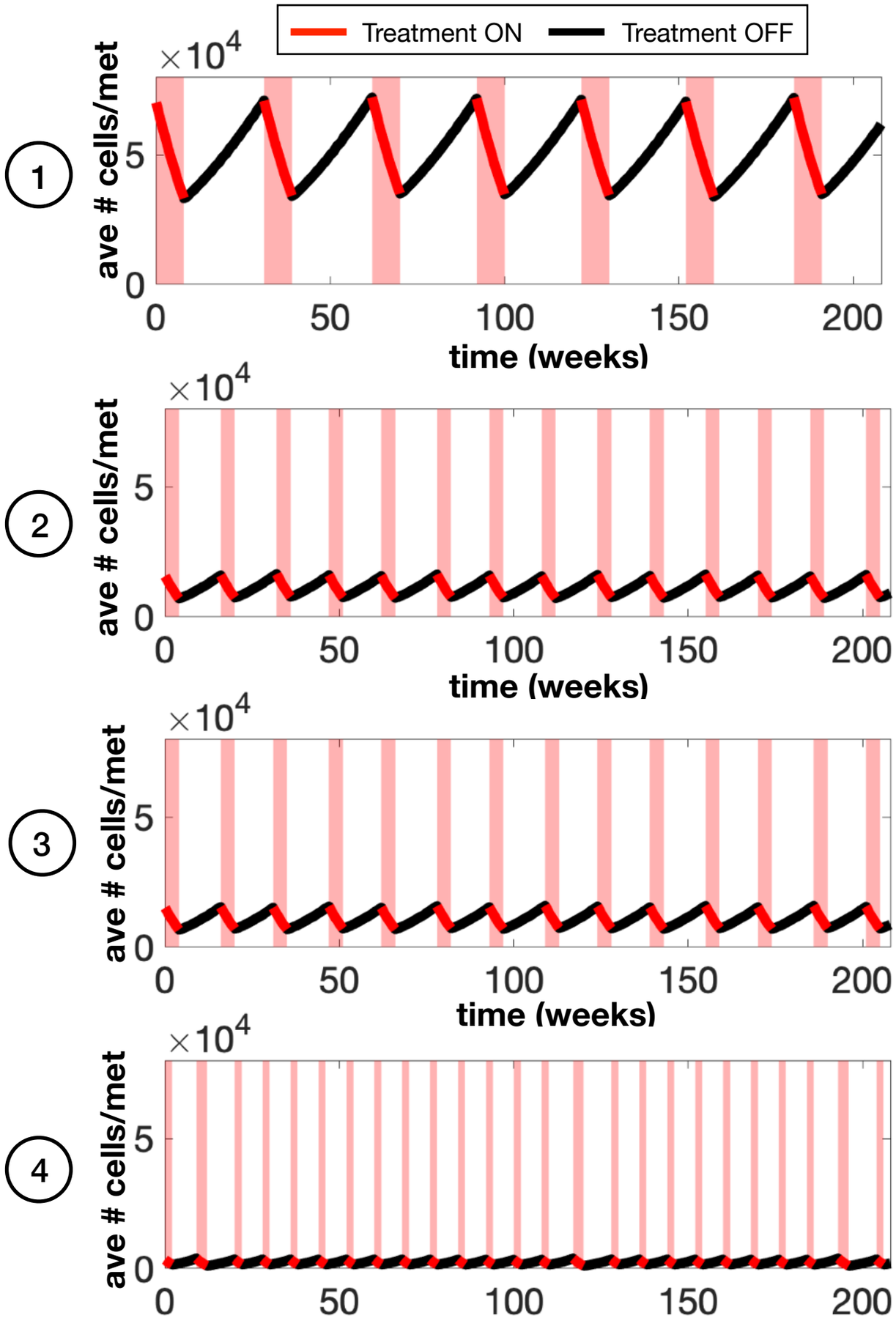
Some correlation with

1. **Shorter cycles: small burden and many mets**
2. **Longer cycles: higher burden and few mets**

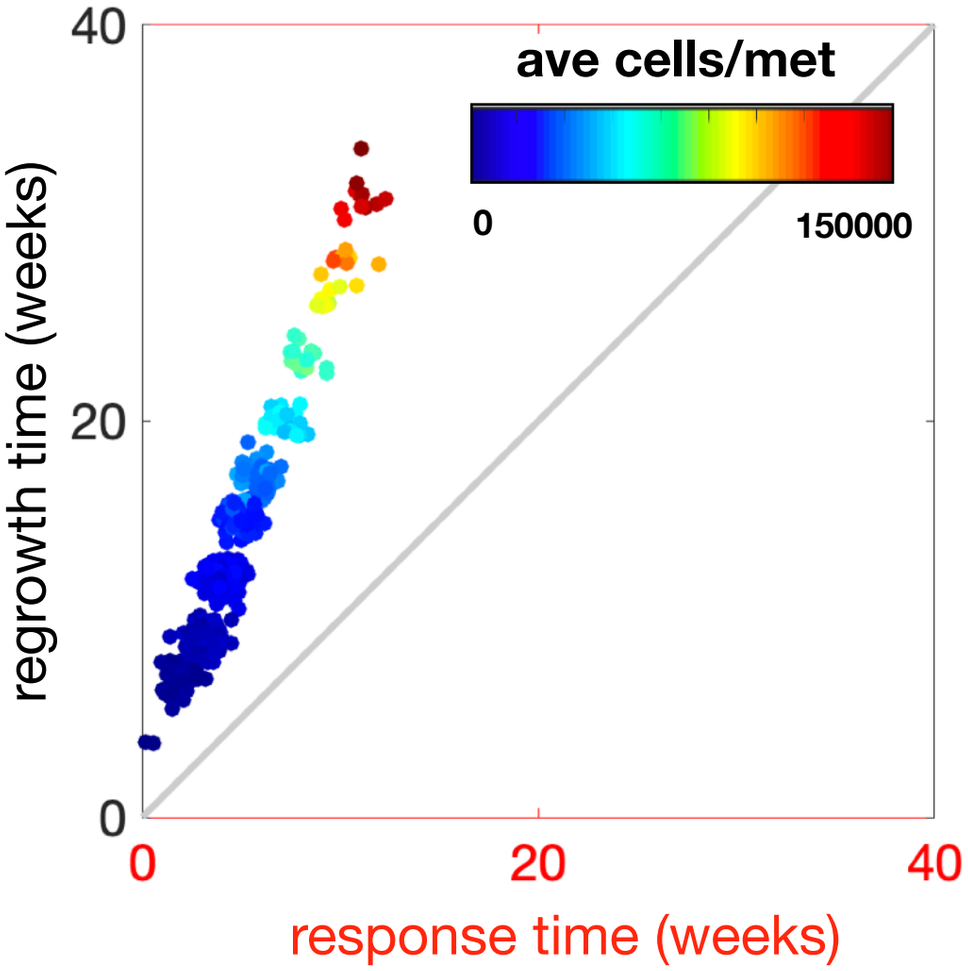


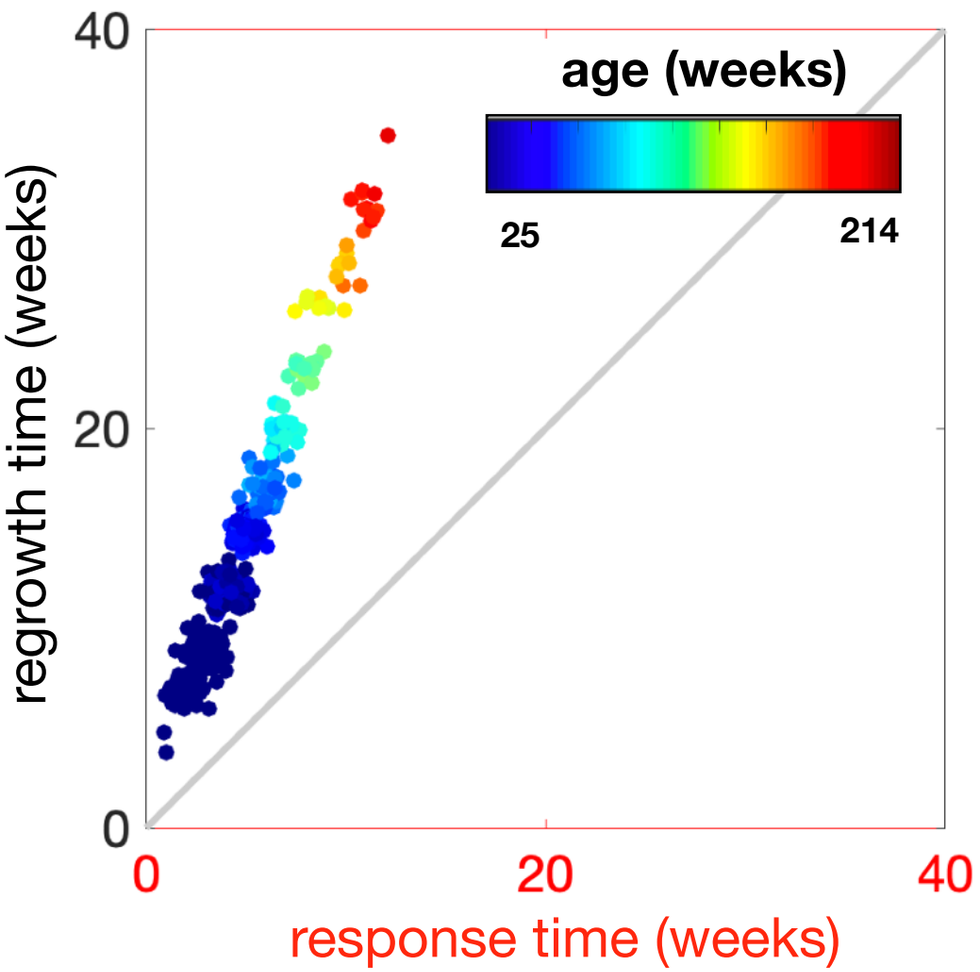



1
2
3
4
$\times 10^4$
16
14
12
10
8
6
4
2
0
burden
2
4
6
8
10
# of metastases
12
1
response time (w)

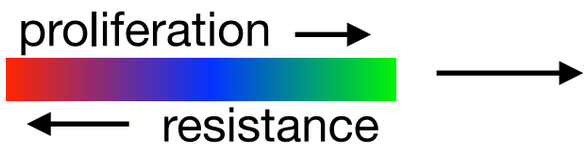

Treatment ON
Treatment OFF
1
2
3
4
$\times 10^4$
ave # cells/met
5
0
0
50
100
150
200
time (weeks)

Shorter cycles: younger and smaller
Longer cycles: older and larger

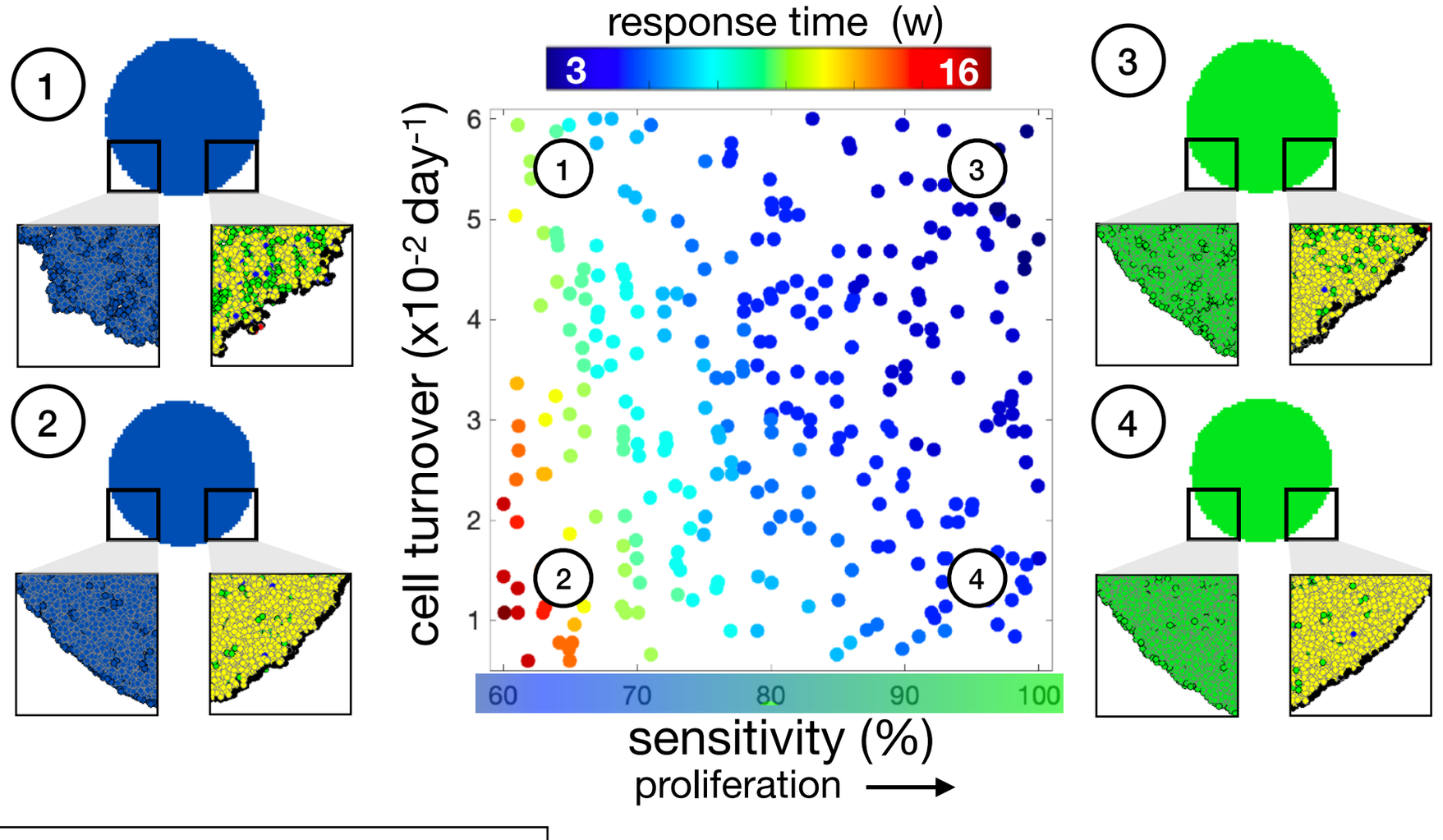


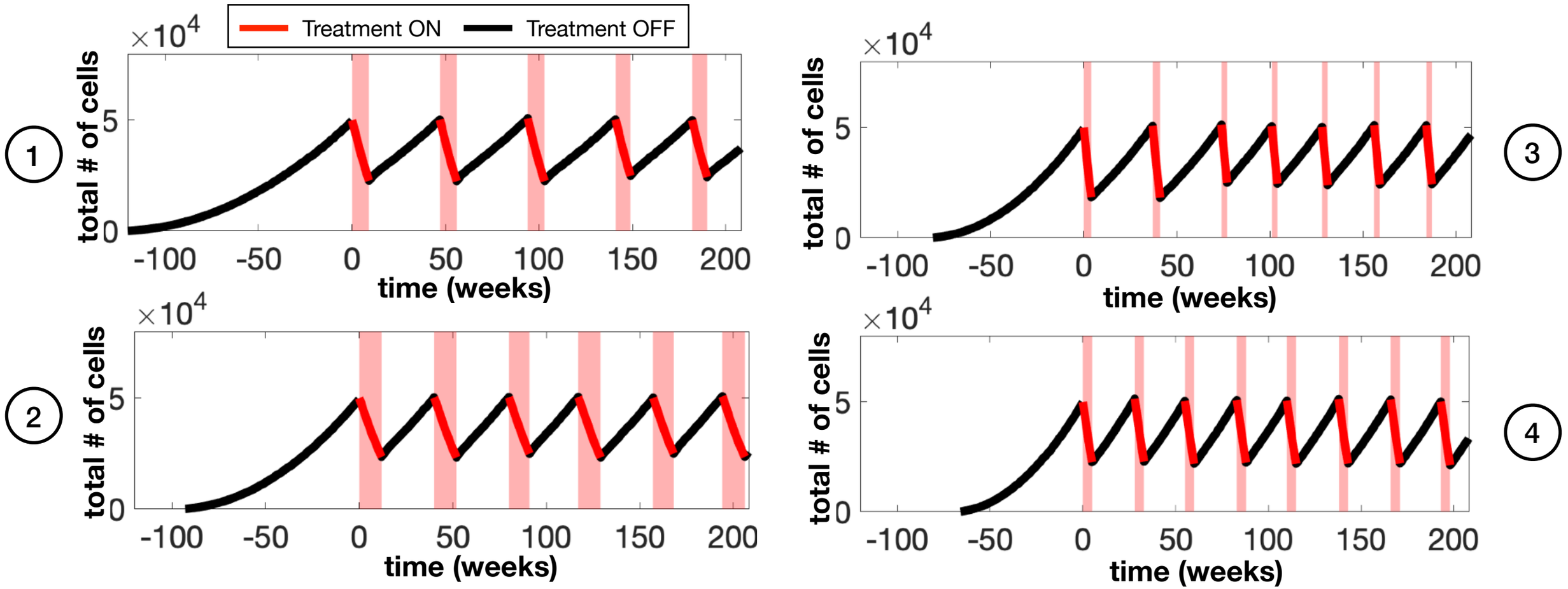


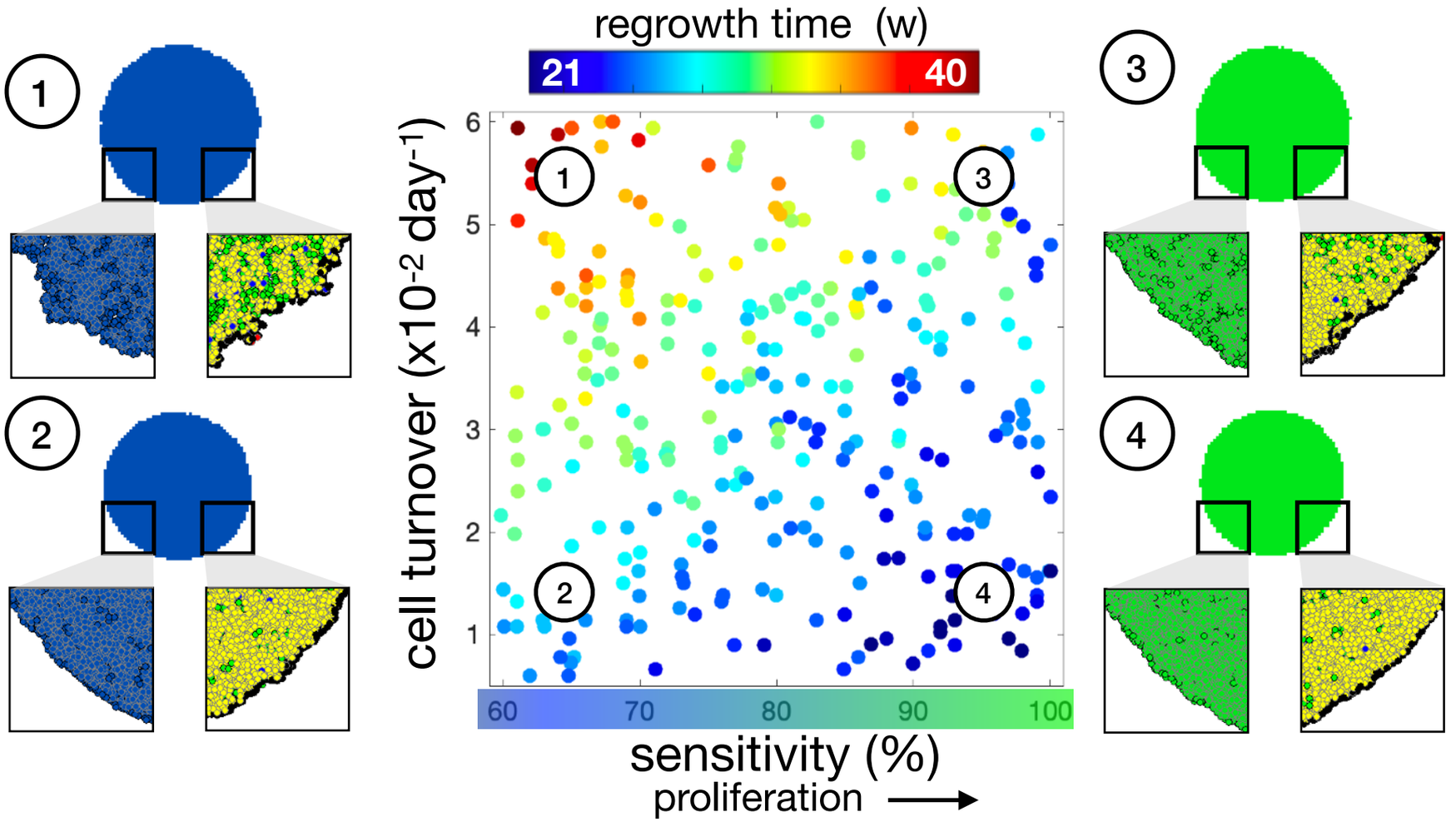
How does *sensitivity* and *cell turnover* affect adaptive therapy cycling?

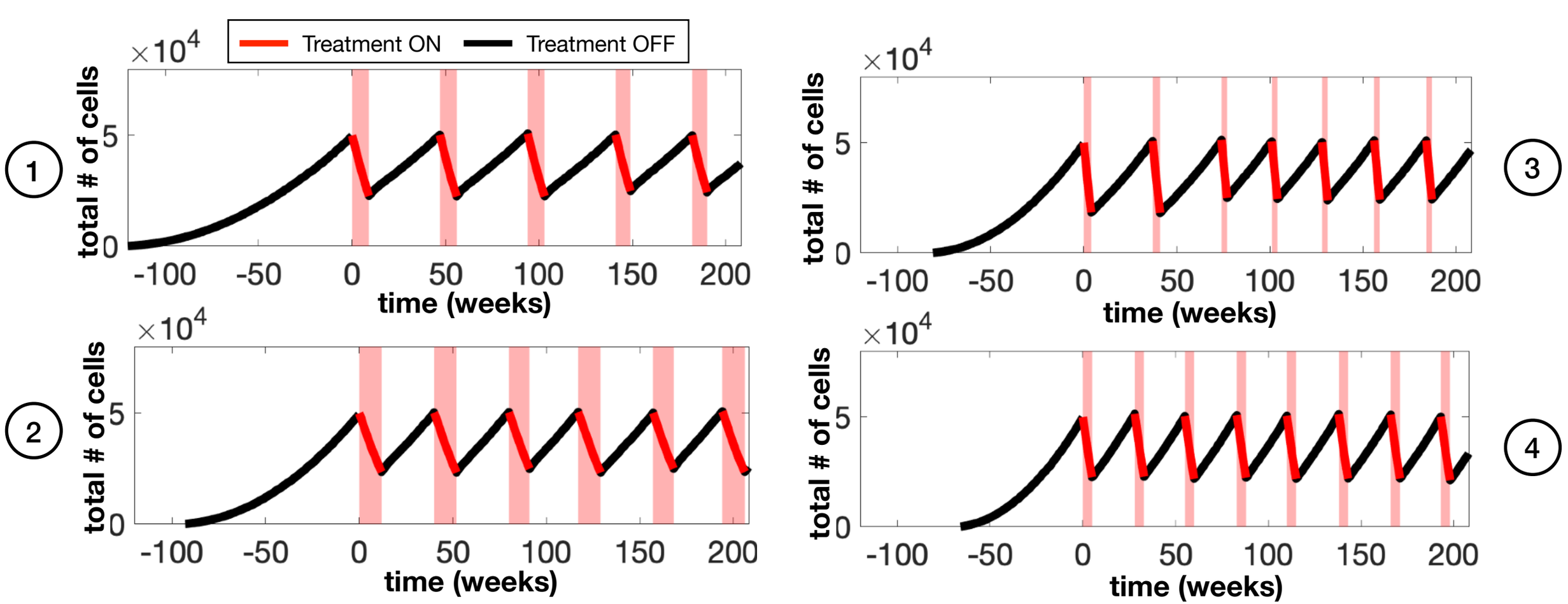


Parameter	Value
b	50,000
m	1
s	60-100
d	0-0.06
σ_{S1}	0
σ_{S2}	0

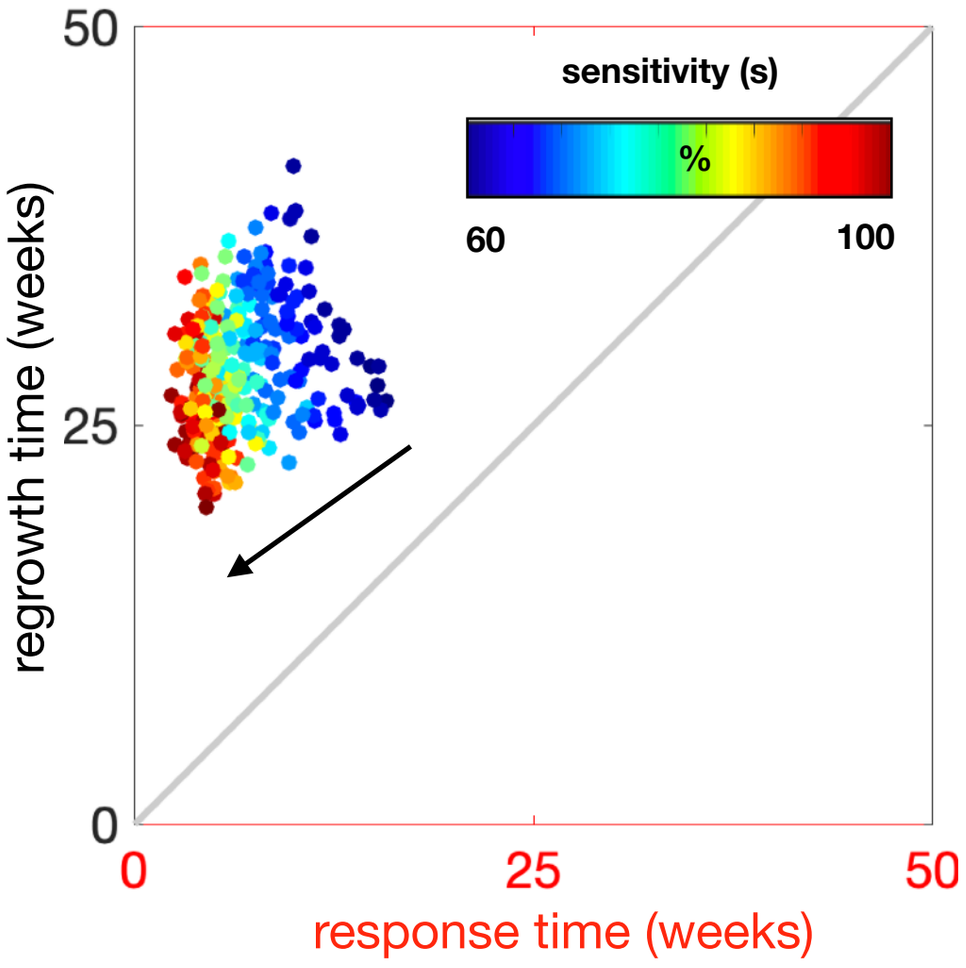

response time (w)
3
16
cell turnover (x10-2 day-1)
6
5
4
3
2
1
60
70
80
90
100
sensitivity (%)
proliferation
1
2
3
4


Treatment ON
Treatment OFF
×10^4
total # of cells
5
0
-100
-50
0
50
100
150
200
time (weeks)
1
2
3
4

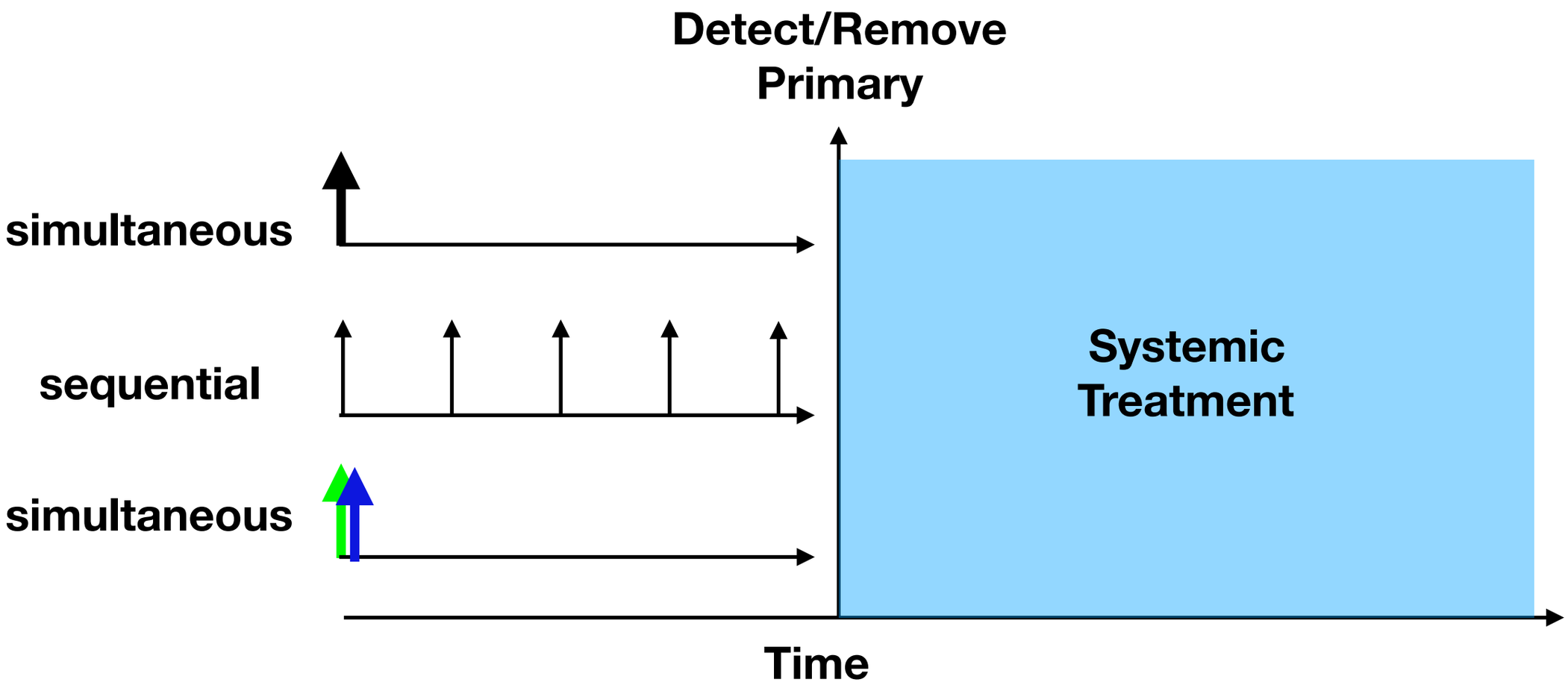

regrowth time (w)
21
40
cell turnover (x10-2 day-1)
6
5
4
3
2
1
60
70
80
90
100
sensitivity (%)
proliferation
1
2
3
4


Treatment ON
Treatment OFF
×10^4
total # of cells
5
0
-100
-50
0
50
100
150
200
time (weeks)
1
2
3
4

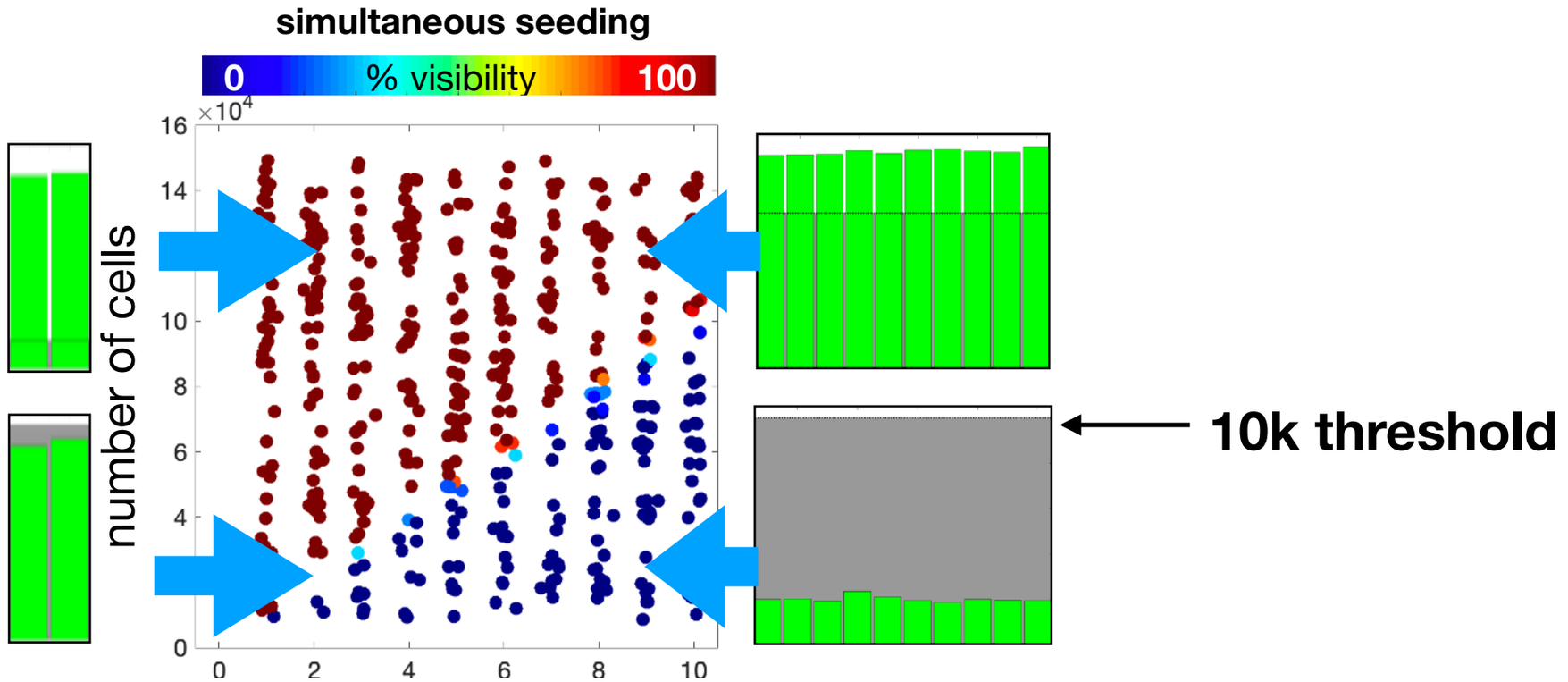
More sensitive: quicker response/regrowth times
More turnover: quicker response times, longer regrowth times

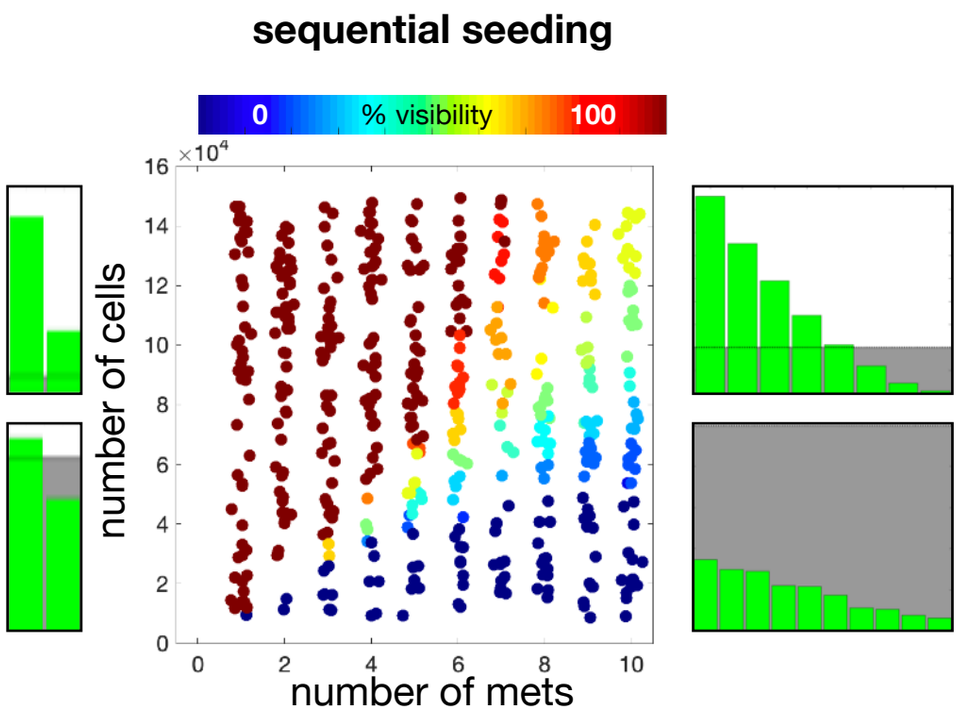


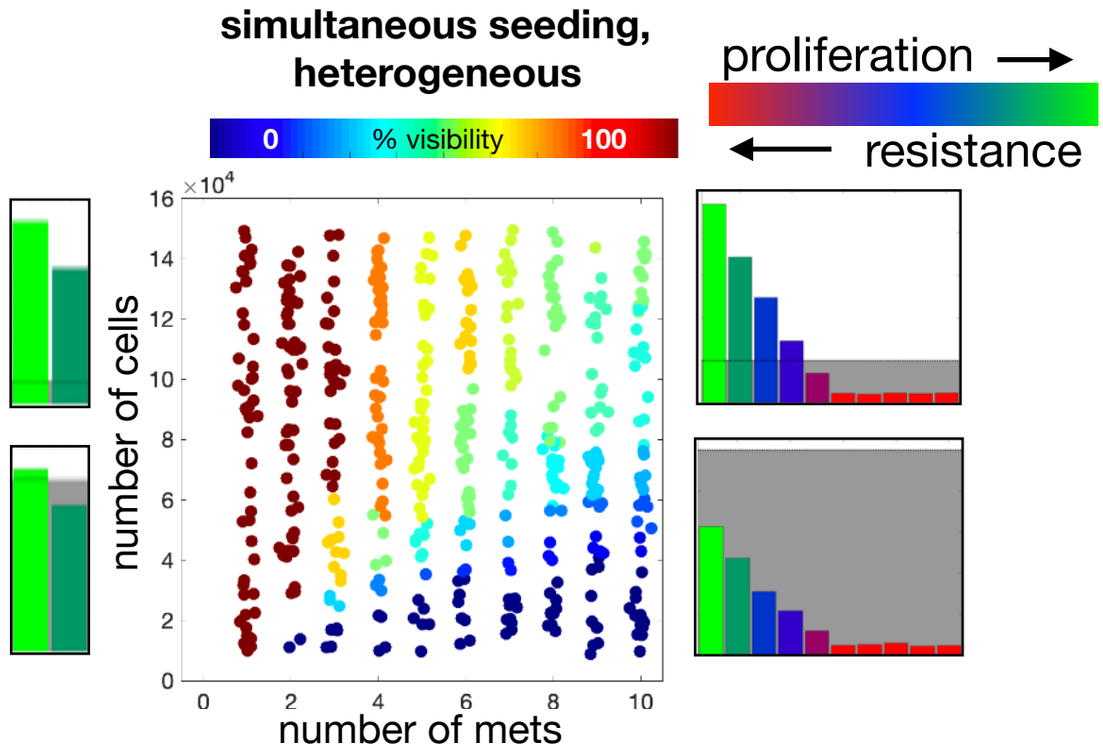
How does seeding/heterogeneity affect observed burden?



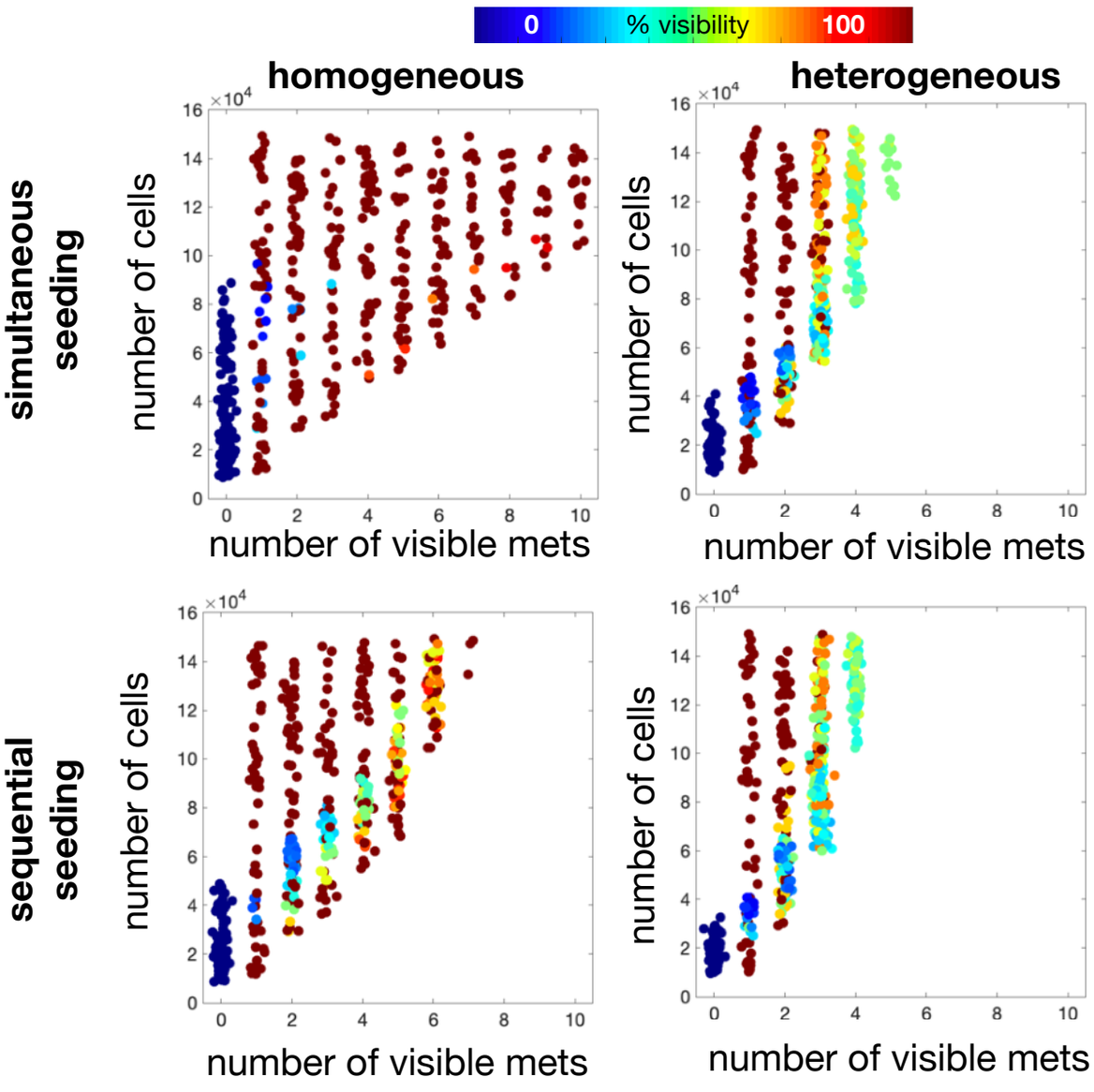
Metastases below the threshold of visibility

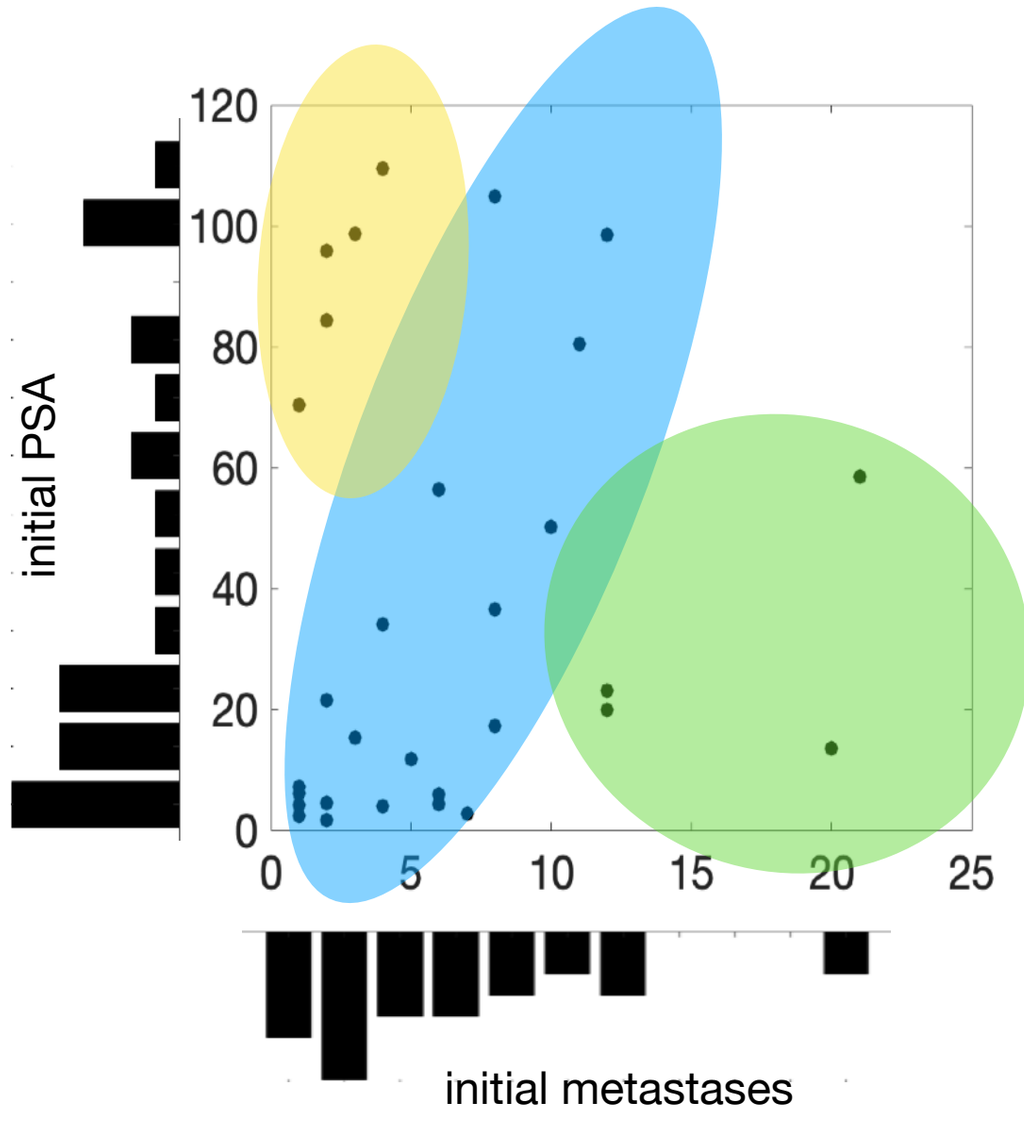






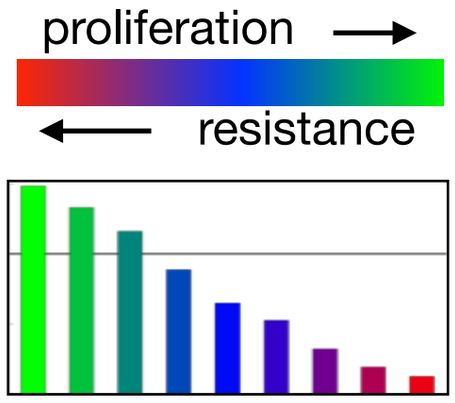
Many mets with low burden could go undetected

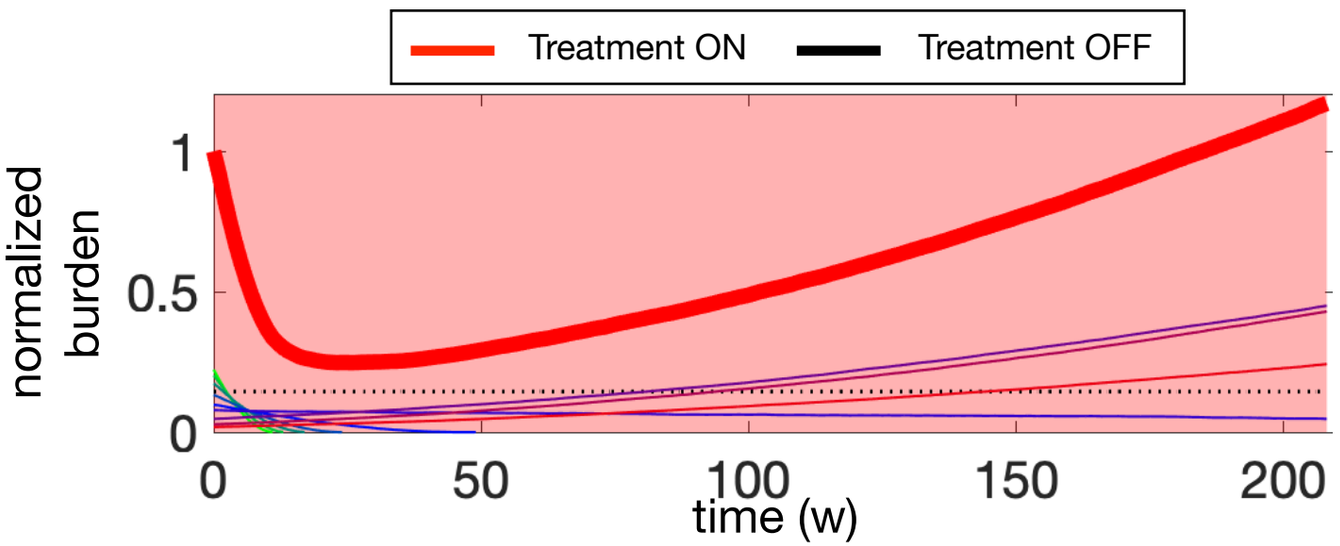


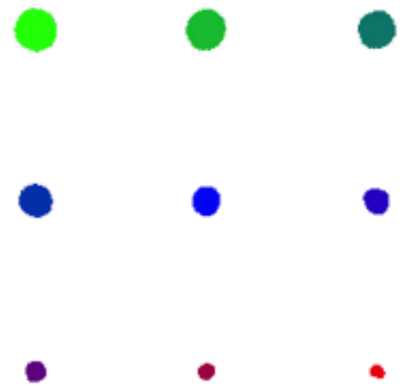


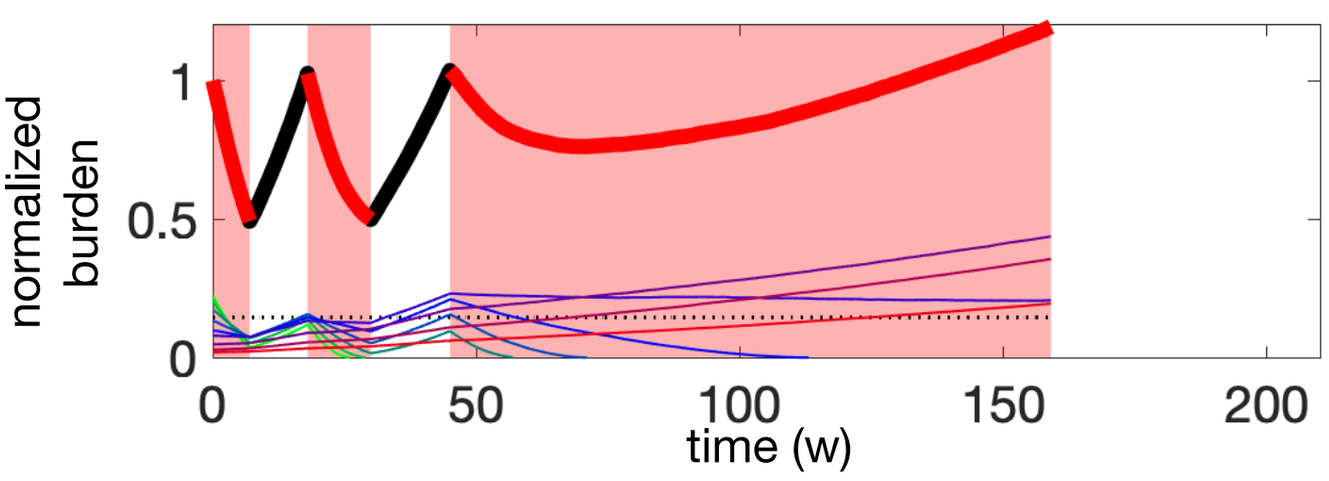
How does heterogeneity affect longer term adaptive therapy dynamics?

CT better with intertumor heterogeneity

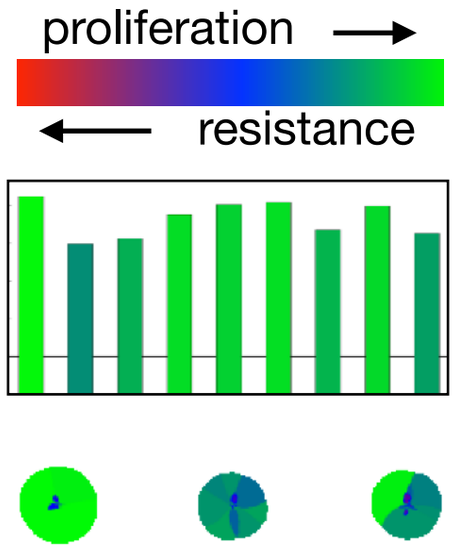


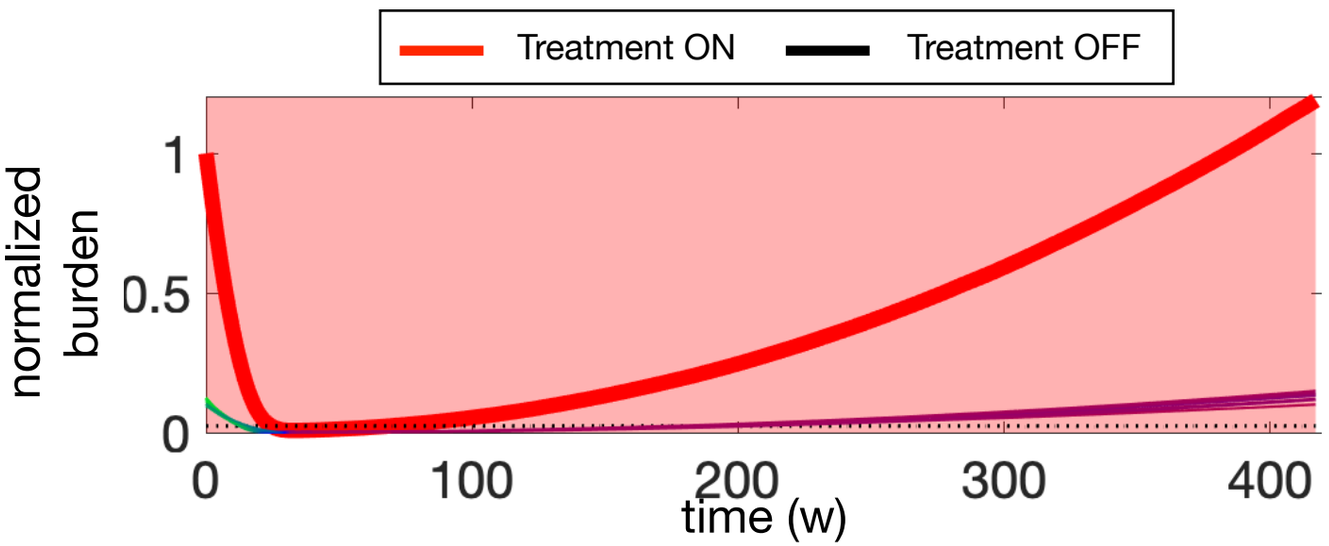


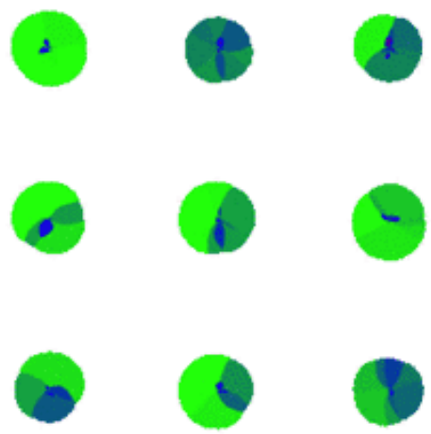


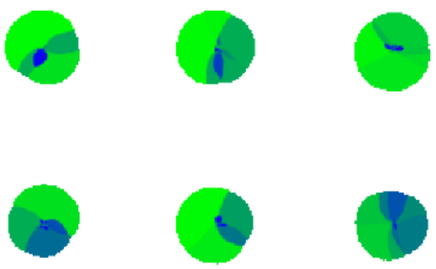


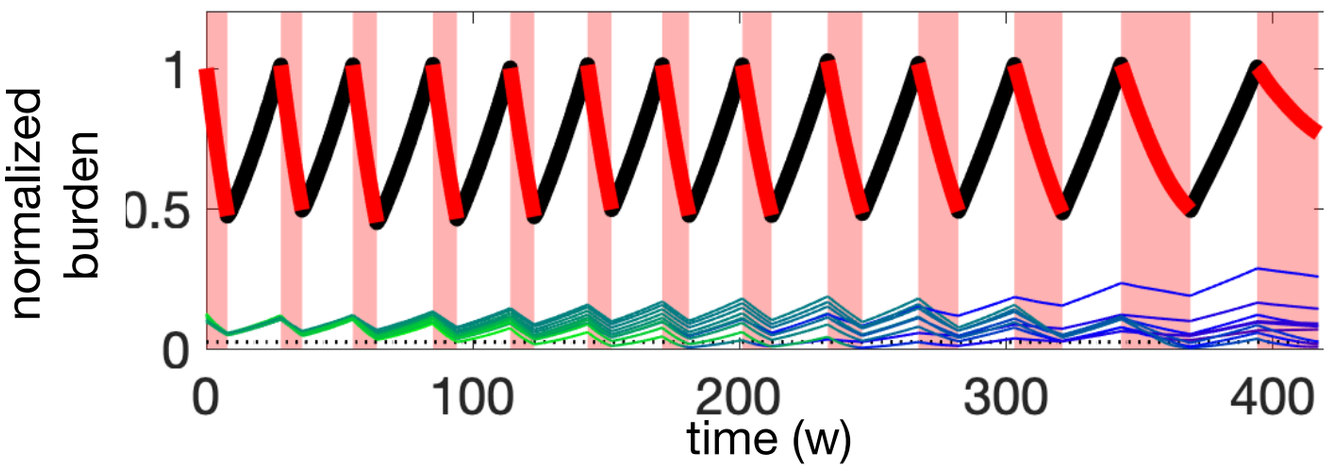
AT better with intratumor heterogeneity

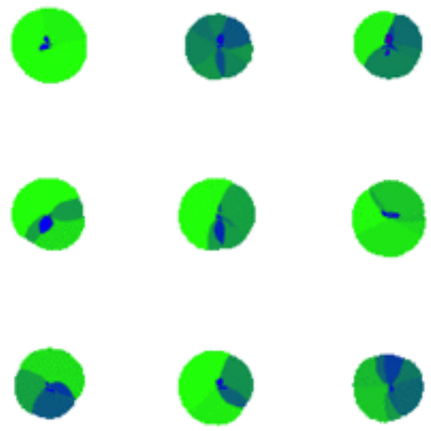












Conclusions

1. **A cell cycle independent drug leads to shorter response times than regrowth times.**

2. **Cycles are semi-correlated with burden and number of mets, but there are clear trends associated with tumor size, age, sensitivity, and cell turnover.**

3. **Micrometastases smaller than the imaging threshold can go undetected but still contribute to tumor burden.**

4. **CT works better with intertumor heterogeneity and AT works better with intratumor heterogeneity.**

5. **Characterizing metastases as only a binary state is inadequate.**

Acknowledgements

Sandy Anderson
Maxi Strobl
Jeff West
Bob Gatenby
Jingsong Zhang
Mark Robertson-Tessi

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Evolutionary Therapy