Unlocking synergy: Navigating Type I Error Control & Heterogeneous Variance in Simulation Studies

Nicholas Hein
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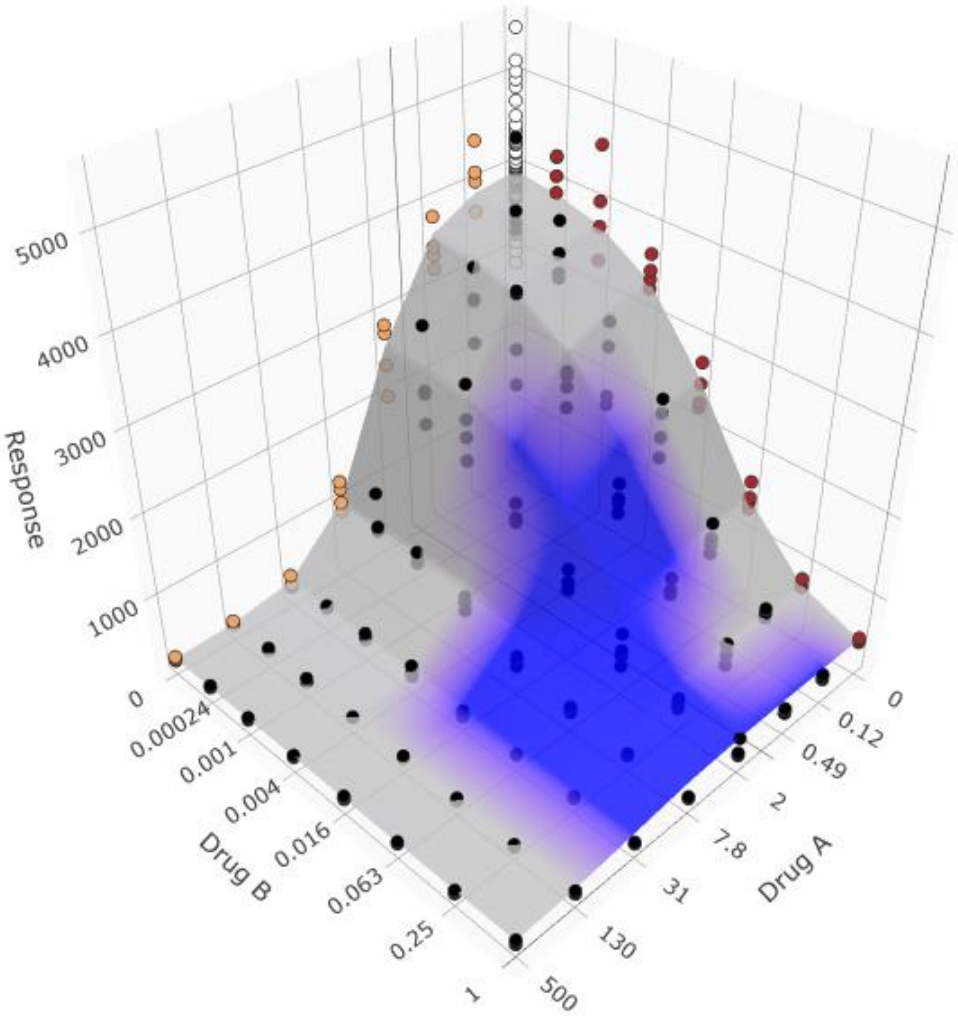
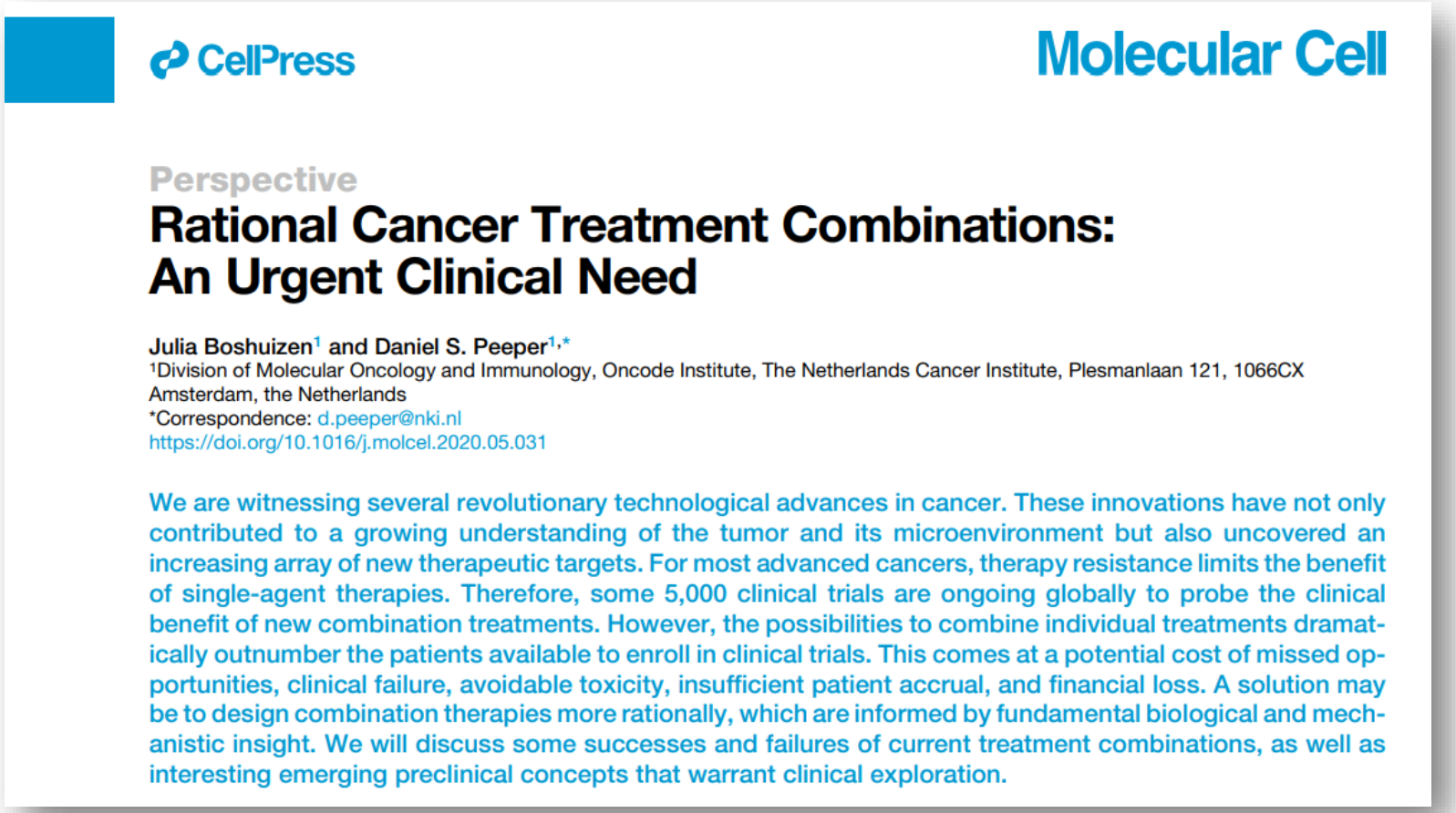
Non-Clinical Statistics Conference

Johnson&Johnson
Innovative Medicine



Already in the 1950s, benefit of combination therapies was realized in cancer treatments



CellPress

Molecular Cell

Perspective

Rational Cancer Treatment Combinations: An Urgent Clinical Need

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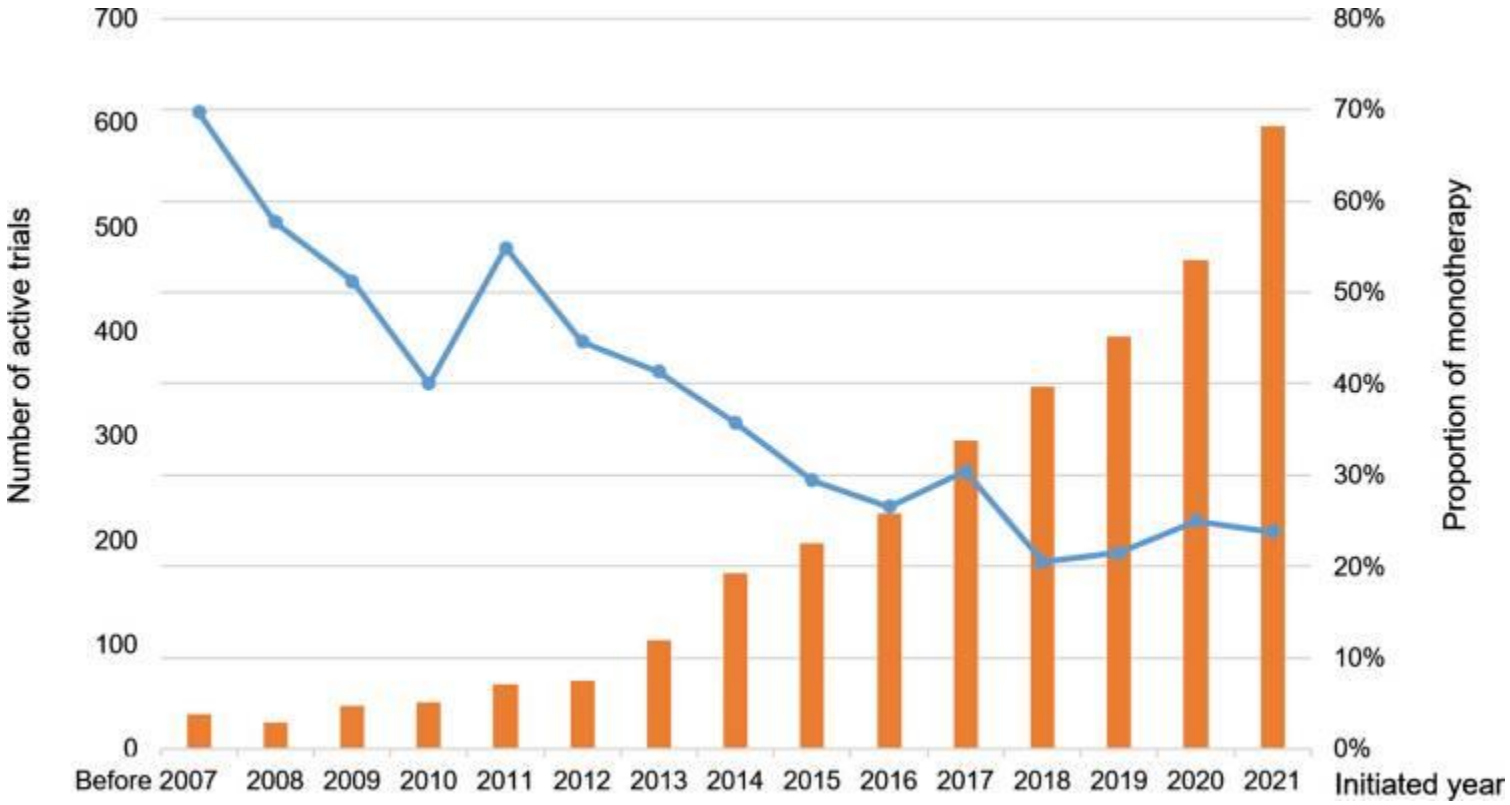
We are witnessing several revolutionary technological advances in cancer. These innovations have not only contributed to a growing understanding of the tumor and its microenvironment but also uncovered an increasing array of new therapeutic targets. For most advanced cancers, therapy resistance limits the benefit of single-agent therapies. Therefore, some 5,000 clinical trials are ongoing globally to probe the clinical benefit of new combination treatments. However, the possibilities to combine individual treatments dramatically outnumber the patients available to enroll in clinical trials. This comes at a potential cost of missed opportunities, clinical failure, avoidable toxicity, insufficient patient accrual, and financial loss. A solution may be to design combination therapies more rationally, which are informed by fundamental biological and mechanistic insight. We will discuss some successes and failures of current treatment combinations, as well as interesting emerging preclinical concepts that warrant clinical exploration.

"Already in 1950, it was realized that the benefit of combining therapies was related to tumor heterogeneity and the selective outgrowth of therapy-resistant tumor clones (Burchenal et al., 1950)."

Boshuizen, J. and Peeper, D.S., 2020. Rational cancer treatment combinations: an urgent clinical need. *Molecular cell*, *78*(6), pp.1002-1018.

Number of clinical trials involving combinations are increasing



Yang, J., Kang, H., Lyu, L., Xiong, W. and Hu, Y., 2023. A target map of clinical combination therapies in oncology: an analysis of clinicaltrials. gov. *Discover Oncology*, *14*(1), p.151.

Statisticians should have the tools and knowledge to design, analyze, and explain combination experiments

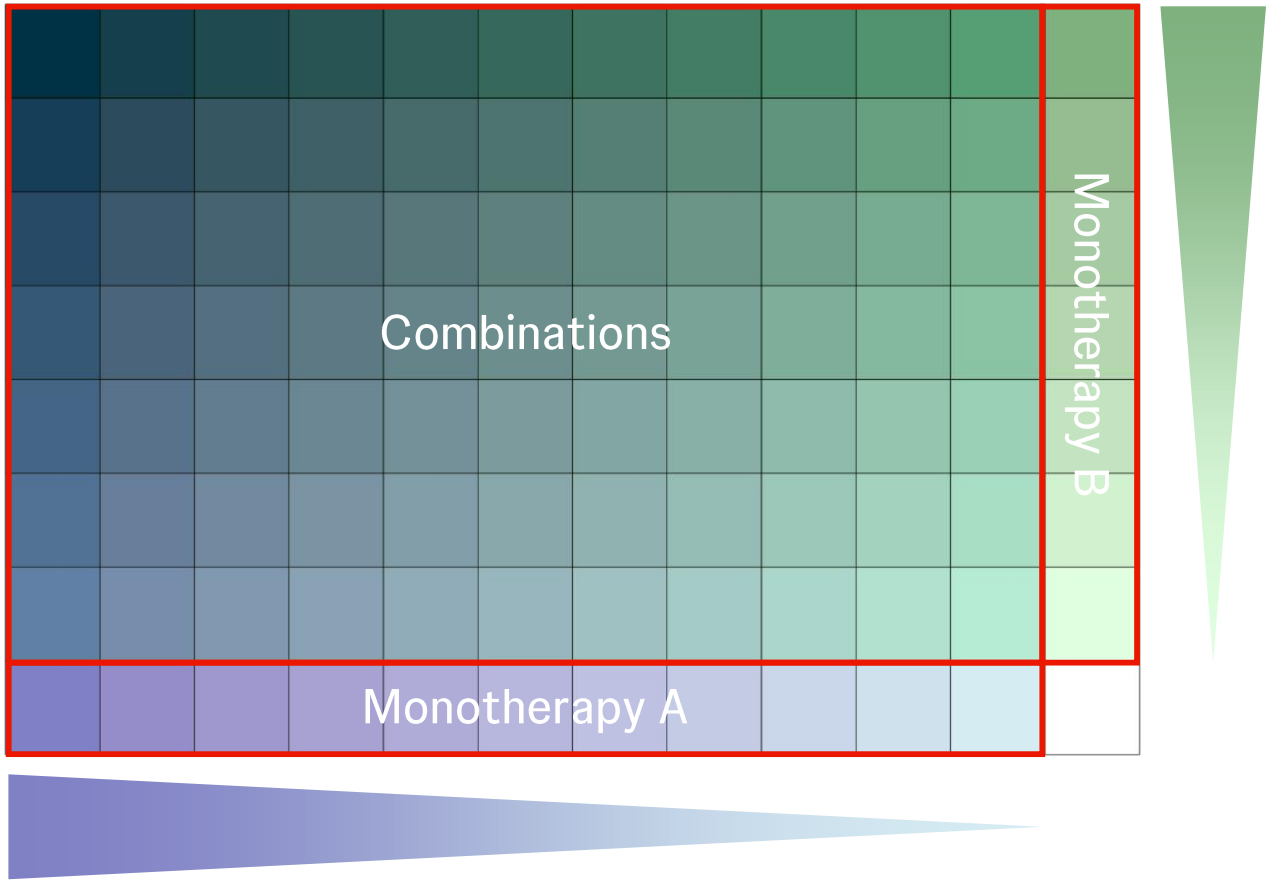
Design	Analyze	Report
	BIGL Package	

https://www.linkedin.com/pulse/requirements-effective-report-muath-alabdulkader-fmp--1e

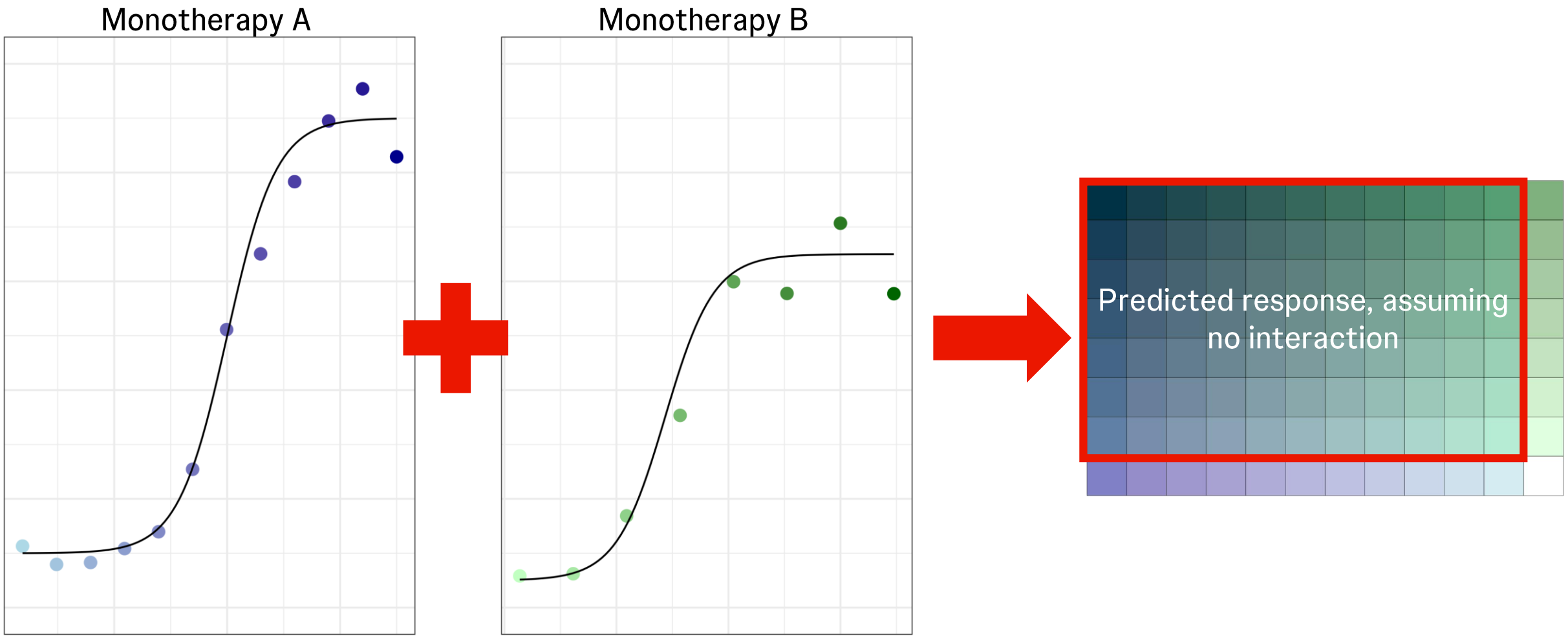
In the next 12-15 minutes...

1. Learn about one possible experimental design for analyzing combination experiments
2. Learn about the difficulties in analyzing in-vitro combination experiments
3. Possible solutions for mitigating these issues
4. Our recommendation for how to analyze in-vitro combination experiments

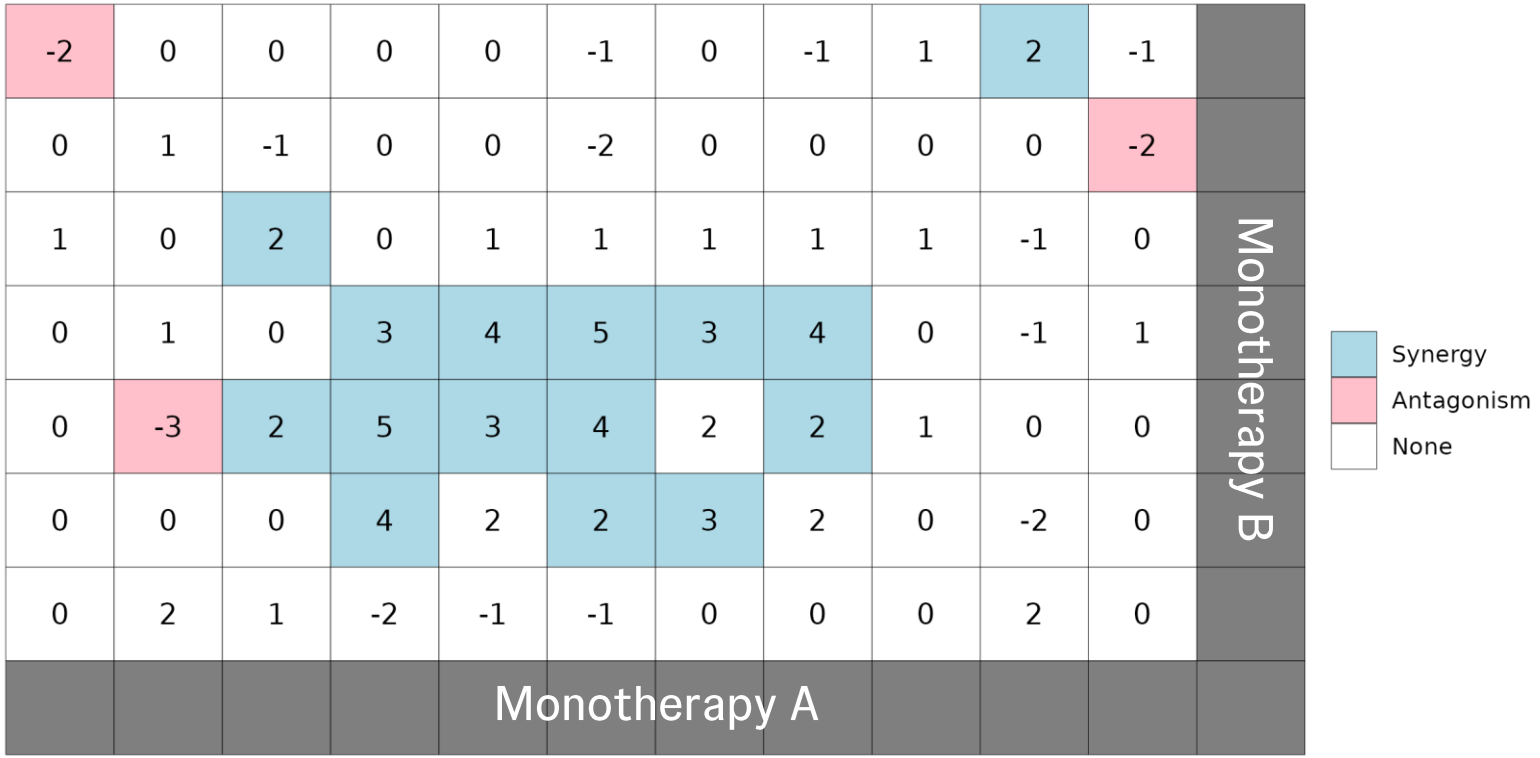
Typical in-vitro experimental design used at J&J discovery



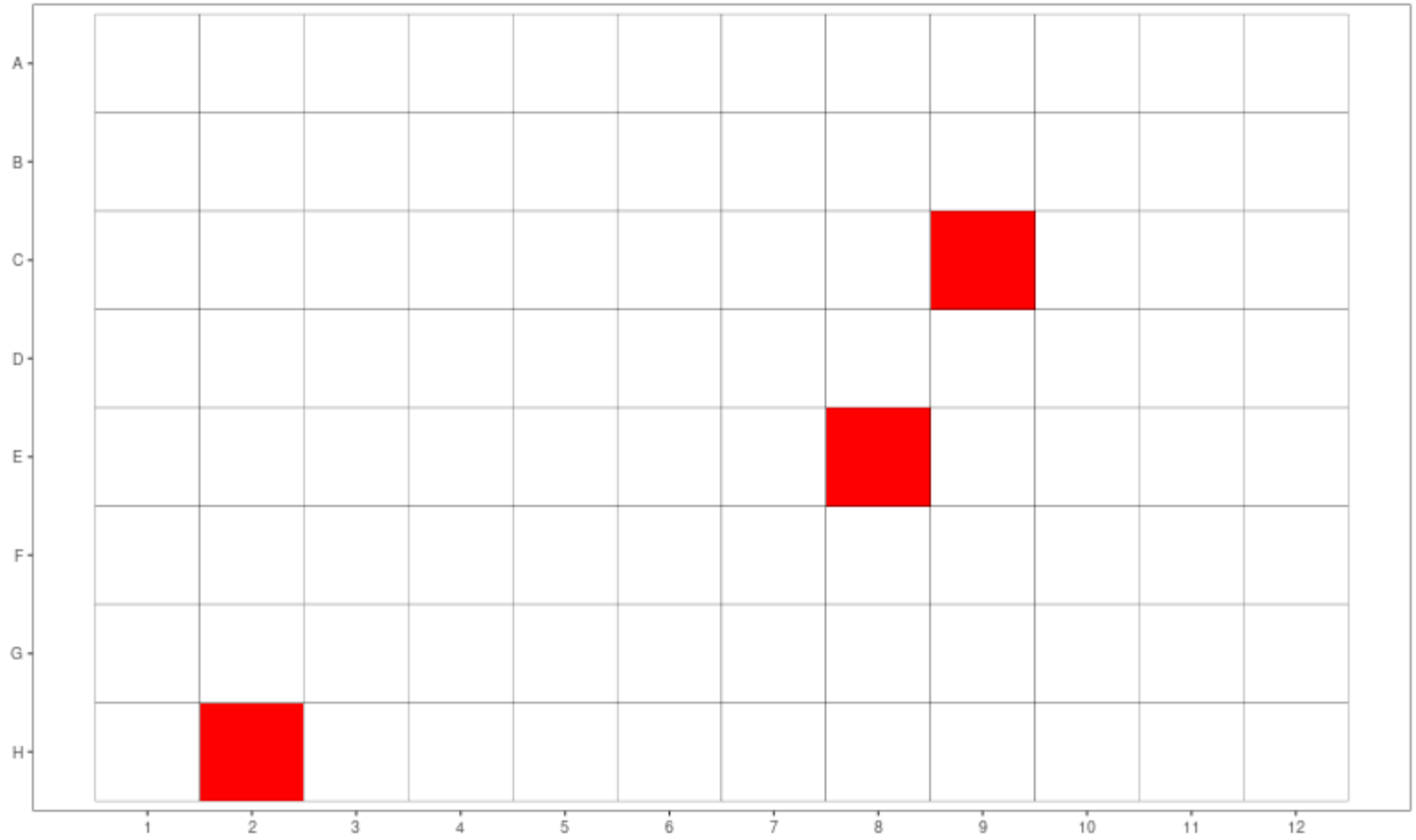
How in-vitro combination experiments are analyzed



The predicted responses and observed responses can be compared

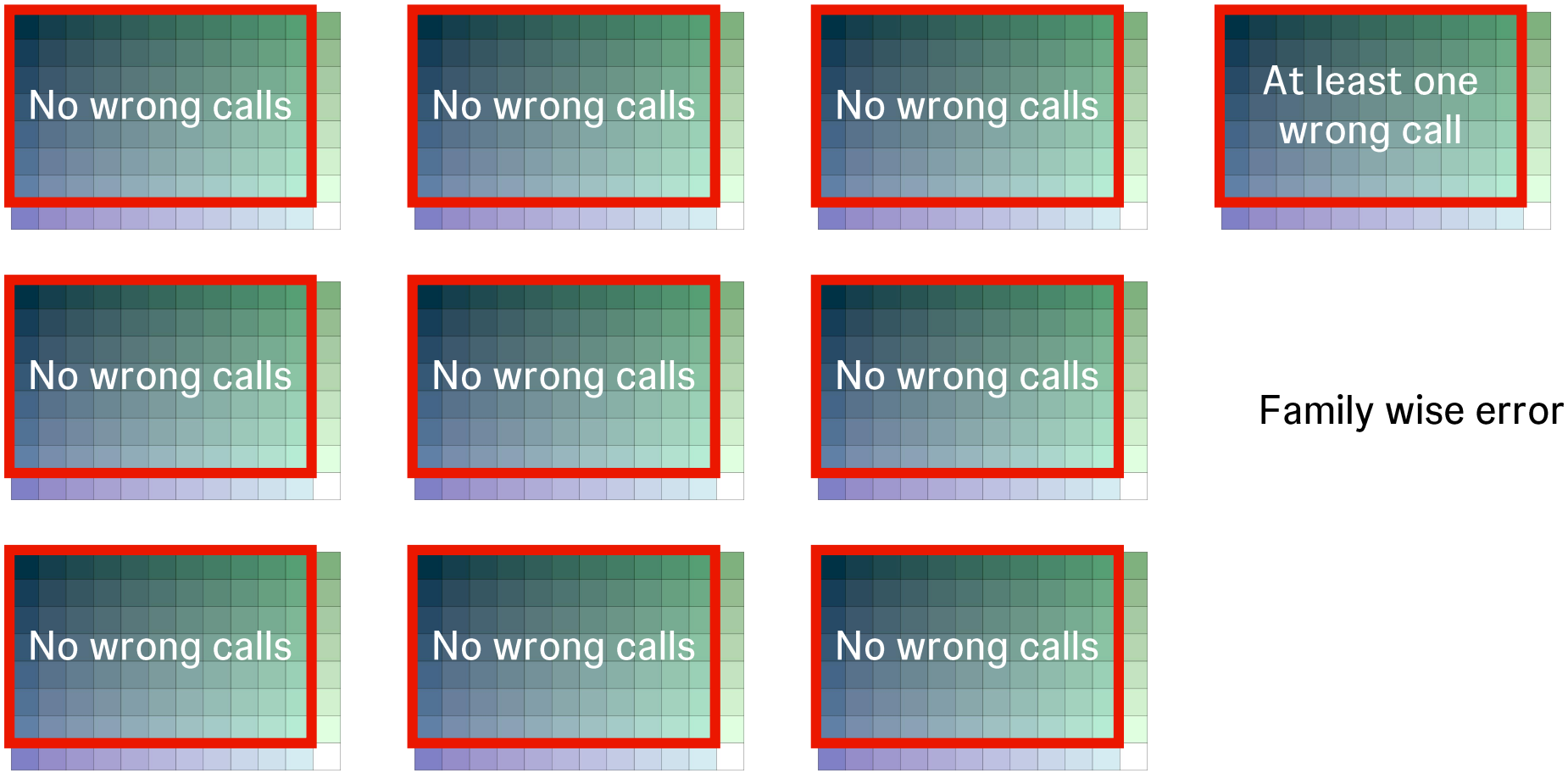


Multiple comparison problem



False Positive

FWER to control the Type I error



Family wise error rate of 10%

How does strict control of type I error impact sensitivity?

0	0	0	0	0	0	0	0	0	0	0	
0	0	0	0	0	0	0	0	0	0	0	
0	0	0	0	0	6	6	6	0	0	0	
0	0	0	0	0	6	6	6	0	0	0	
0	0	0	0	0	0	0	0	0	0	0	
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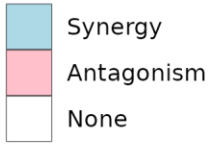
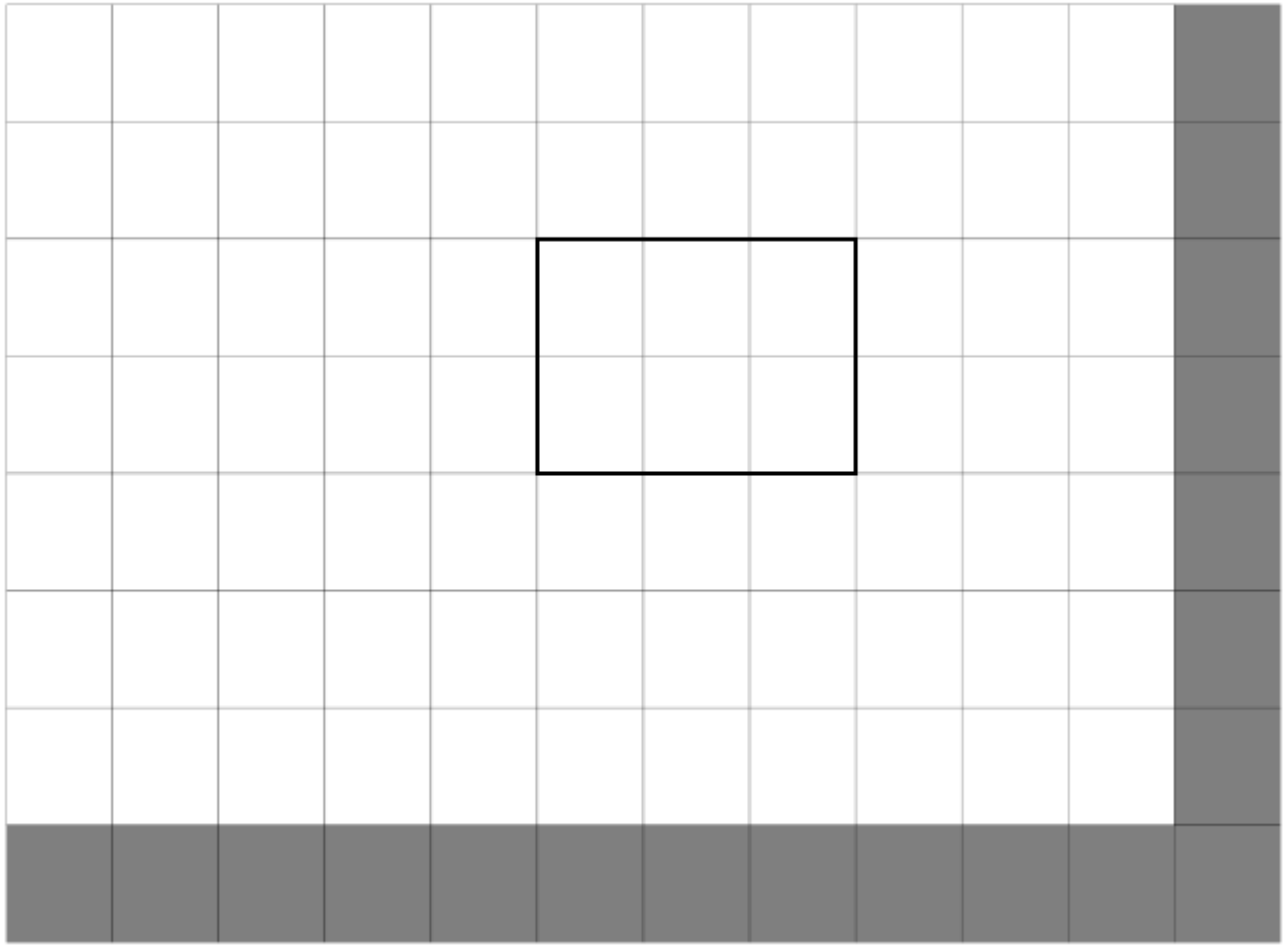
0	0	0	0	0	0	0	0	0	0	0	



- 3 replicates/well
- SD = 3
- Synergy around EC50s of the monotherapies
- Bliss null model
- 200 simulations
- 5% α-level

Type I error controlled using FWER at the expense of sensitivity



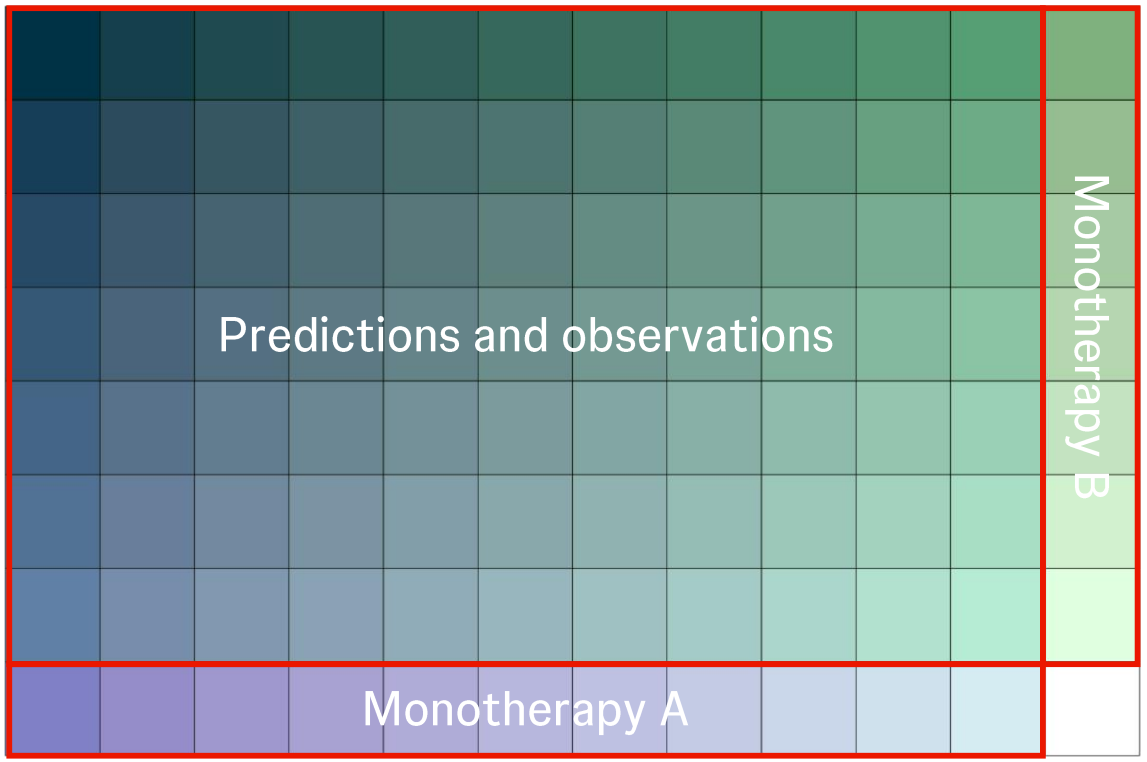
Average # false positives per simulation
< 1 well

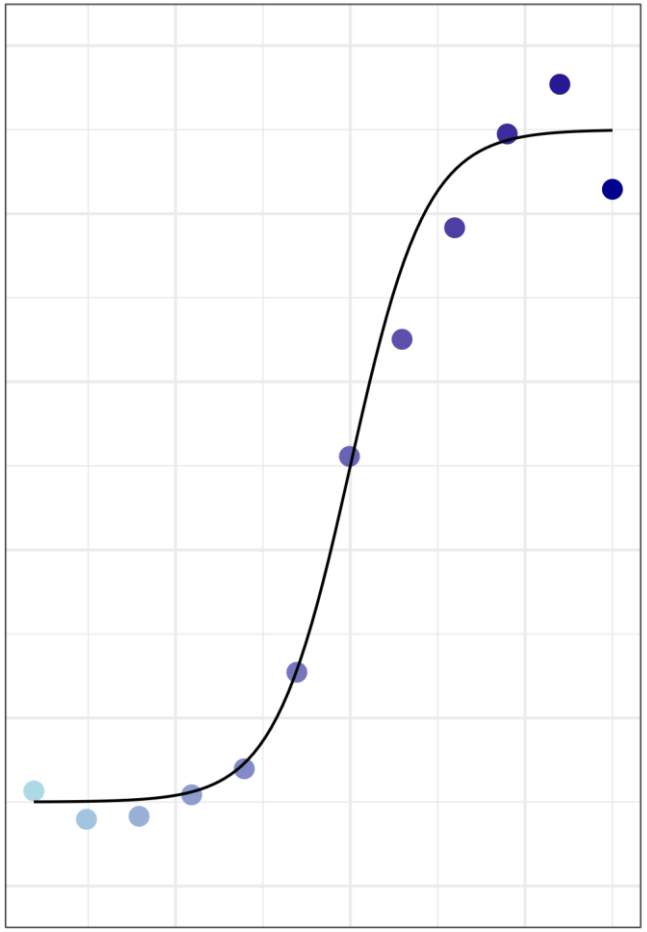
Average # Synergy wells detected per simulation
<2 wells

Detected Synergy

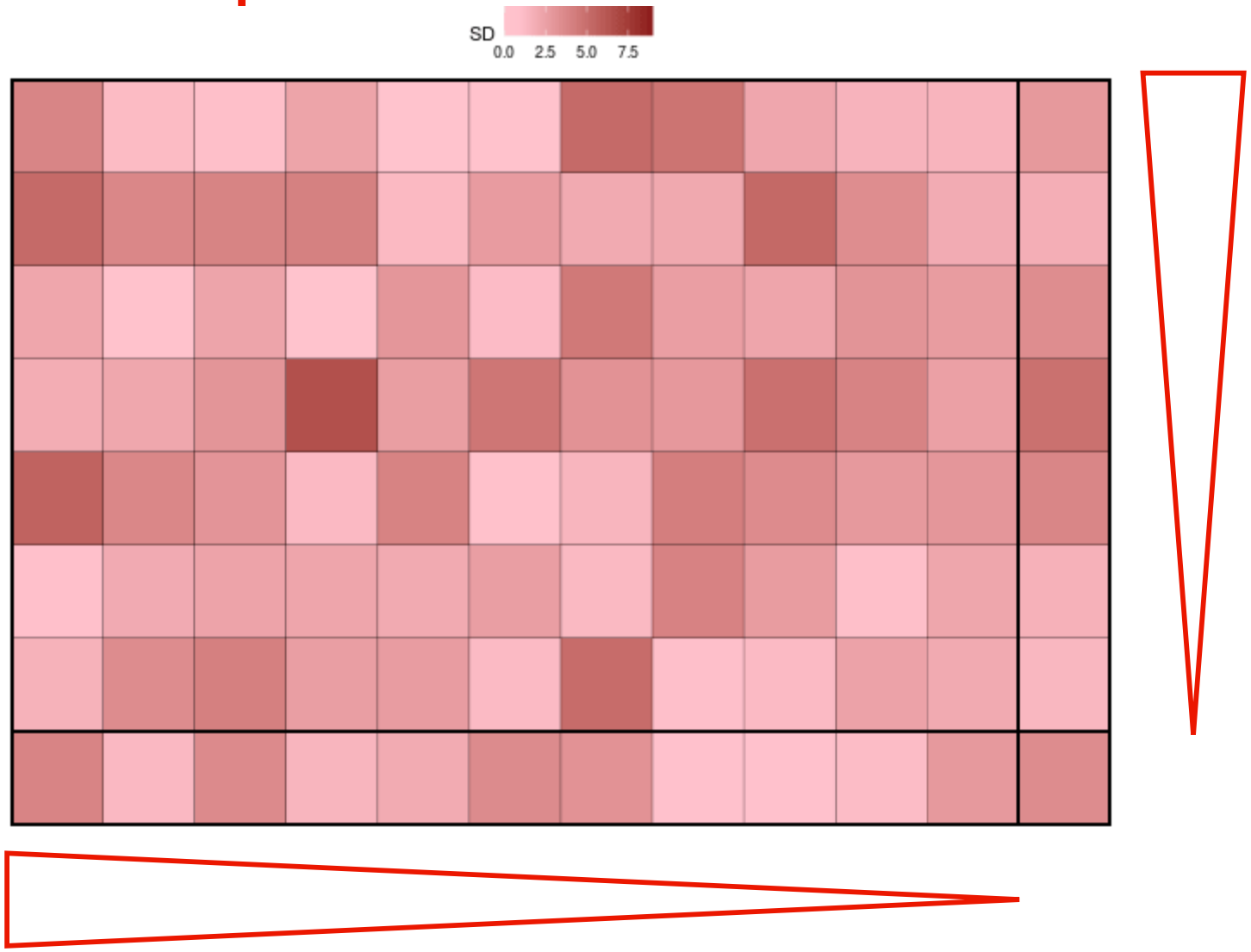
False Positive

Multiple components required to estimate variance of effect size

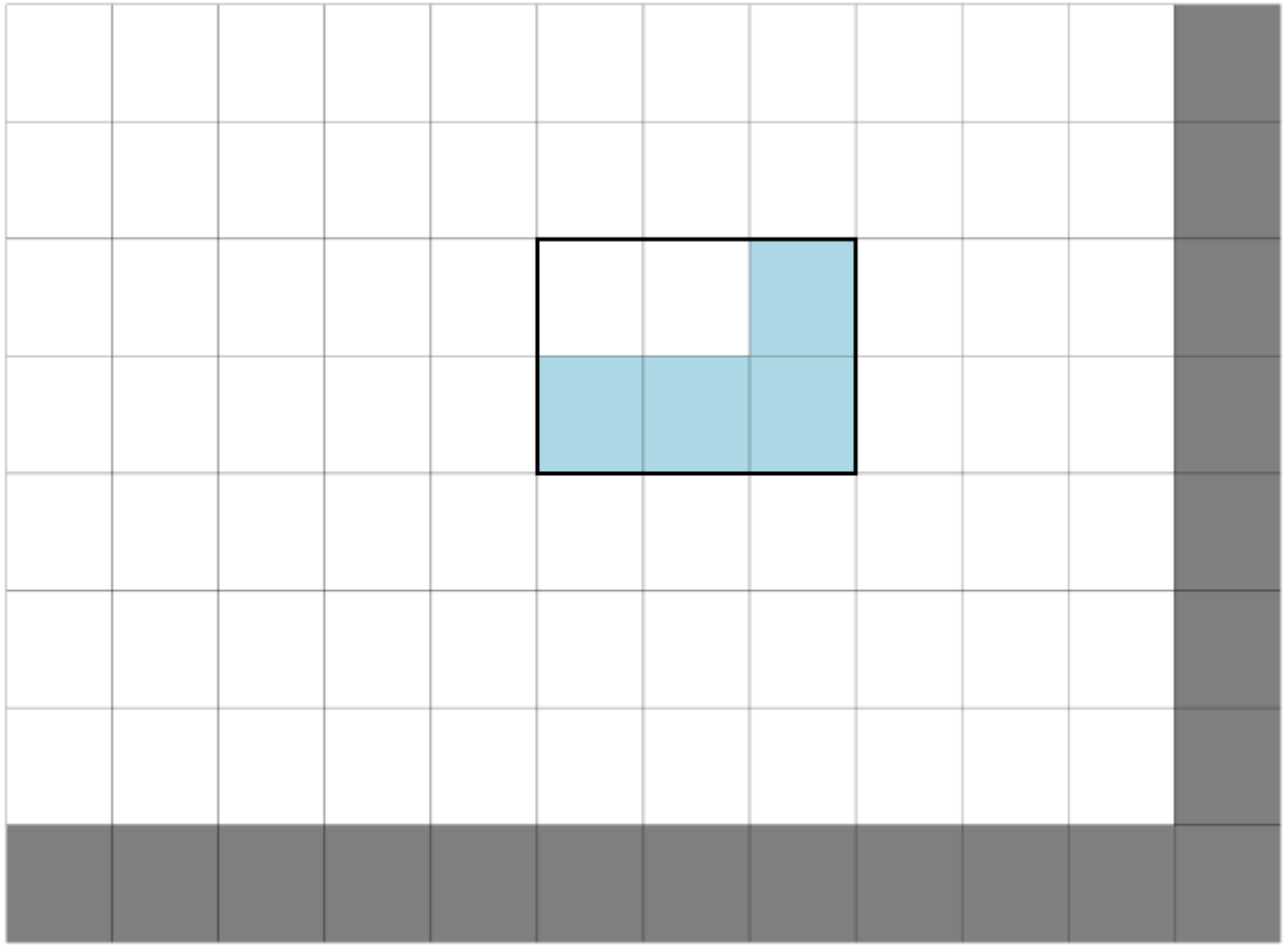




Heterogeneous variance complicates the multiple comparison problem



Type I error can still be controlled by modelling the variance as a function of the response



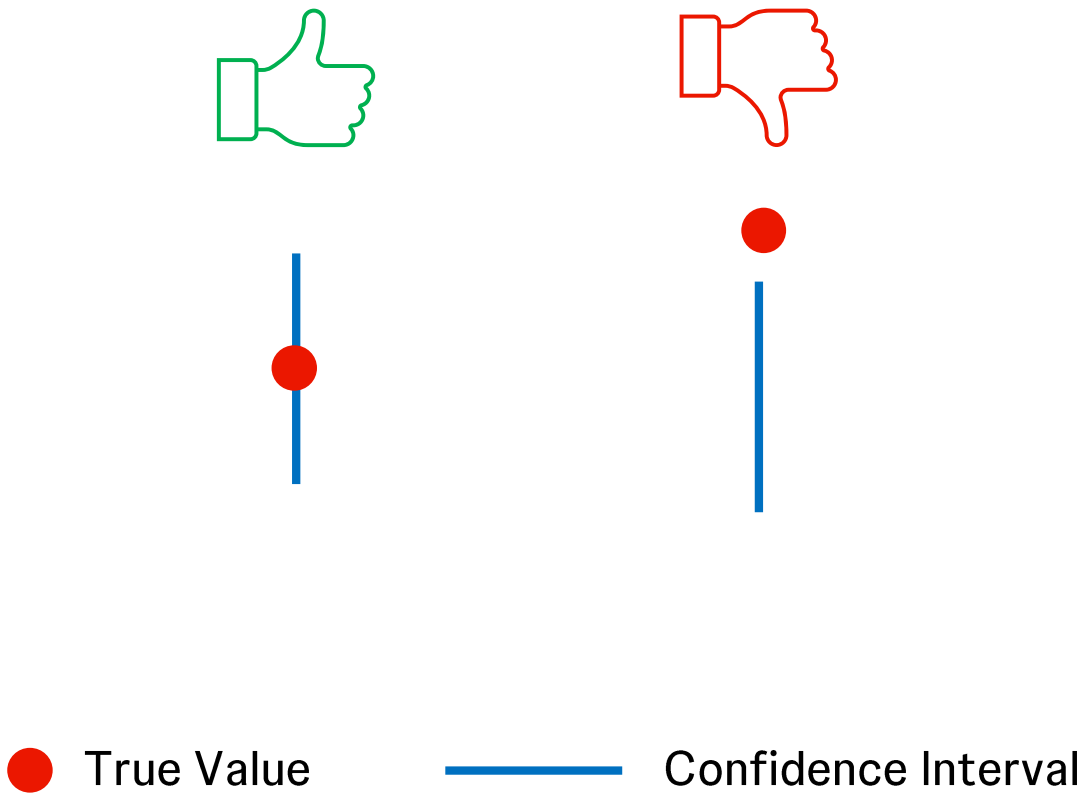
Average # false positives per simulation
< 1 well

Average # Synergy wells detected per simulation
< 2 wells

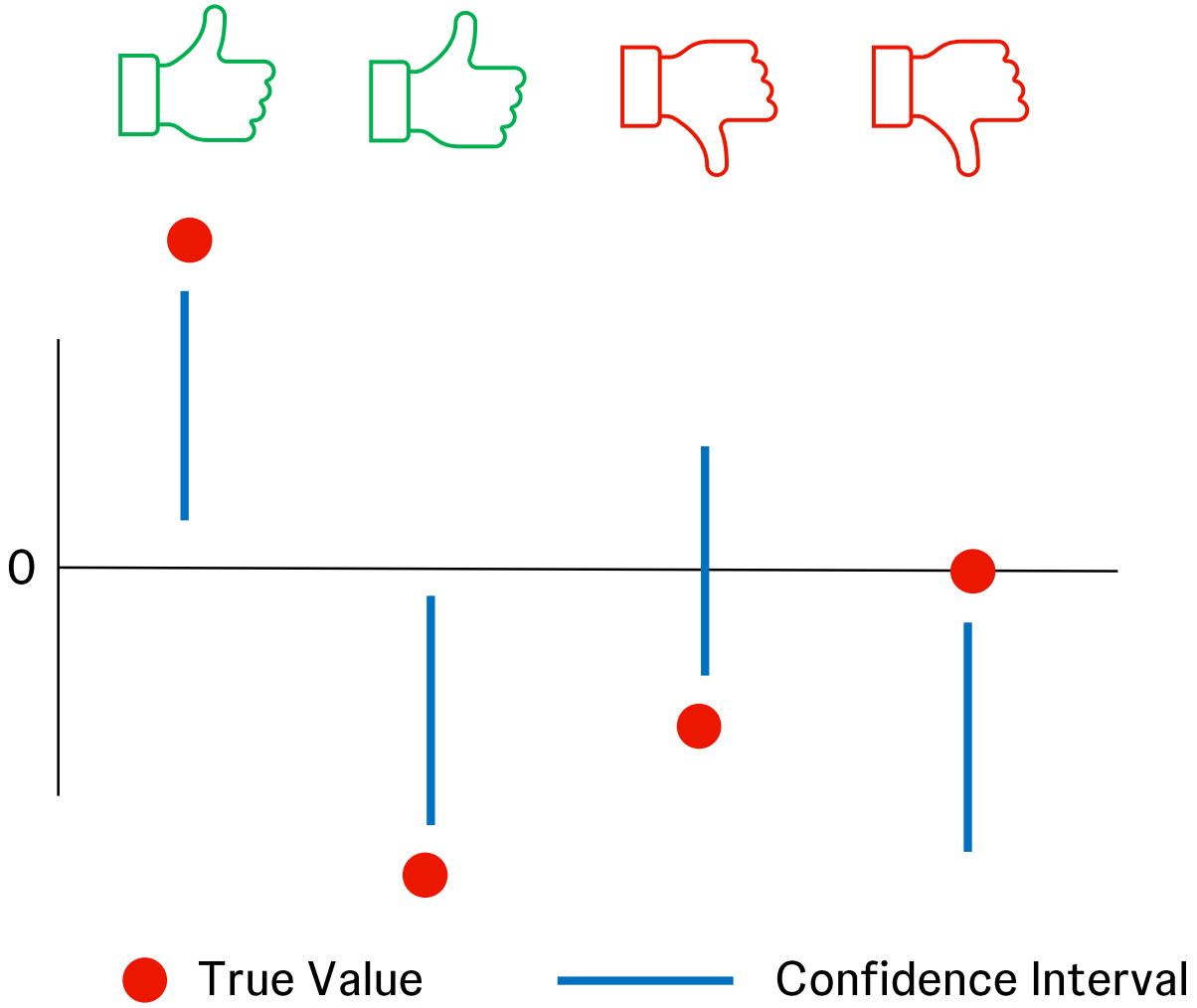
Detected Synergy

False Positive

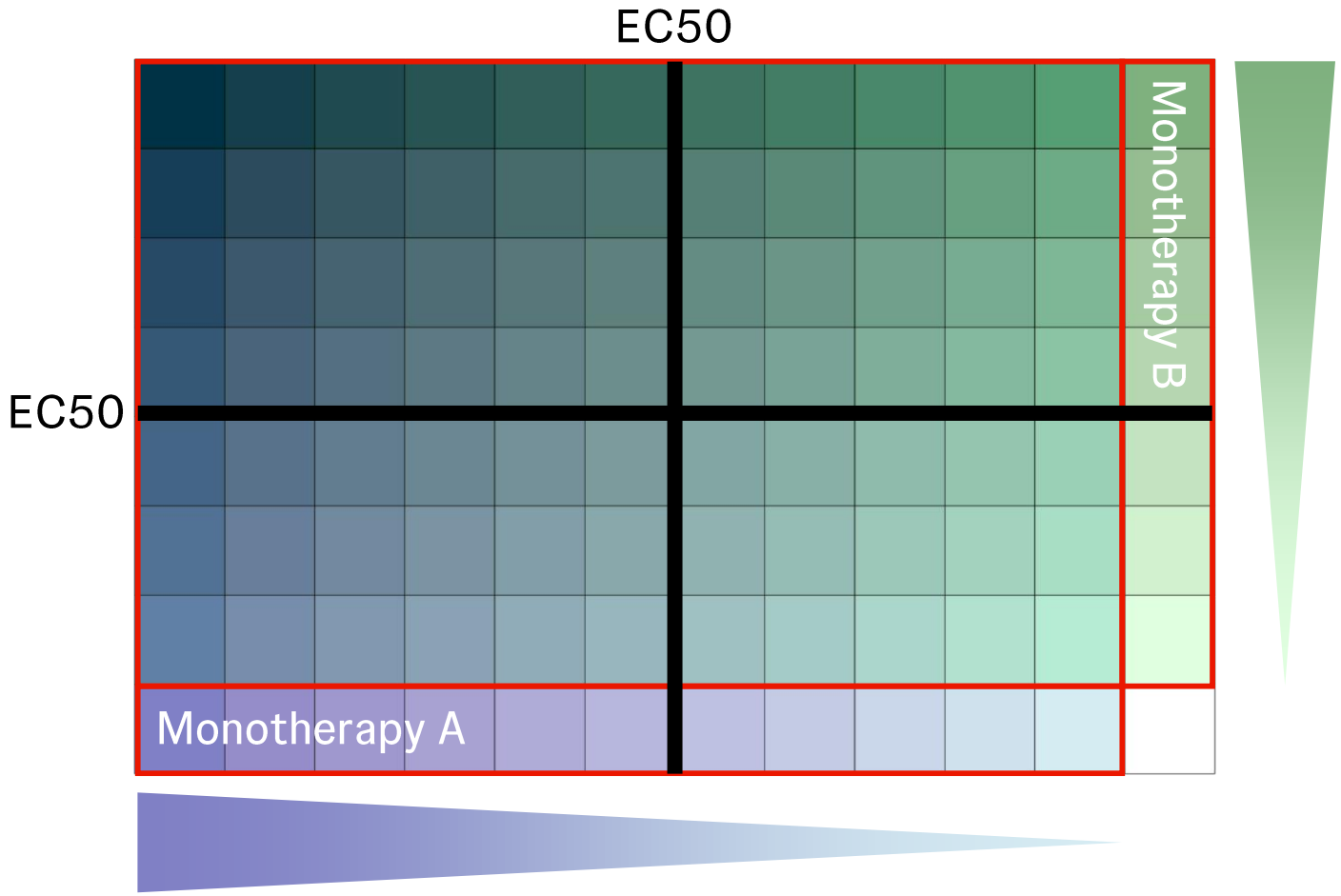
Using False Coverage Rate (FCR) to relax Type I error control



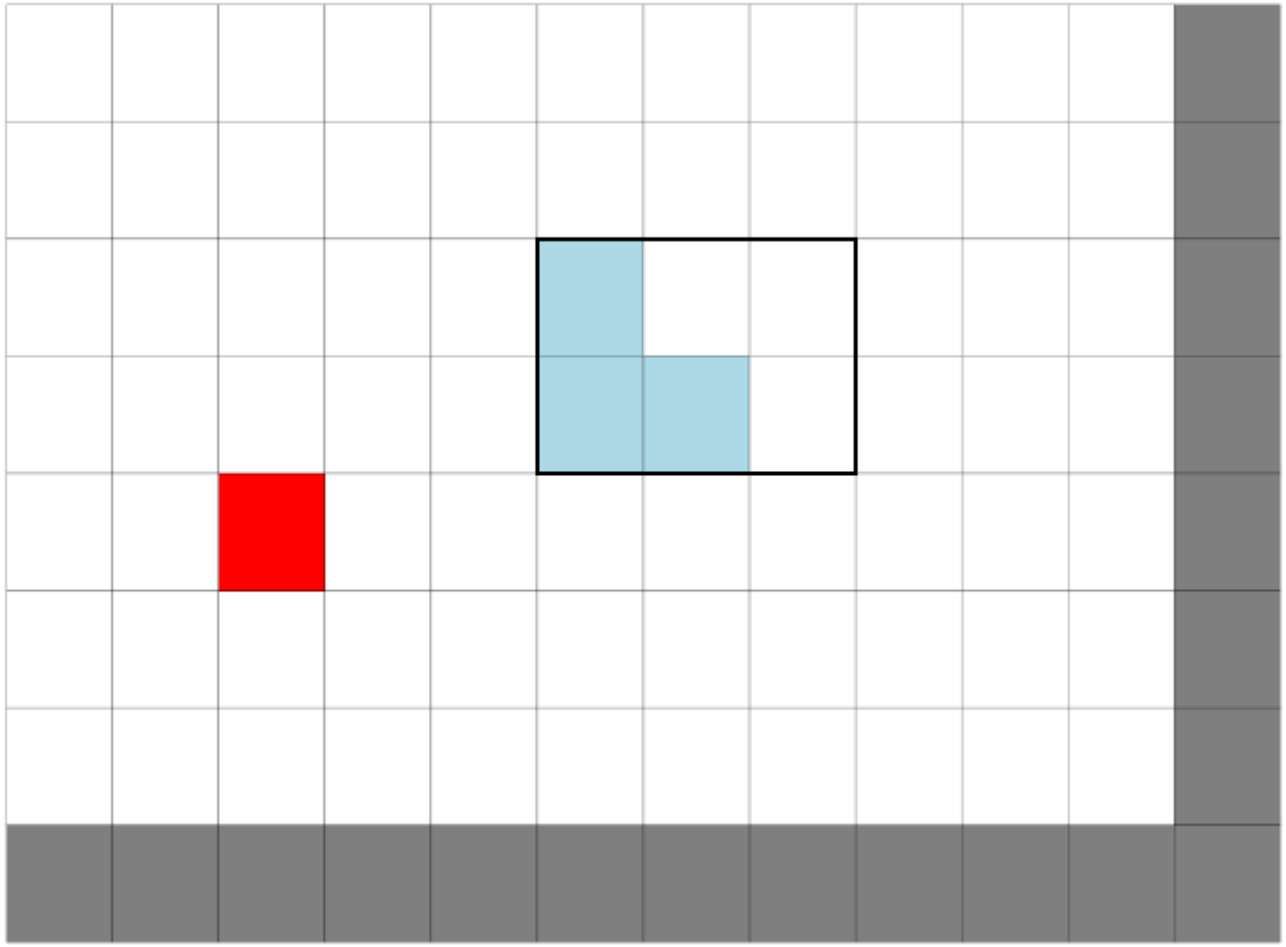
Improving FCR with the direction (dFCR)



Accounting for heterogeneous variance using a local bootstrap



Relaxing the Type I error and adjusting variance estimate increases sensitivity



Average # false positives per simulation
2

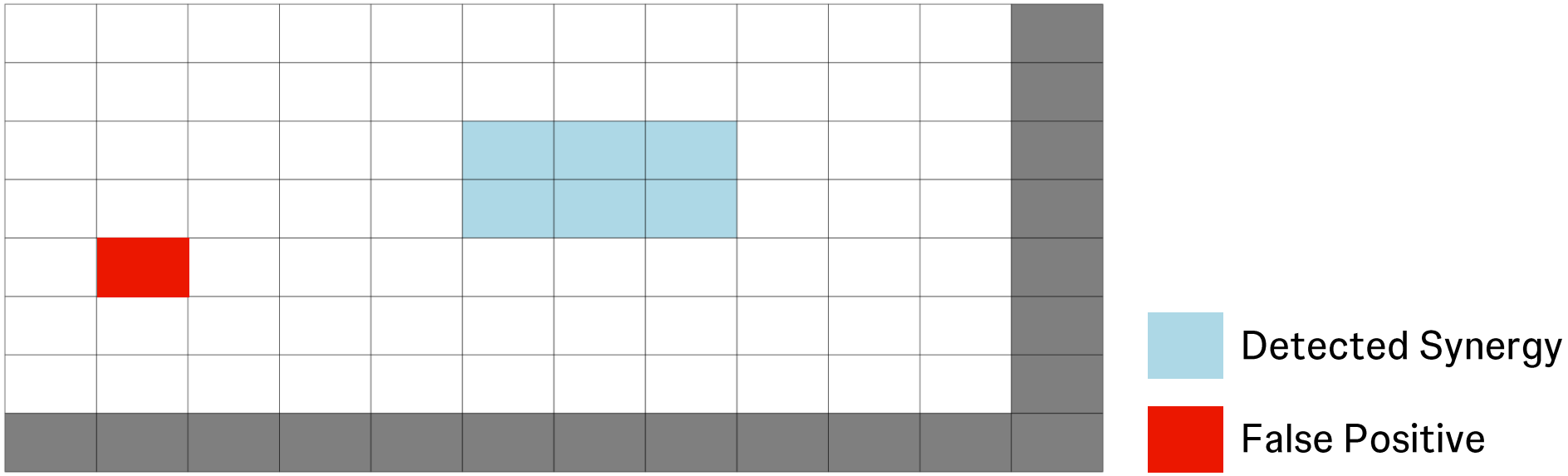
Average # Synergy wells detected per simulation
<5

Detected Synergy

False Positive

Sensitivity is a balancing act with the Type I error control

	FWER Model	dFCR Model	dFCR Local
Average # false positives	<1	4	2
Average # synergy detected	<2	5	<5



Summary of our simulation study (all results not shown)

If strict control of type I error rate is required, use FWER at an α-level of 10%

Relaxing type I error rate increases sensitivity at the cost of increased false positives.

This cost can be partially mitigated by using a local bootstrapping method.

More work needs to be done to refine the local bootstrapping method.