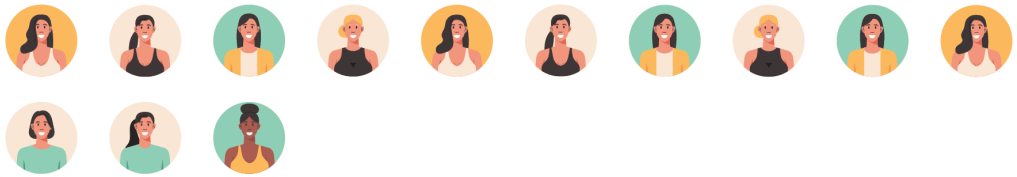
Steering Cancer Extinction in Metastatic Breast Cancer Using an Integrative Toxicity Metric

Team Indigo Extinction

11 IMO WORKSHOP

MOFFITT CANCER CENTER

Breast cancer

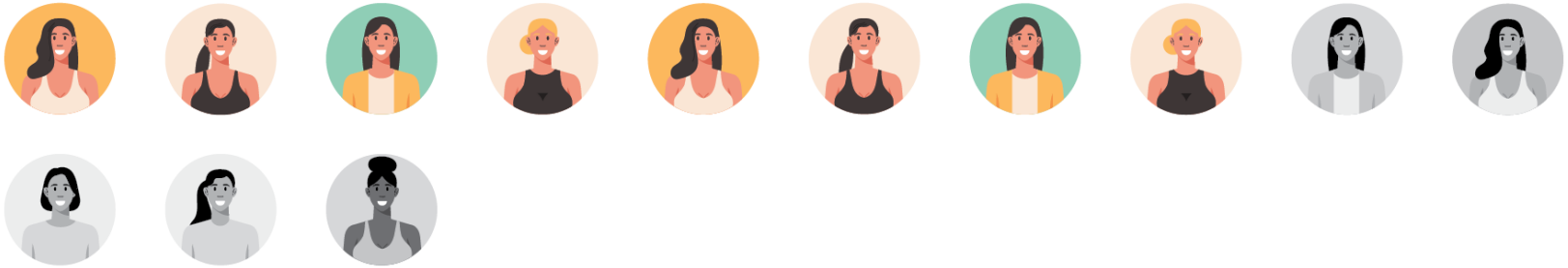


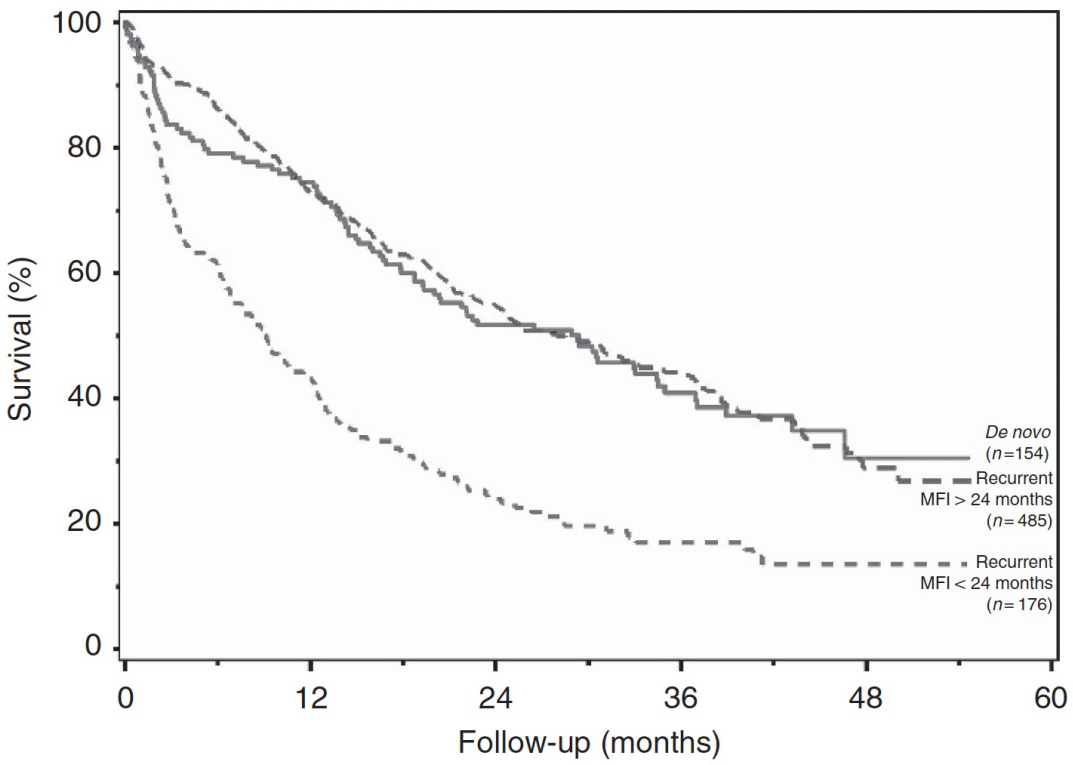
Breast cancer affects

1 in 8

women

Breast cancer





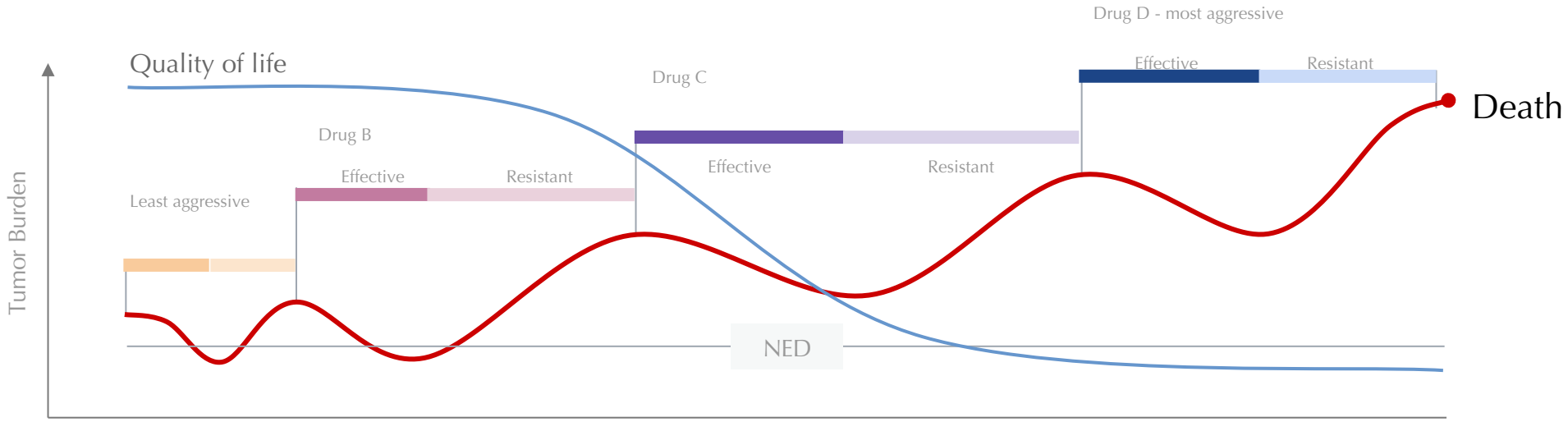
30%

develop recurrent or metastatic disease

where median survival ranges between 9 to 30 months

Lobbezoo, D. J. A., et al. 2015

Standard Care: Continuous treatment with the maximum tolerated dose (MTD) always leads to drug resistance and death.



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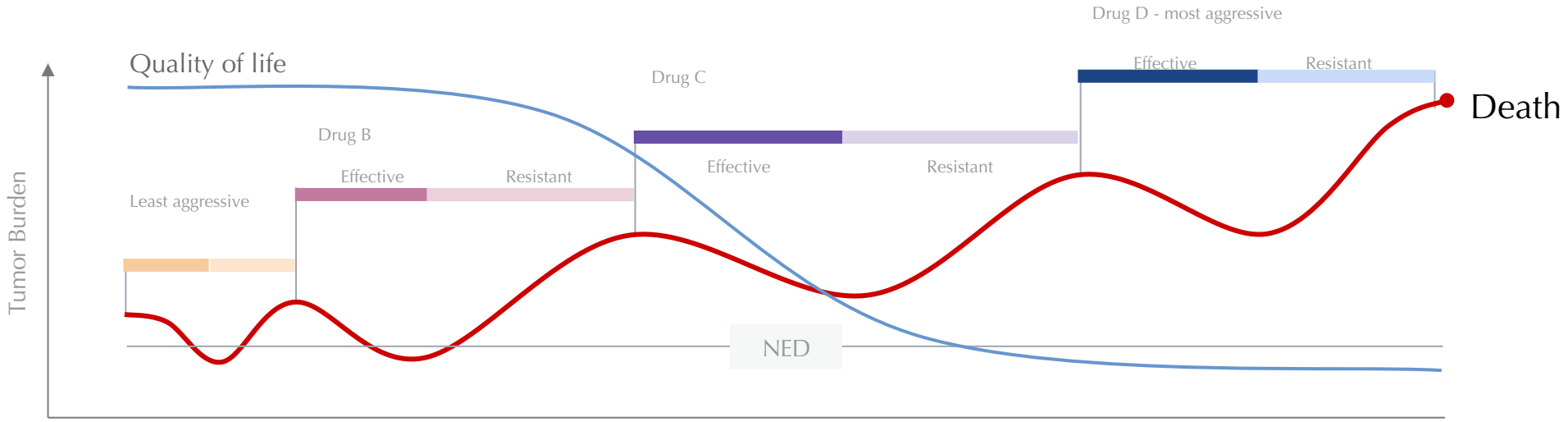
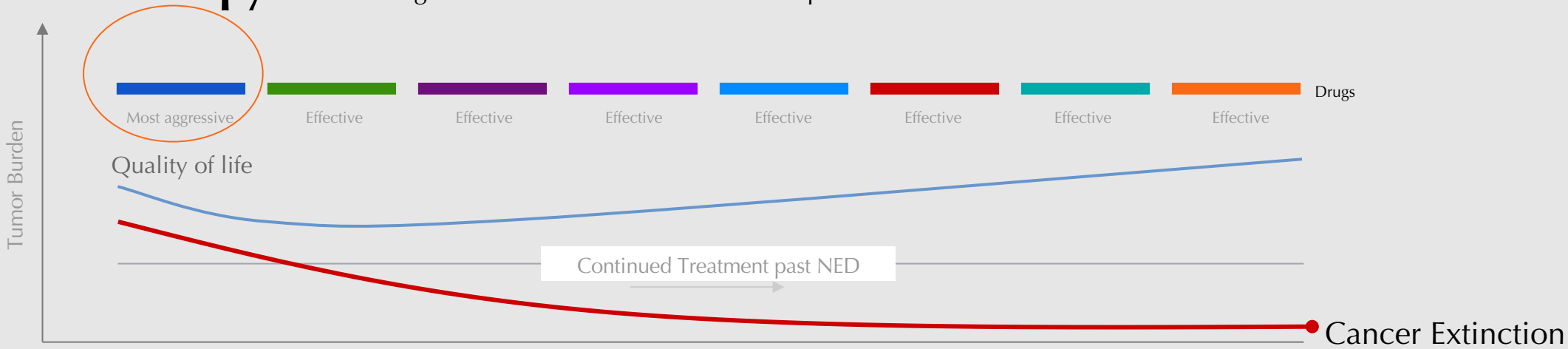


Extinction Therapy: Precise drug rotations control the disease and prevent resistance.



The extinction clinical trial

Clinical Study Protocol

A Pilot Study of Sequential ("First Strike, Second Strike") Therapies, Modeled on Evolutionary Dynamics of Anthropocene Extinctions, for Hormone Positive Metastatic Breast Cancer

Inclusion:
Hormone-positive, HER2 negative/low metastatic breast cancer

Elevated tumor markers

Aixa Soyano, MD Renee Brady-Nicholls, PhD Dana Ataya, MD

The extinction clinical trial

	1	2	3	4
Strike				
Cycle	● ● ● ●	● ● ● ●	● ● ● ●	● ● ● ●
Drug	Taxotere Cytoxan	Sacituzumab govitecan	Capecitabine	Fulvestrant + ribociclib
Class	Intravenous combination chemotherapy	Antibody drug conjugate	Oral chemotherapy	Hormonal and CDKi

Biomarker monitoring

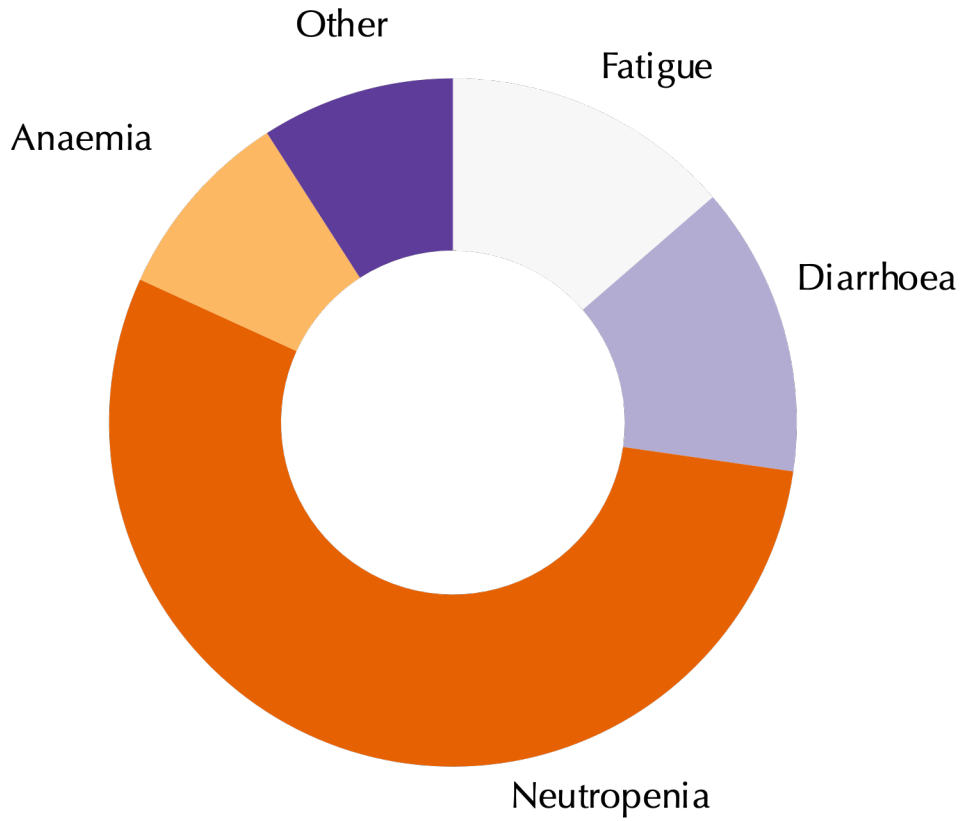
Decision making with the patient

Indi

D_{MTD}

Dose Limiting Toxicity

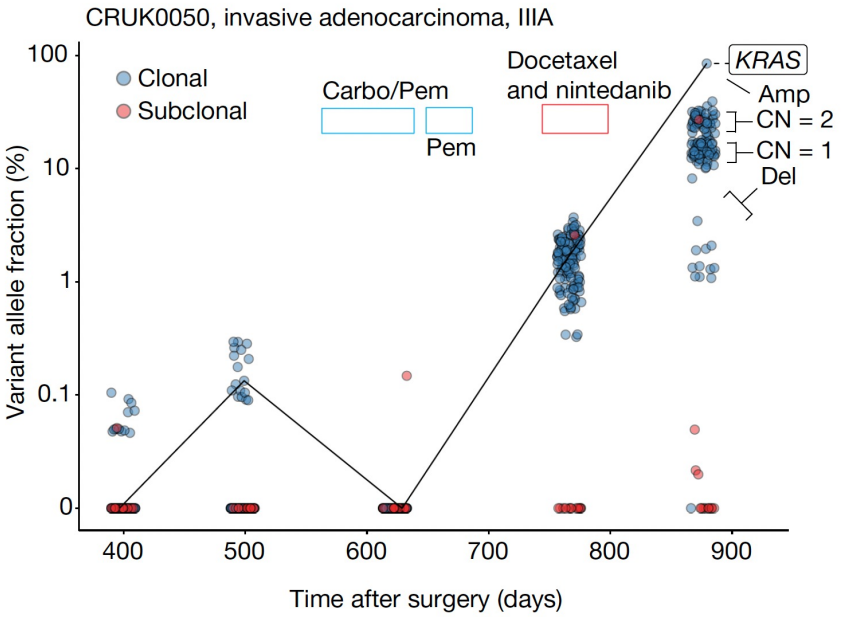
- Bone marrow toxicity
- Patient tolerability
- GI toxicity



Dose limiting toxicity with sacituzumab govitecan (Phase I data)

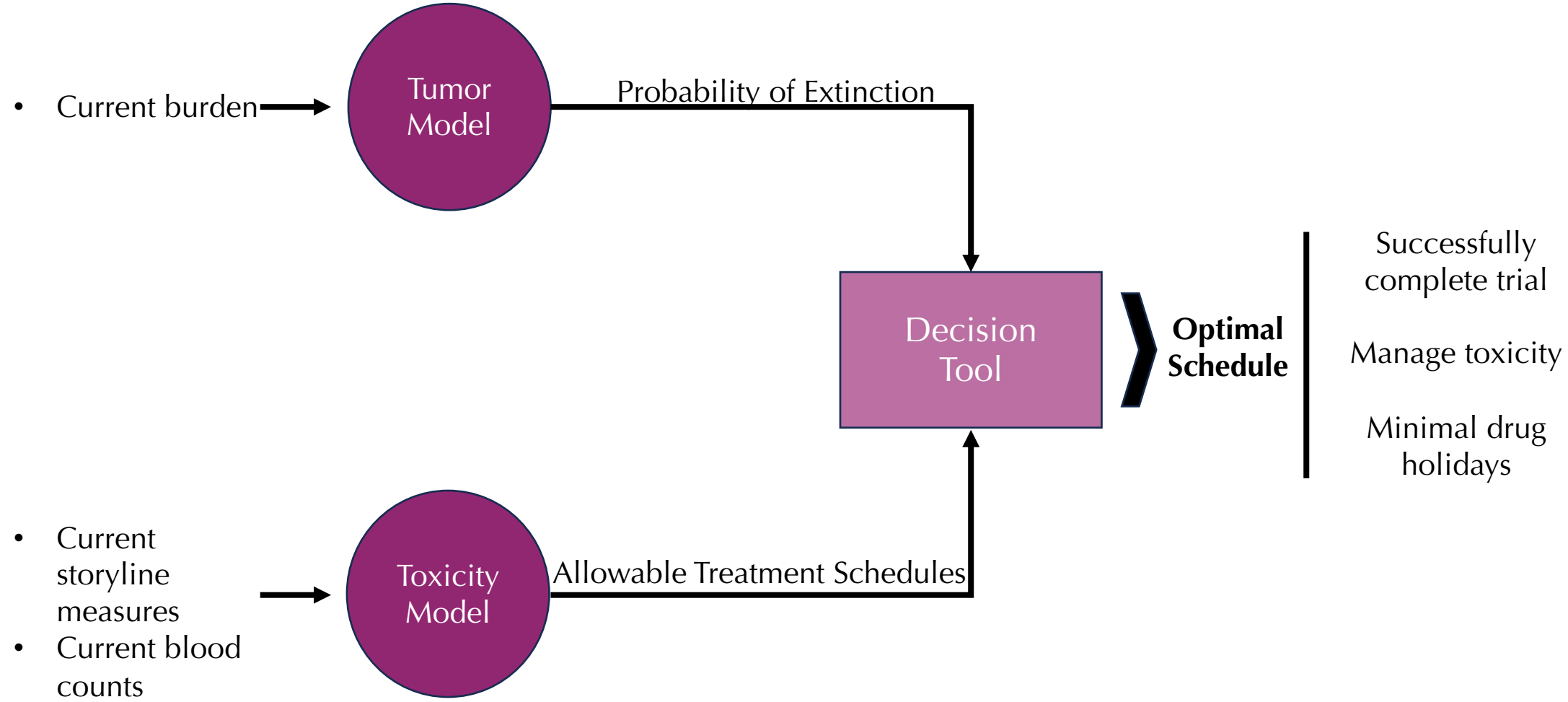
Unmeasurable Disease Burden

- Biomarkers
  - Carcinoembryonic antigen
  - CA 15-3
  - CA 27-29
  - ctDNA
- But biomarkers have their limitations



Abbosh et al., 2023

A comprehensive model of multi-strike extinction therapy



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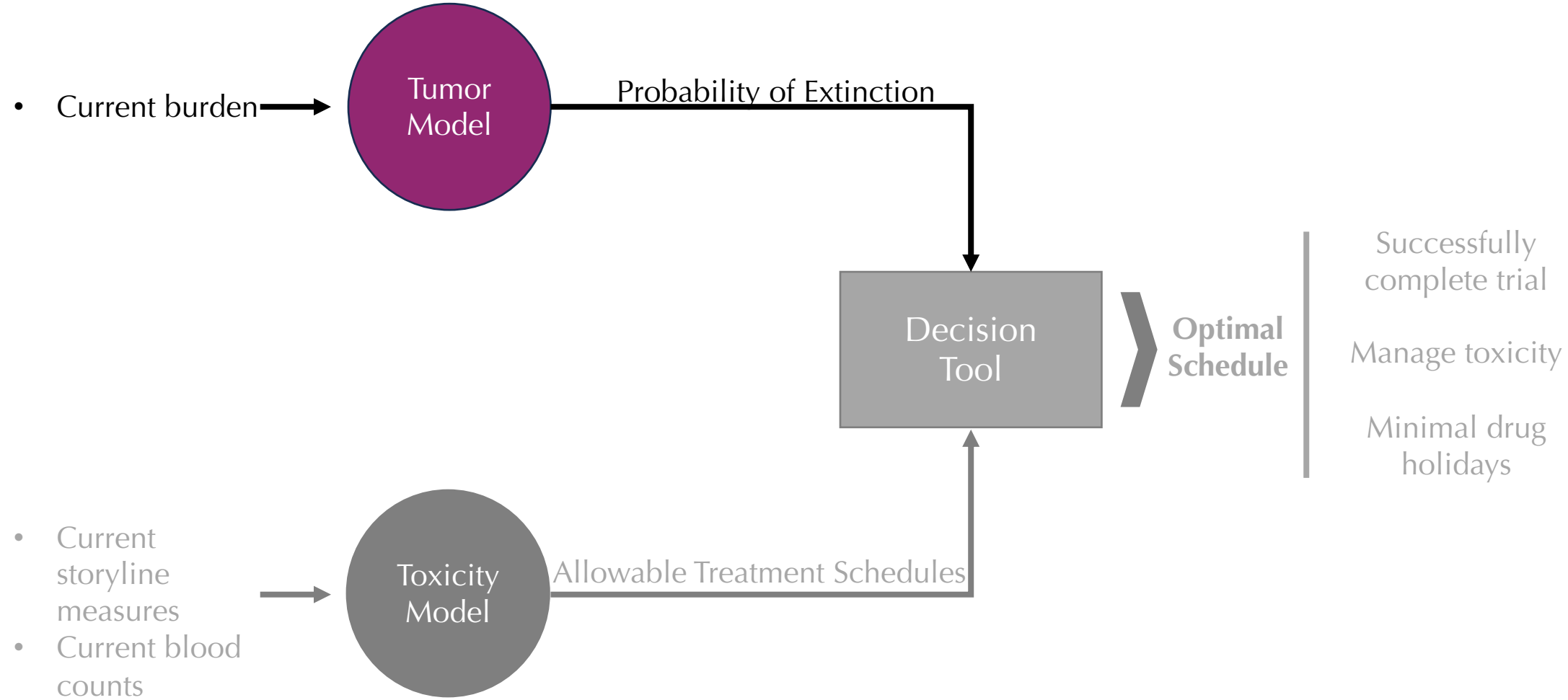


Tumor model

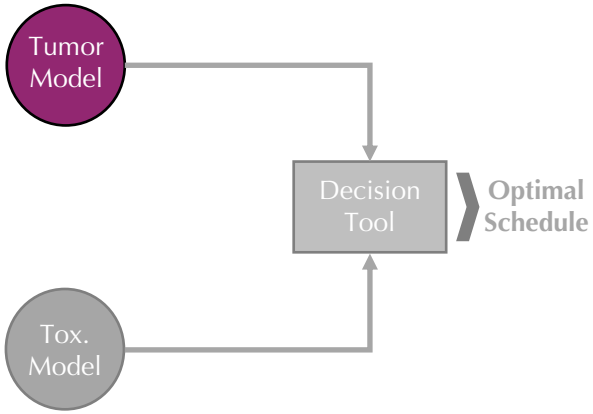
Desired Model Features

Exponential growth

Slow tumor regrowth

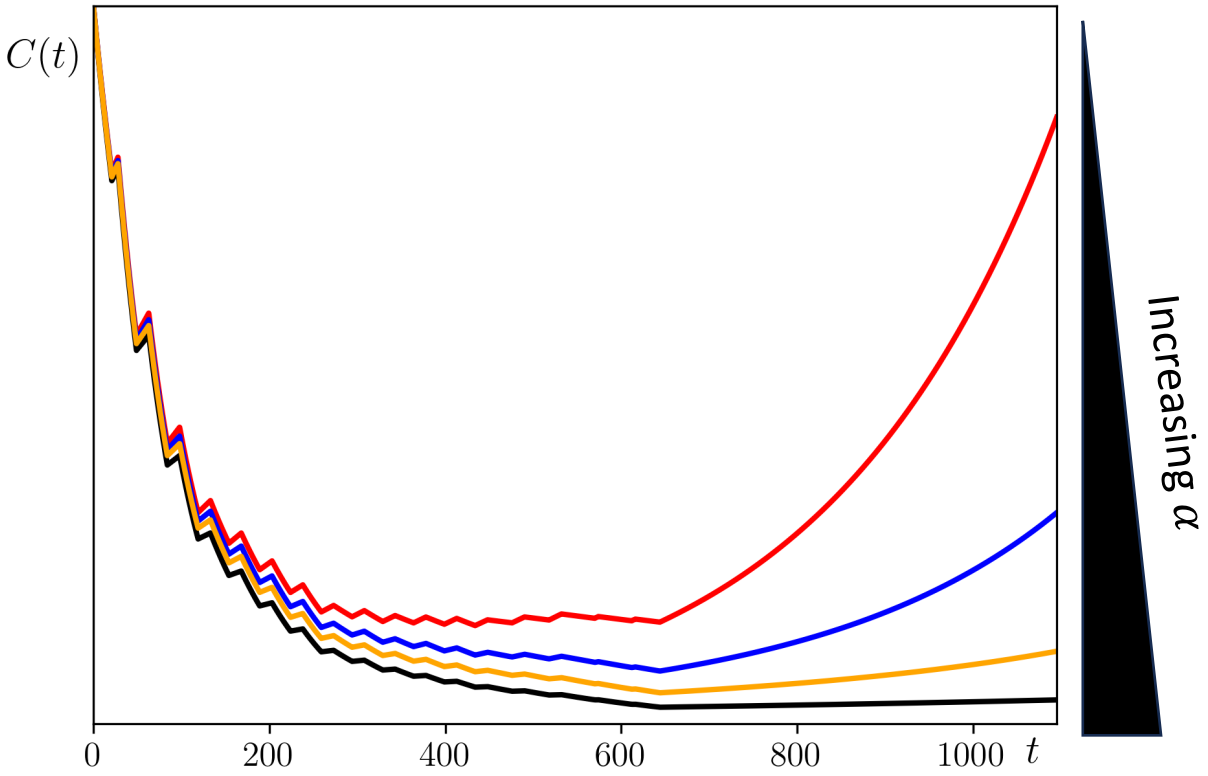
Growth dampened by the weak Allee effect

$$\frac{dC}{dt} = \frac{\gamma C^2}{C + \alpha}$$

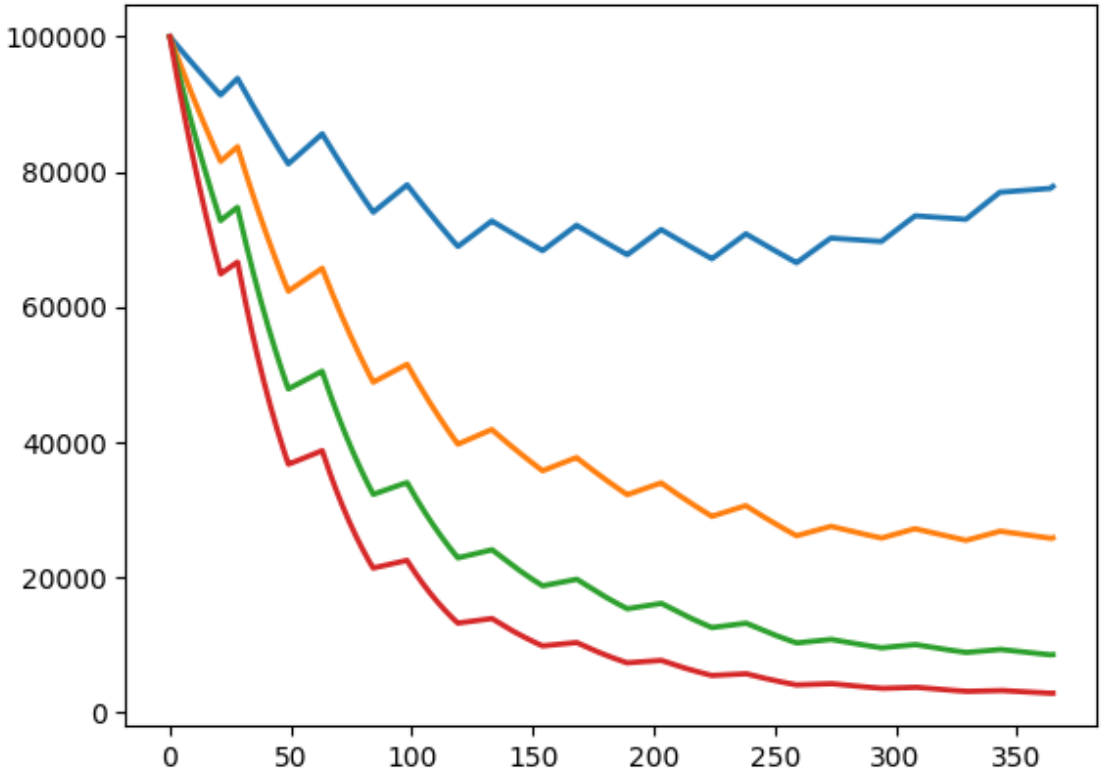


Virtual patient examples

Effect of the Allee parameter, α

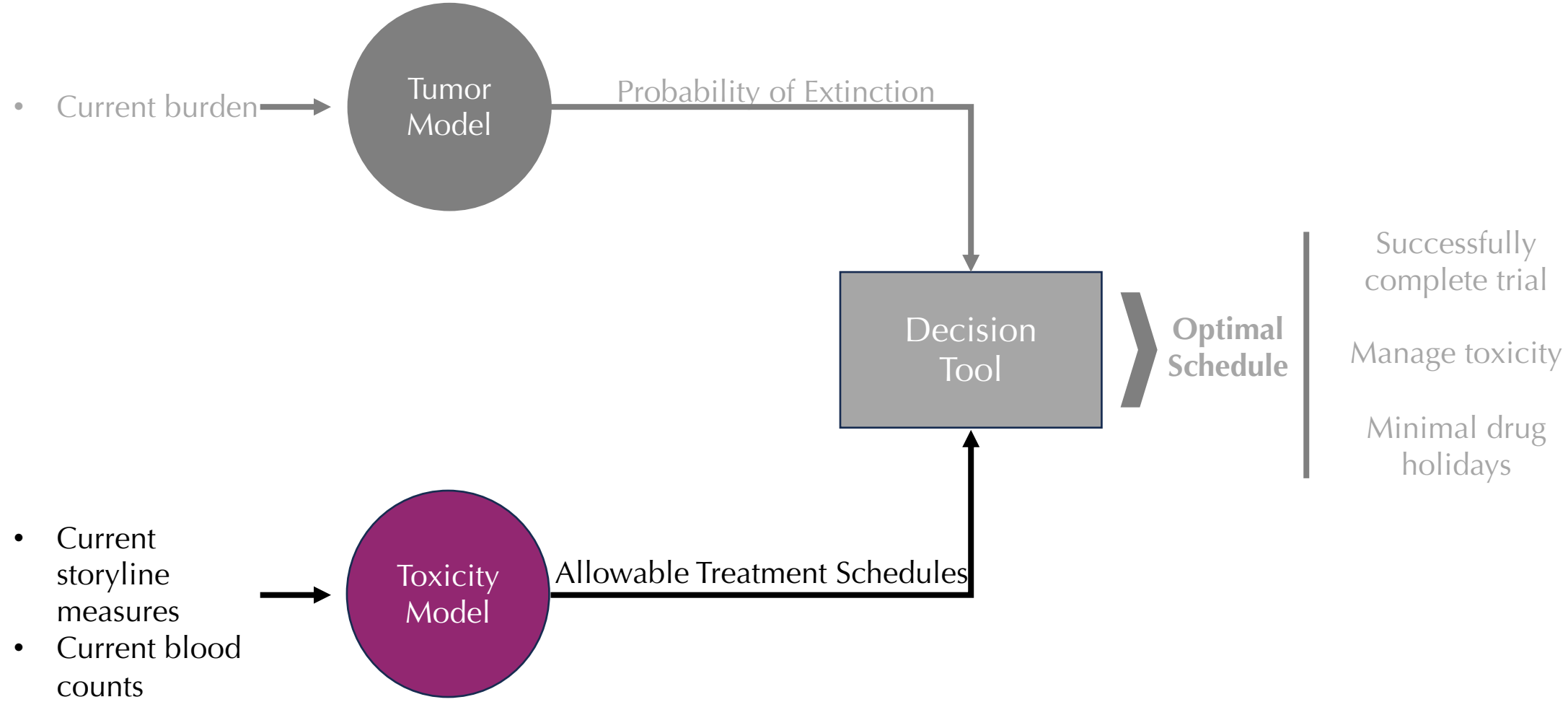


Effect of the treatment sensitivity parameters, σ_i

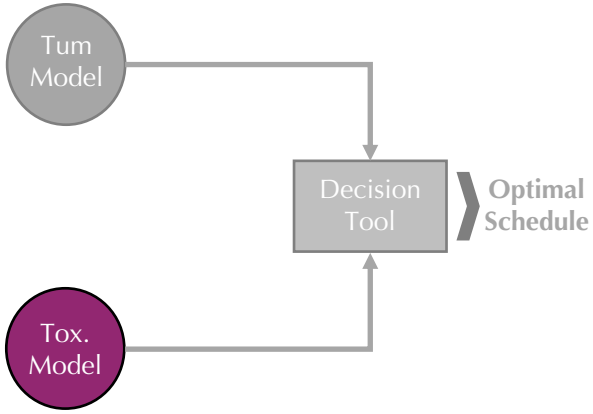


All undergoing the same treatment schedule

A comprehensive model of multi-strike extinction therapy



Clinical assessments of toxicity are **reactive** and come too **late.** The damage is done.



Old World

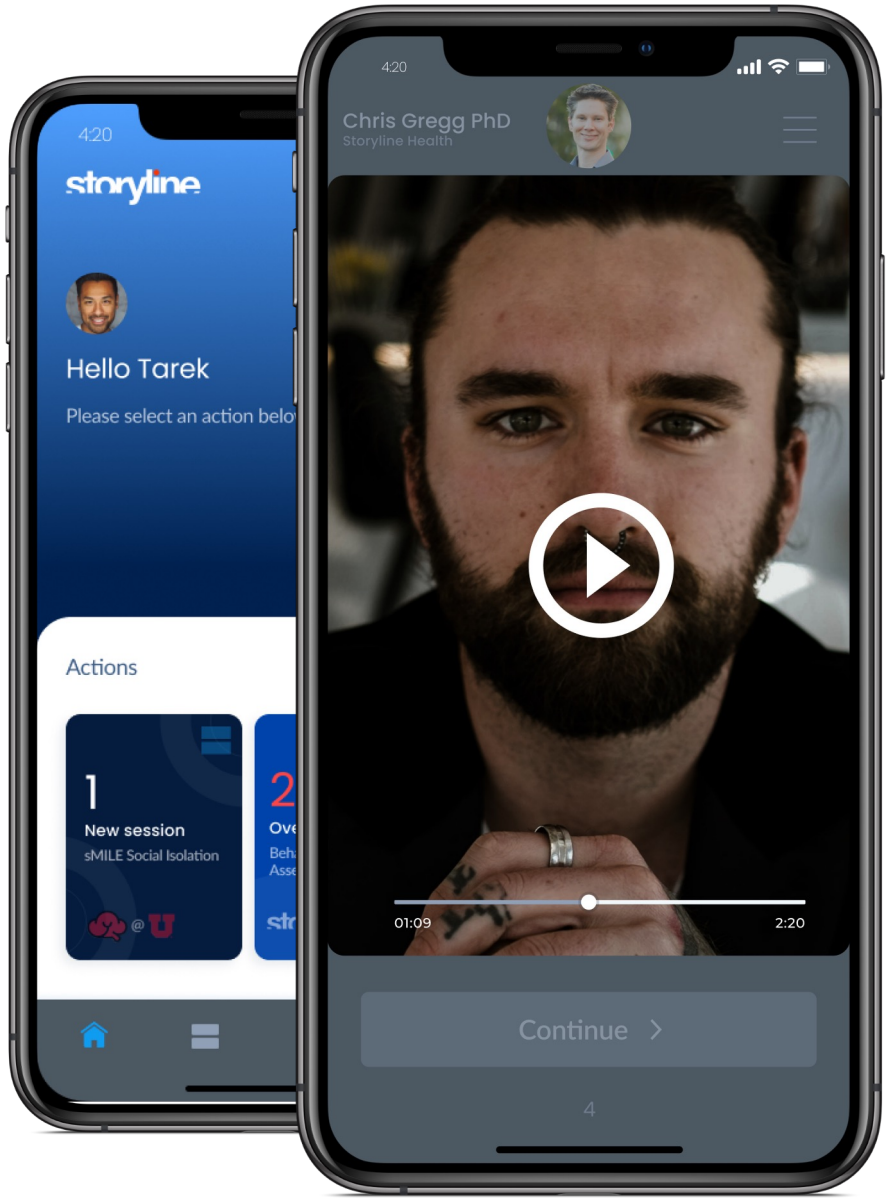
Neutropenia / GI Damage / Subjective Wellness Assessment

The Problem

All decisions start by understanding patient behaviors and symptoms.

…but the methods are crude, overly simplistic, and subjective for precision medicine and toxicity predictions.

Easy data capture



Simple

Patients answer video questions on their own phone anywhere, at any time.

Scalable

Removes time costs and access. Provides continuous patient access..

Cleaner Data

The highest quality and most valuable data.

Richer Data

5 minutes of video captures 100,000X more data than current tools.

Flexible

Every use case and assessment.

storyline

A.I. Symptom Analysis

+20,000 features measured and structured for modeling and statistical analysis.

Video

- Pupil Dilation
- Eye Tracking
- Head Movement
- Blood Flow
- Respiration
- Response Time
- Micro-Expressions
- Cognitive Load
- Emotional Response
- Eyelid Ptosis
- Temperature Change
- Articulation

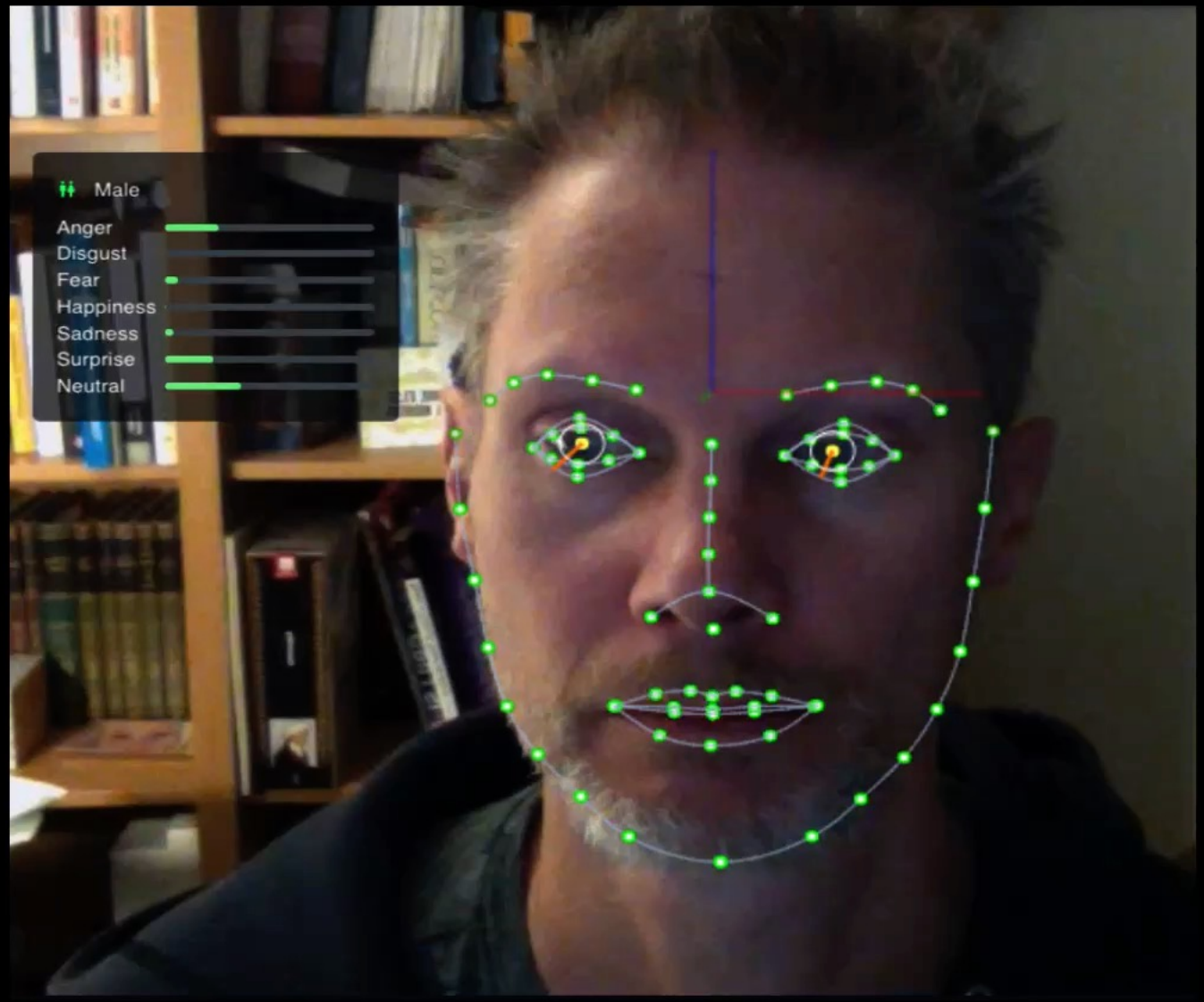
Speech

- Word Choice
- Sentence Structure
- Personality Traits
- Speech Patterns
- Education Level
- Engagement
- Vocabulary
- Time Stamping
- Utterances
- Sentiment
- Thought Patterns
- Frequency
- Complexity
- Outlook

Audio

- Vocal Micro-Tremors
- Pitch & Tone Changes
- Pronunciation
- Valence
- Stress

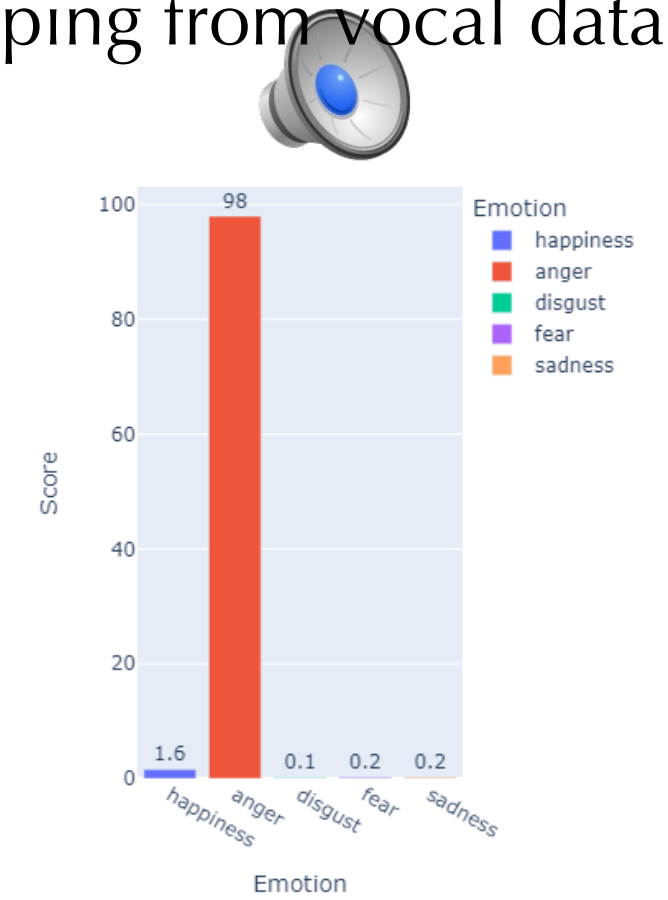
storyline



Clinical grade facial tracking solutions

Vocal Analysis

- **Vocal measures (thousands):** Emotional and vocal expression classification and subtyping from vocal data



Standardized Data Files

De-identified data for modeling, sharing and multi-omics

StoryARC

Thousands of features elegantly structured for modeling and statistical analysis using your existing tools.

StoryTIME

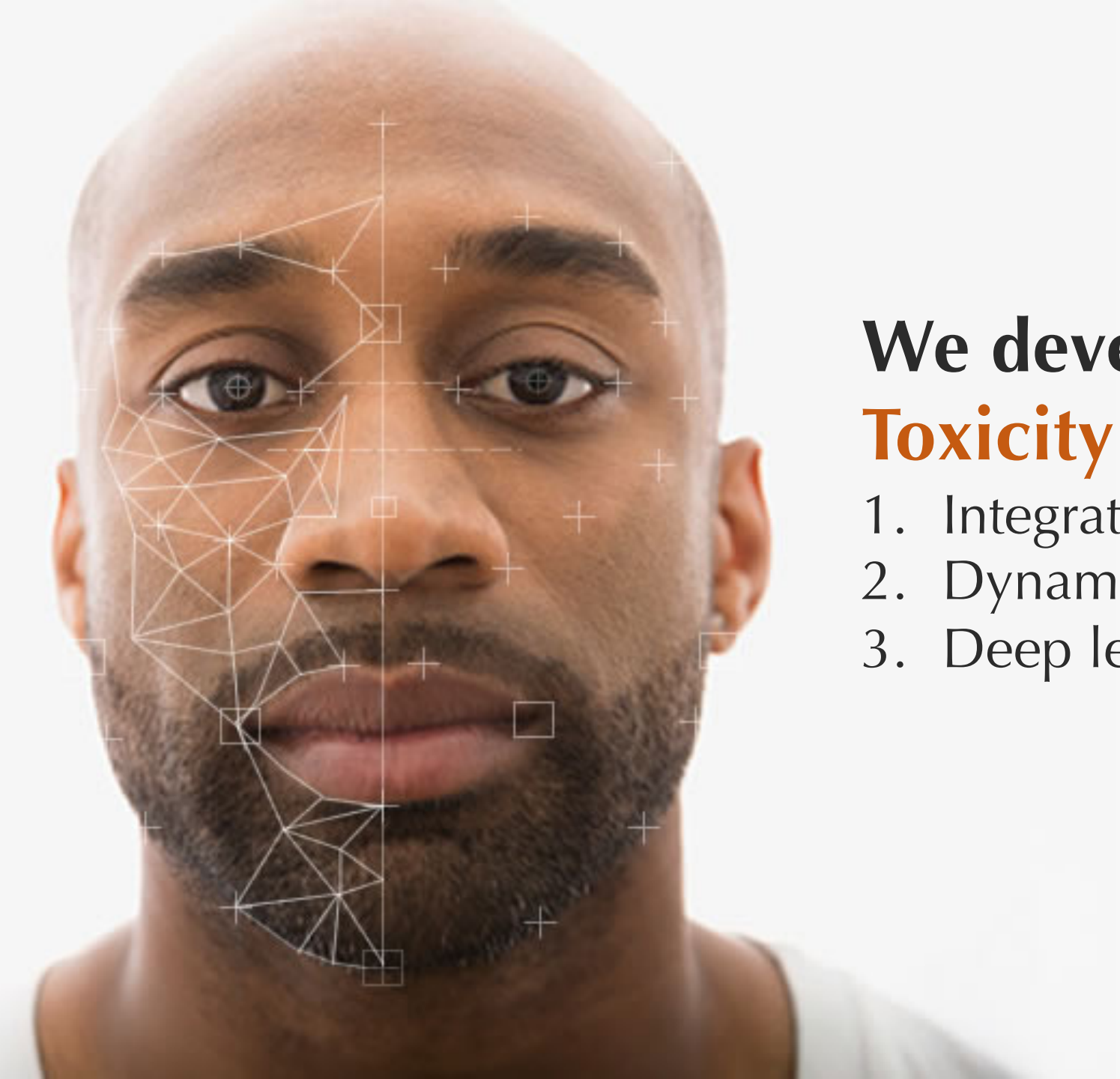
Massive new data collections oriented by time in an easy to analyze data format for discovery and invention.

Poem

A.I. discovery of behavioral segments and expressions across individuals, groups, and populations.

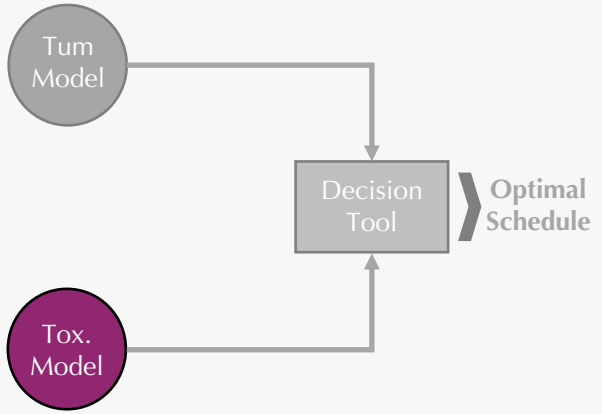
storyline

Aim 1. Define an integrative toxicity metric to monitor metastatic breast cancer patients and predict treatment response and dose adjustments.

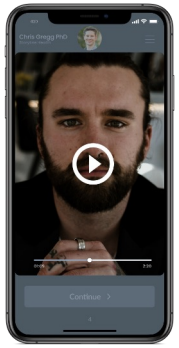


We developed three Novel Toxicity Scores

1. Integrative toxicity index
2. Dynamic toxicity monitor
3. Deep learning toxicity predictor



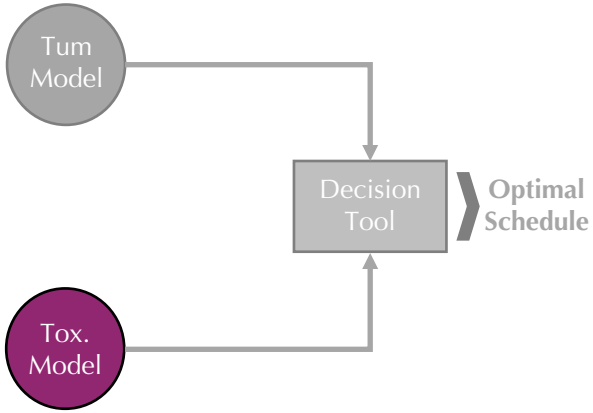
Integrative toxicity index



Storyline AI Deep Symptom Phenotyping

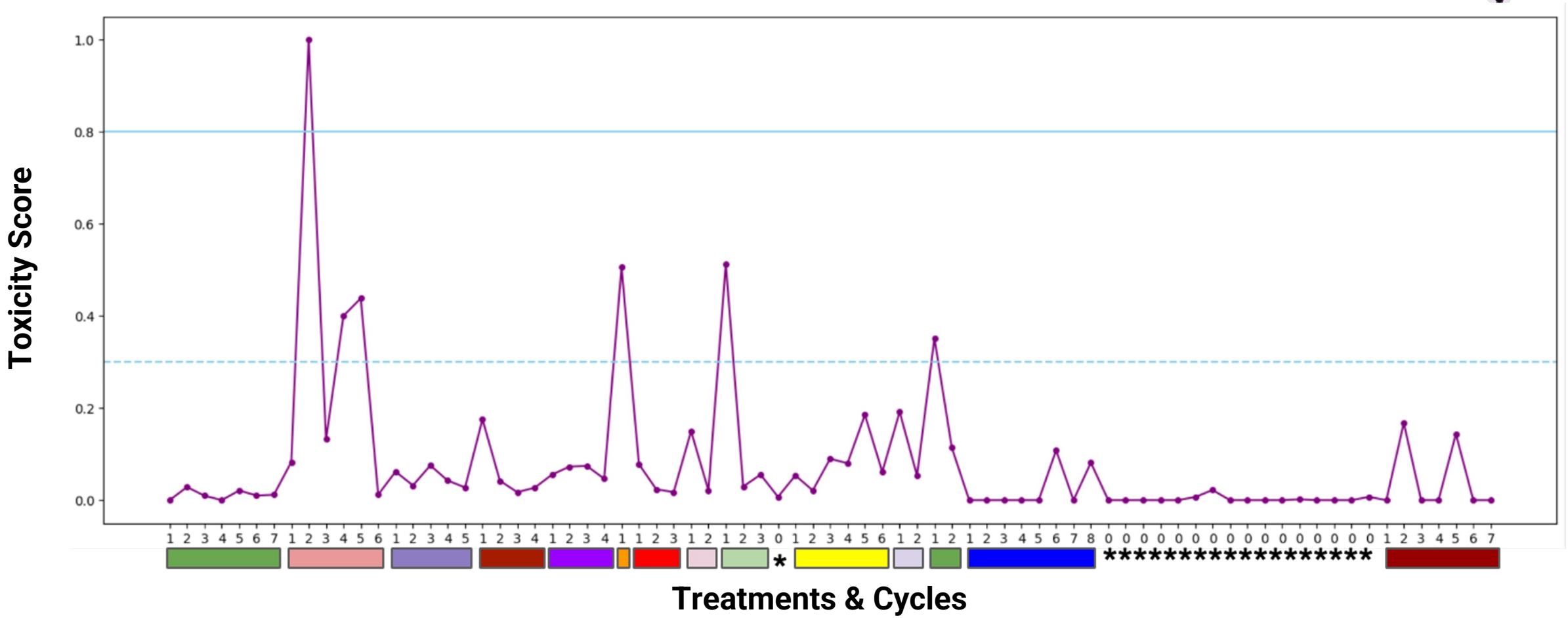
+

Standard lab tests



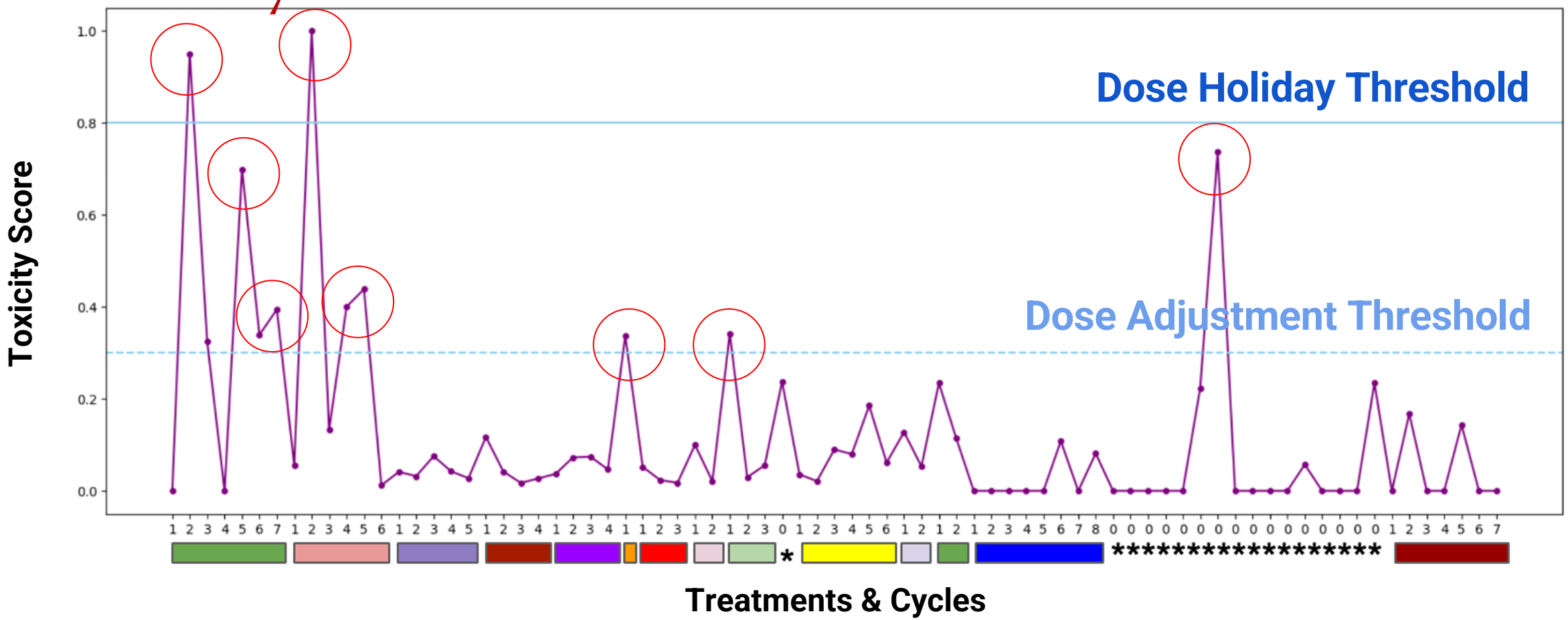
	Value	Step Adjustment	Weights	Normalized Score
Storyline sentiment score	-0.84		1	-0.598
…[100s of other measures]	…		1	…
Liver toxicity (AST level)	33	$\frac{\text{Value} - \mu}{\sigma}$	1	-0.232
Neutrophil count	2.41		1	0.078
Red blood cell count	4.59		1	0.942
Lymphocyte count	1.08		1	1.952
…			…	…
Total Toxicity Index				**2.4**

Dynamic Toxicity Monitor Based on Labs



Tamoxifen, Taxotere/Cytoxan, Adriamycin, Xeloda,Navelbine,Arimidex/Zoloadex, Arimidex/Ibrance, Xeloda/Cytoxan, Aromasin/Verzenio, Pembrolizumab/Abraxane, Tetrathiomolybdate, Fulvestrant Verzeneo

Dynamic Toxicity Monitor Based on Labs + Storyline AI



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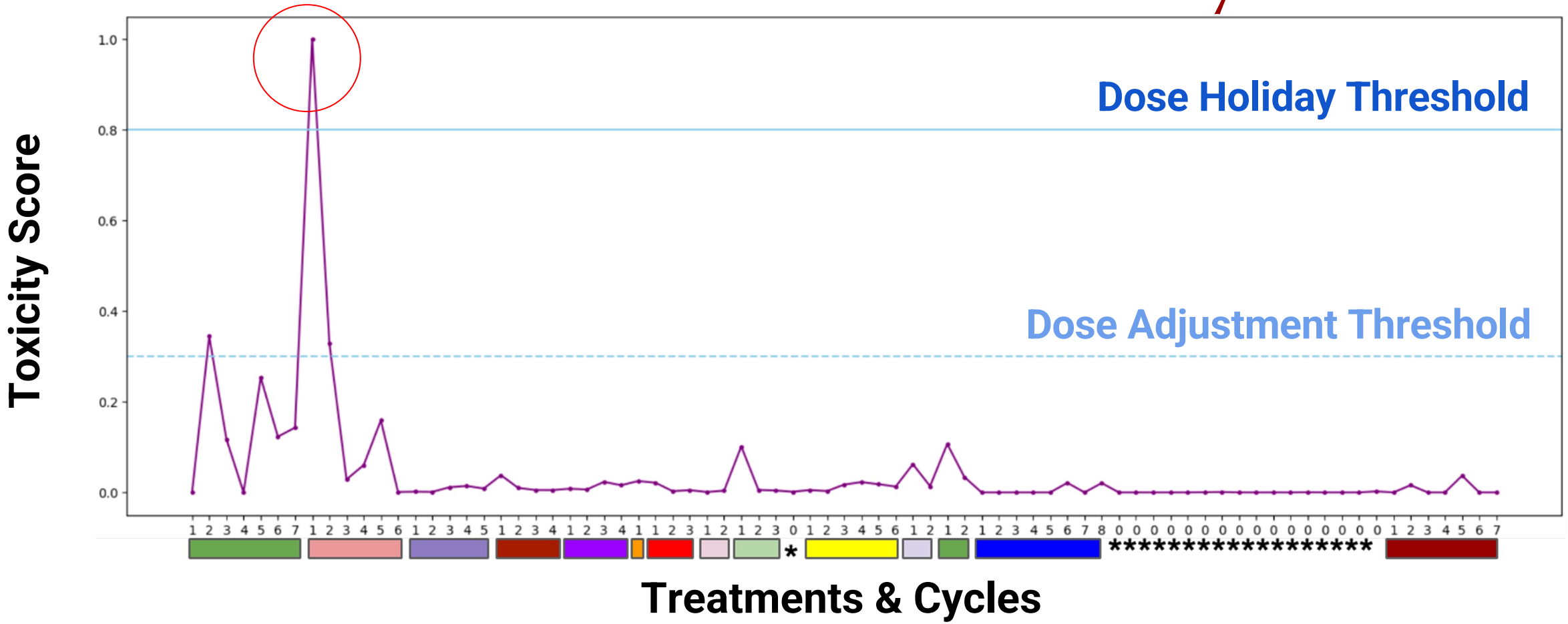
Now we can derive a **predicted toxicity score** that shows the expected toxicity if we perform **dose de-escalation when the score crosses the toxicity threshold**

$$P(T|d_i) = f(\text{dose}) + f(\text{lab data}) + f(\text{delay}) + f(\text{Storyline})$$

Predicted Toxicity Score - After a 50% Dose Reduction Based on Standard Labs **+ Storyline AI**



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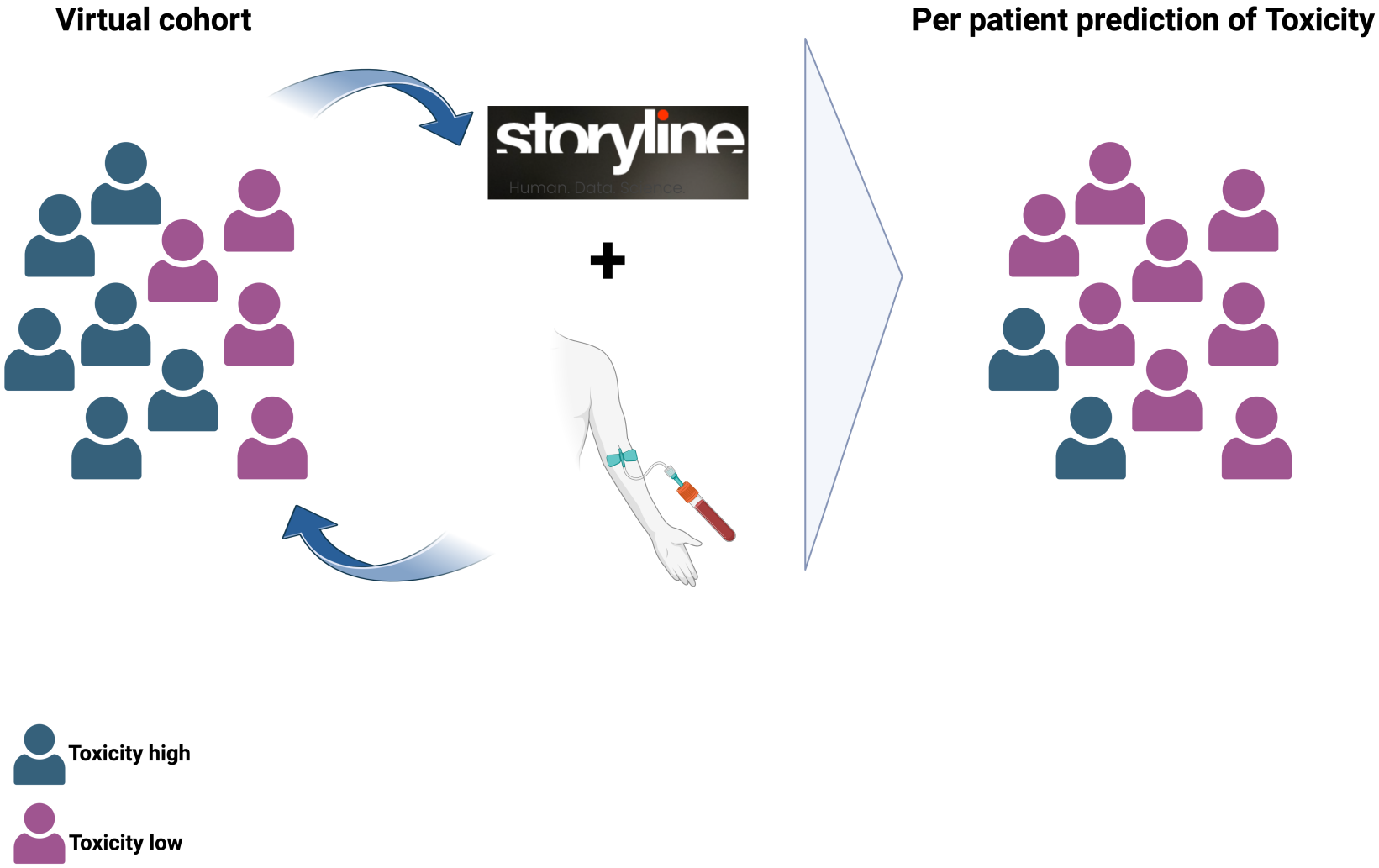
Deep Learning Toxicity Predictor



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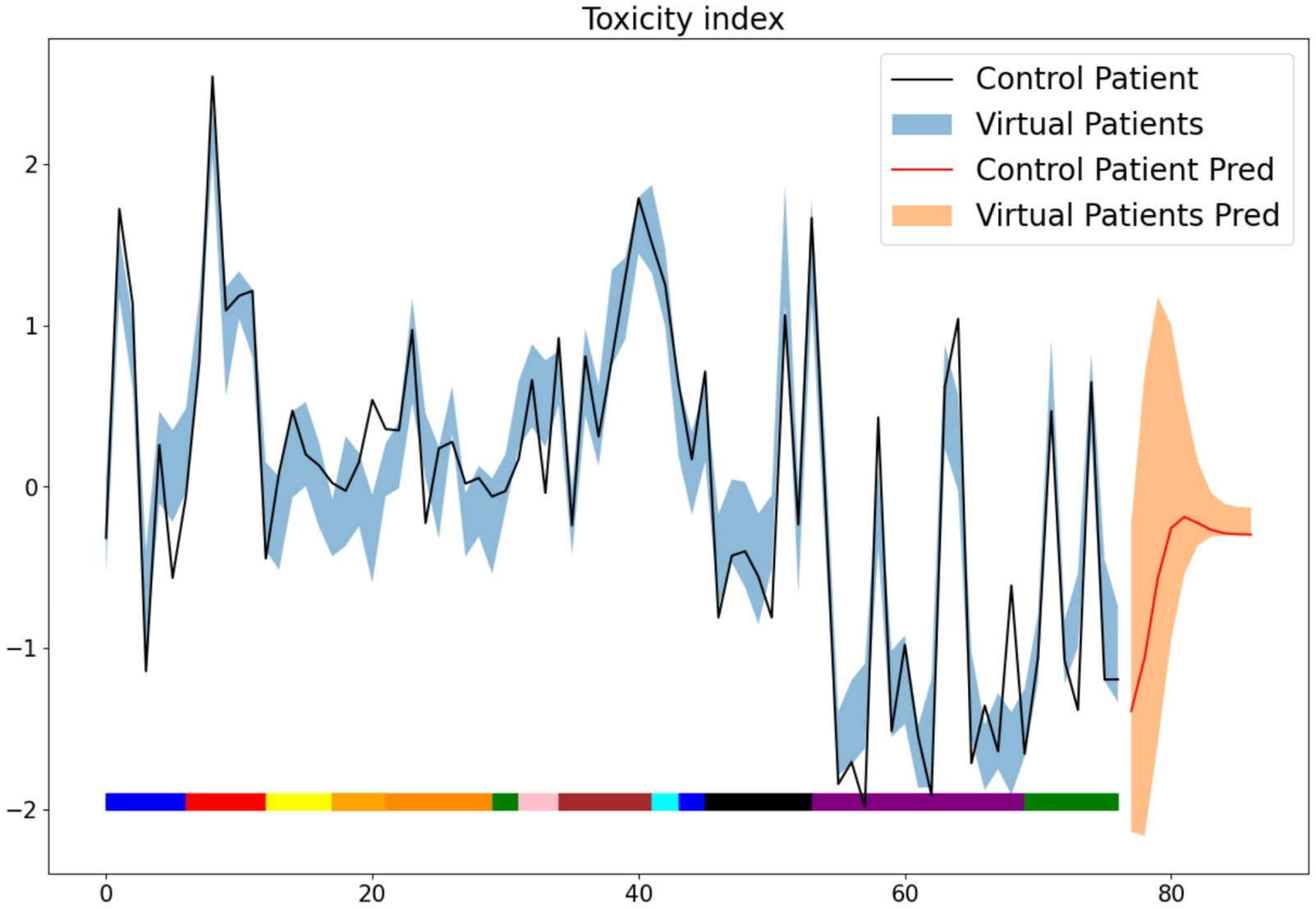
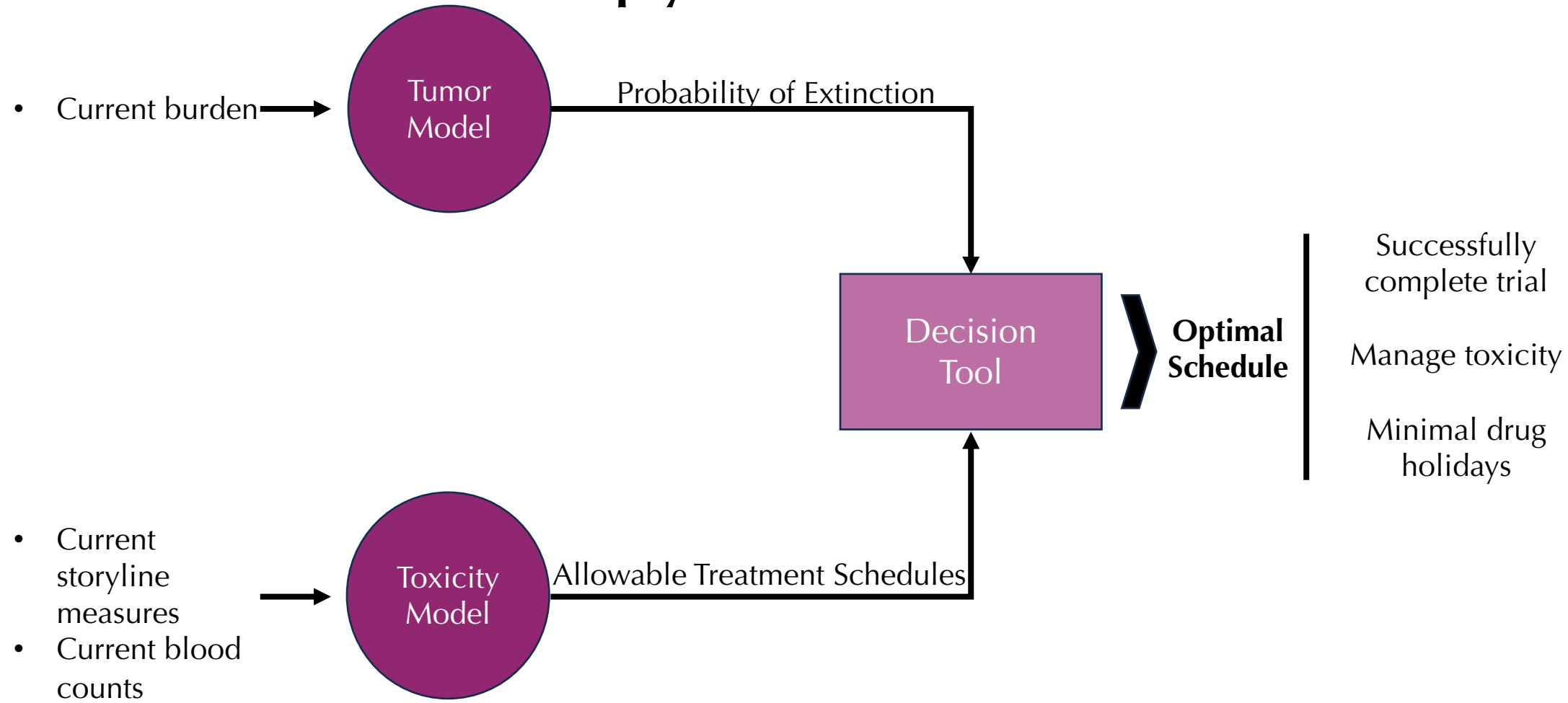


Aim 2. Create a decision algorithm that adaptively integrates toxicity and treatment response metrics to determine the optimal dose and schedule for each treatment cycle during sequential therapy to maximize the probability of success for each patient.

A comprehensive model of multi-strike extinction therapy

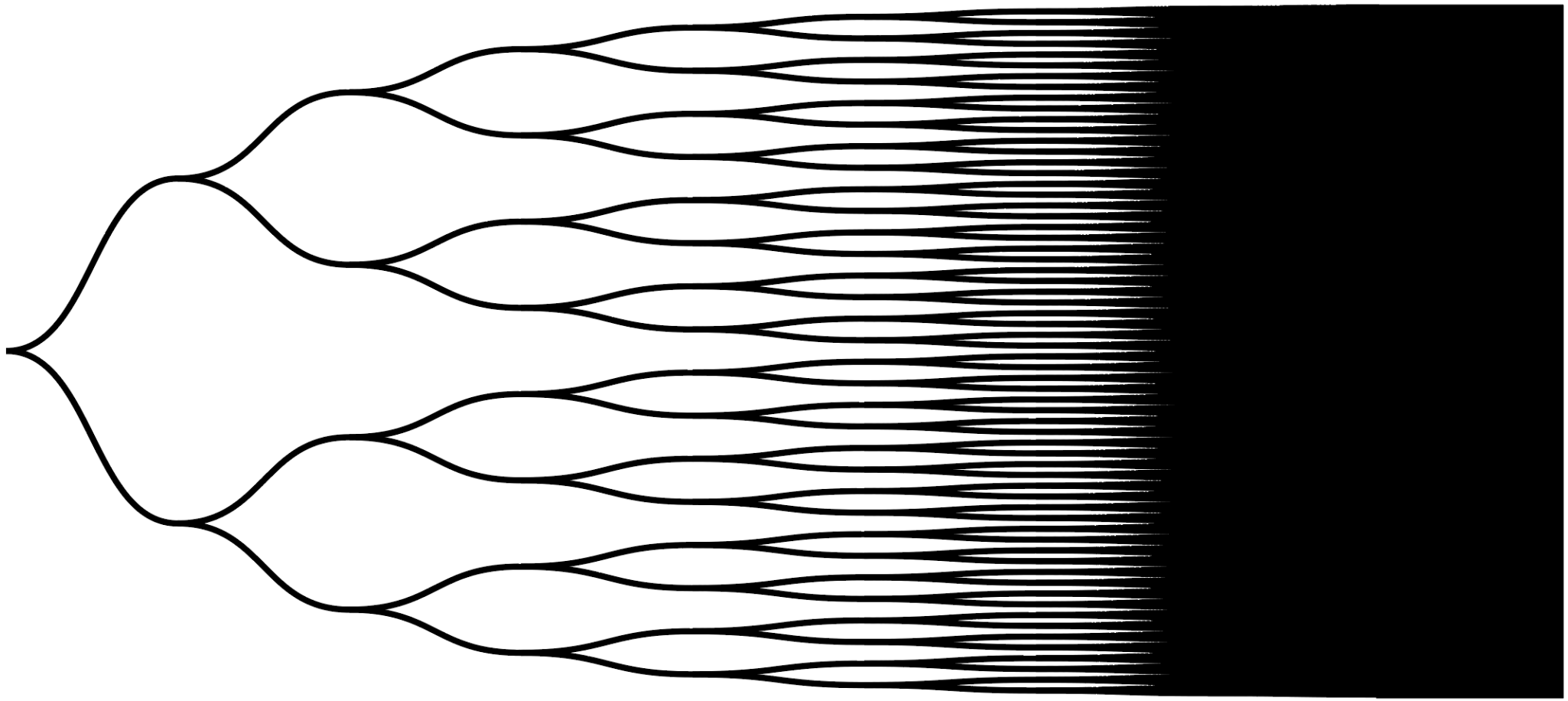


The extinction clinical trial

	1	2	3	4
Strike				
Cycle	● ● ● ●	● ● ● ●	● ● ● ●	● ● ● ●
Drug	Taxotere Cytoxan	Sacituzumab govitecan	Capecitabine	Fulvestrant + ribociclib
Class	Intravenous combination chemotherapy	Antibody drug conjugate	Oral chemotherapy	Hormonal and CDKi

Biomarker monitoring

A comprehensive model of multi-strike extinction therapy



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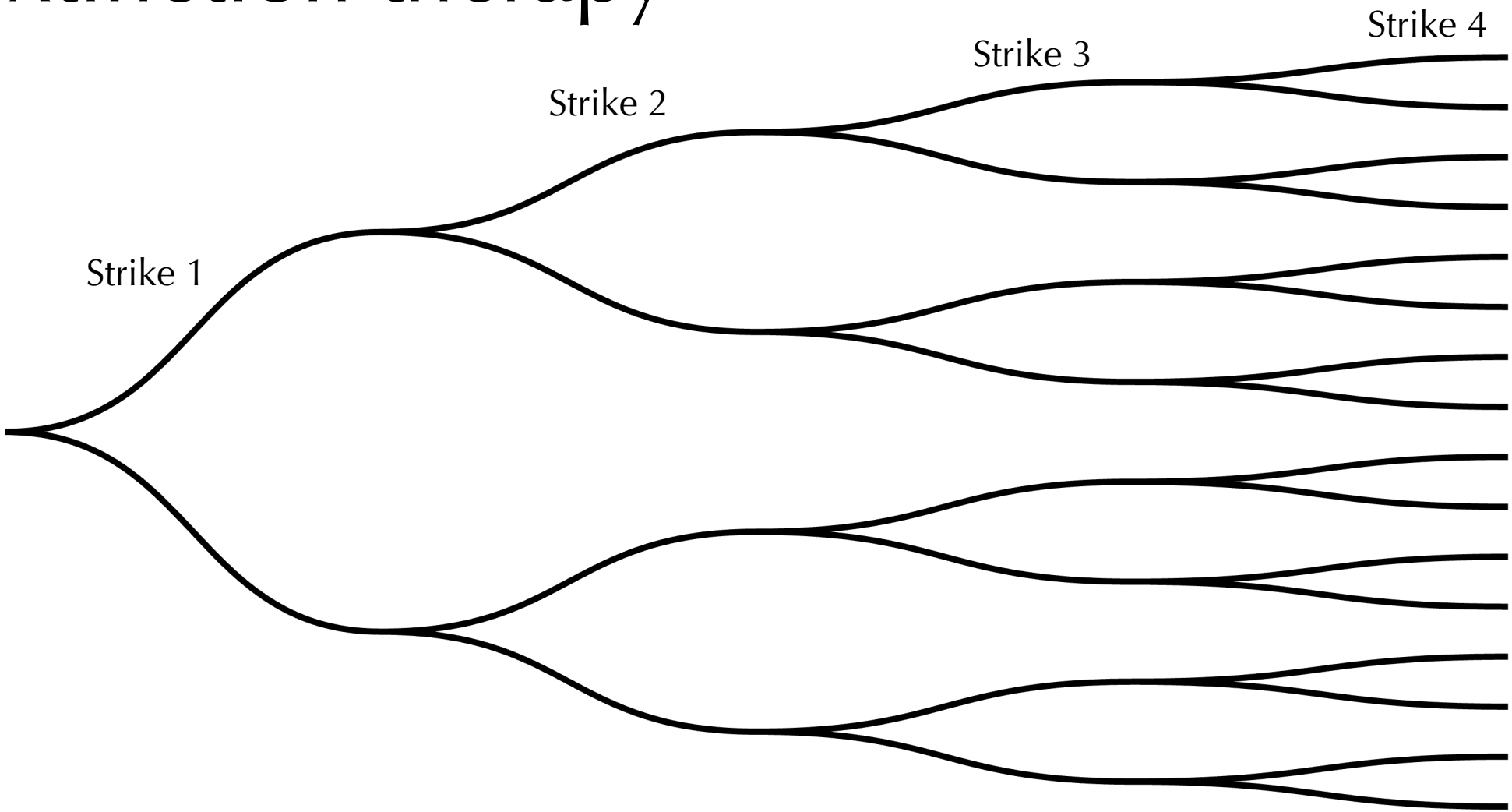

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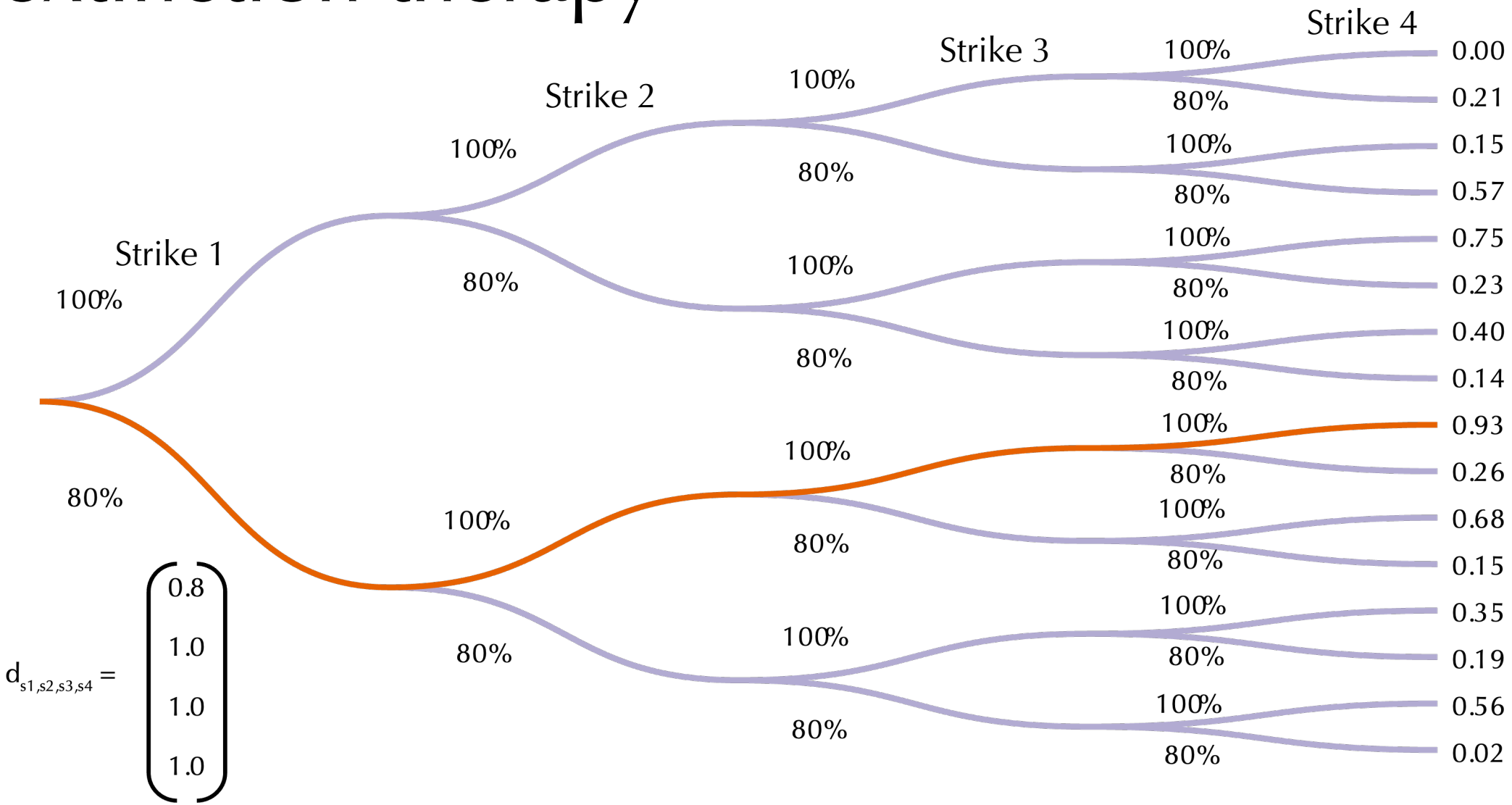

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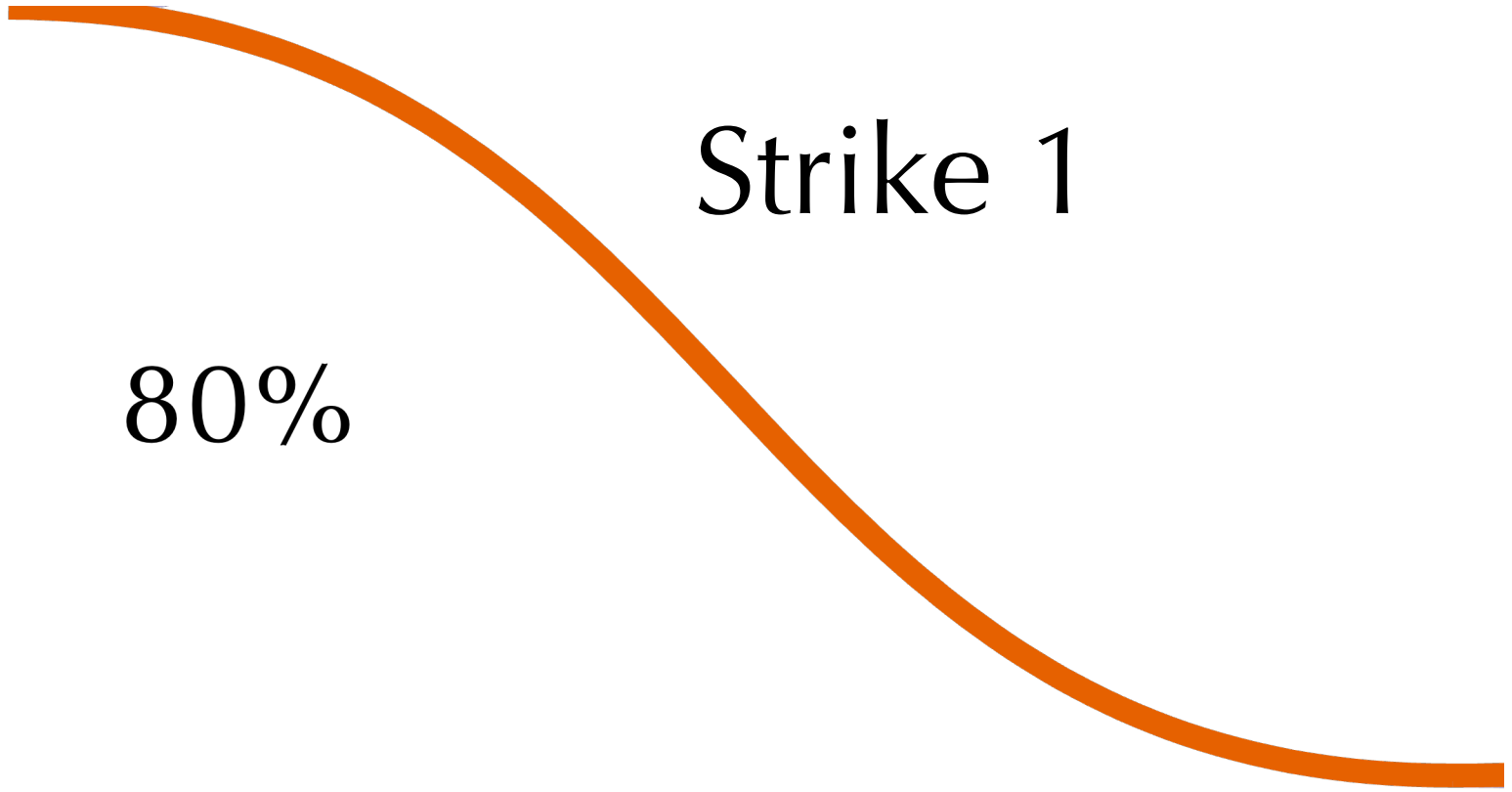
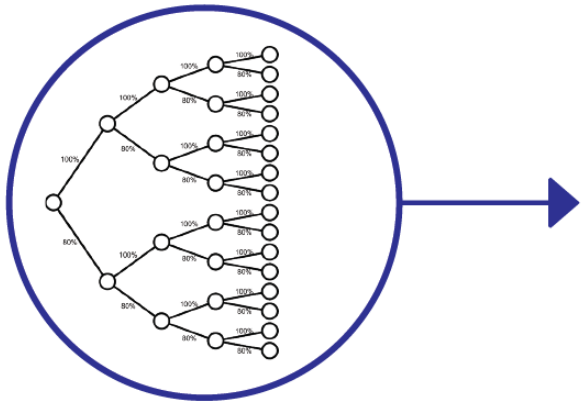


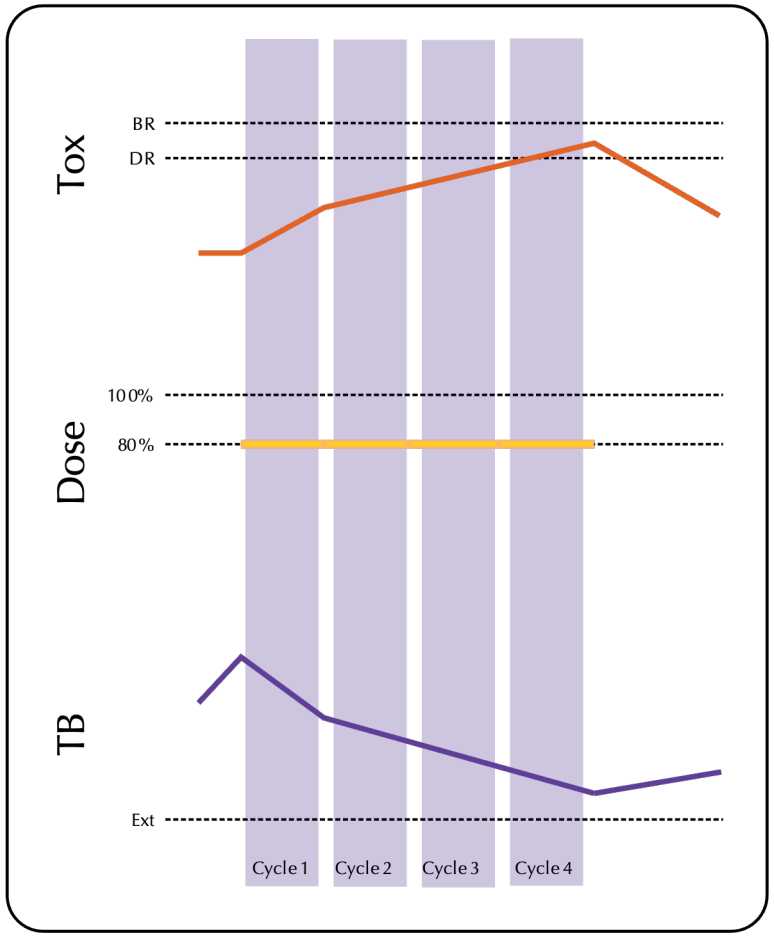
Model Workflow



Decision Tree

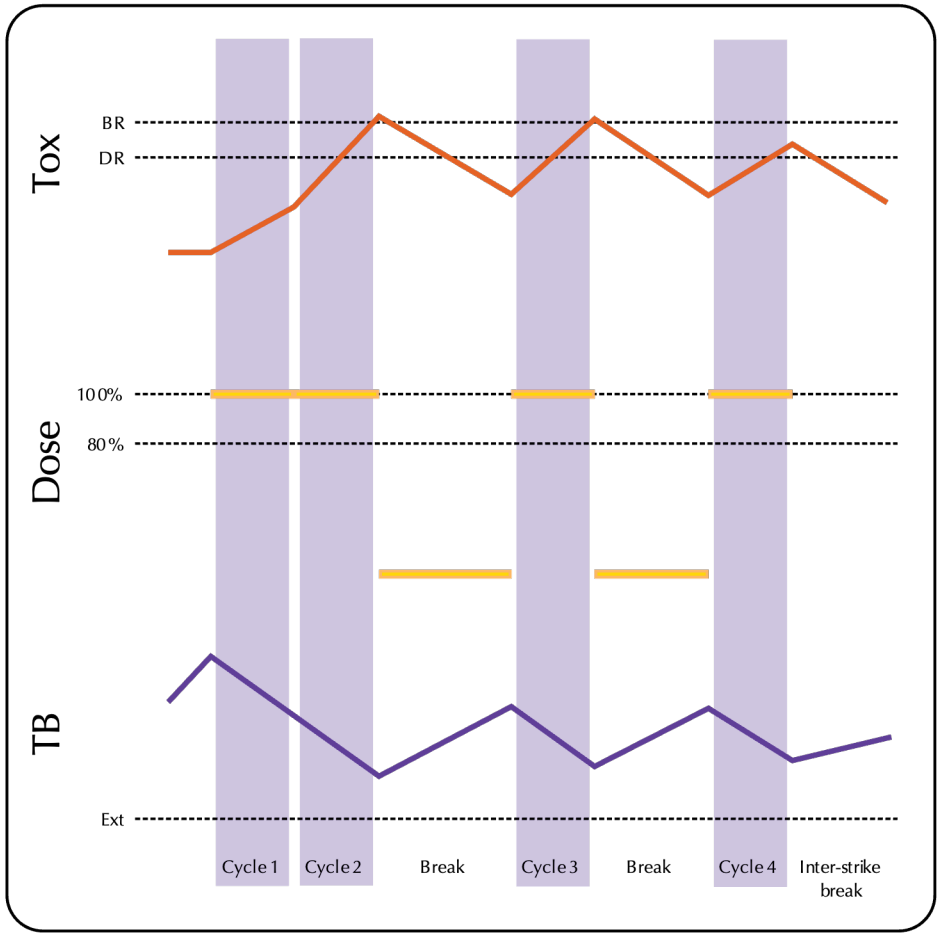
A comprehensive model of multi-strike extinction therapy

d_{s1} = 80%

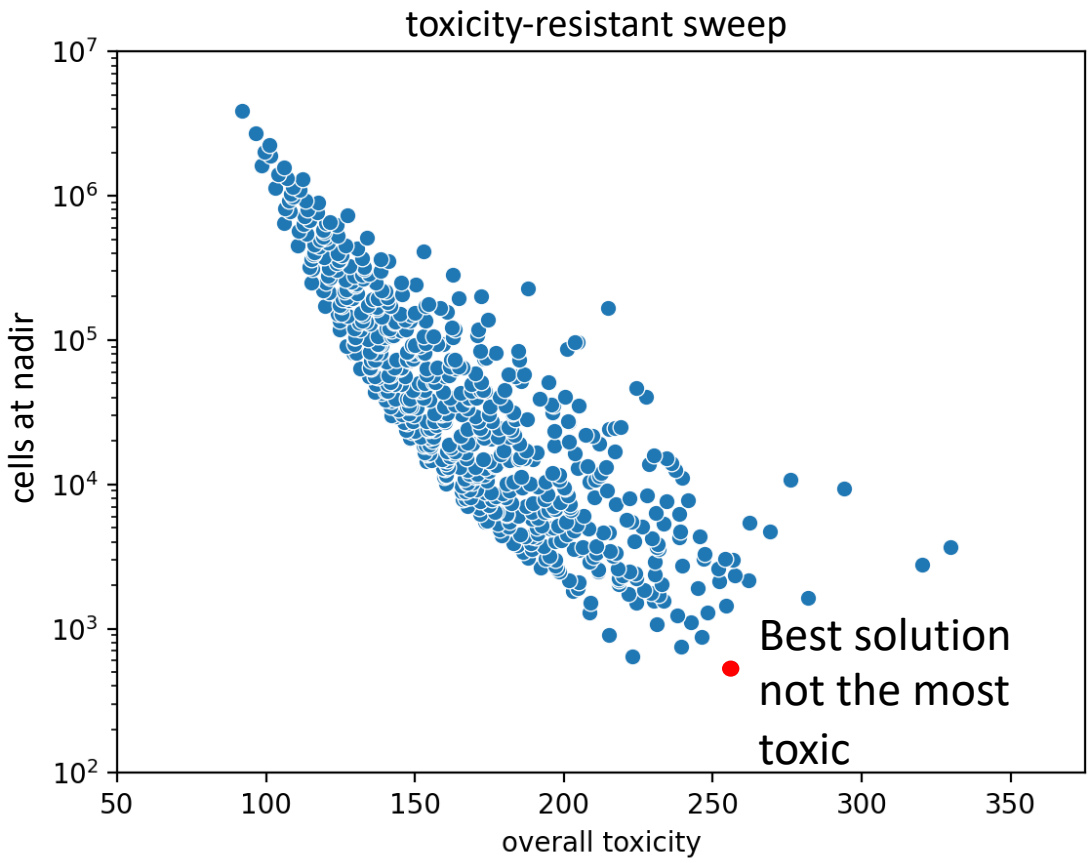


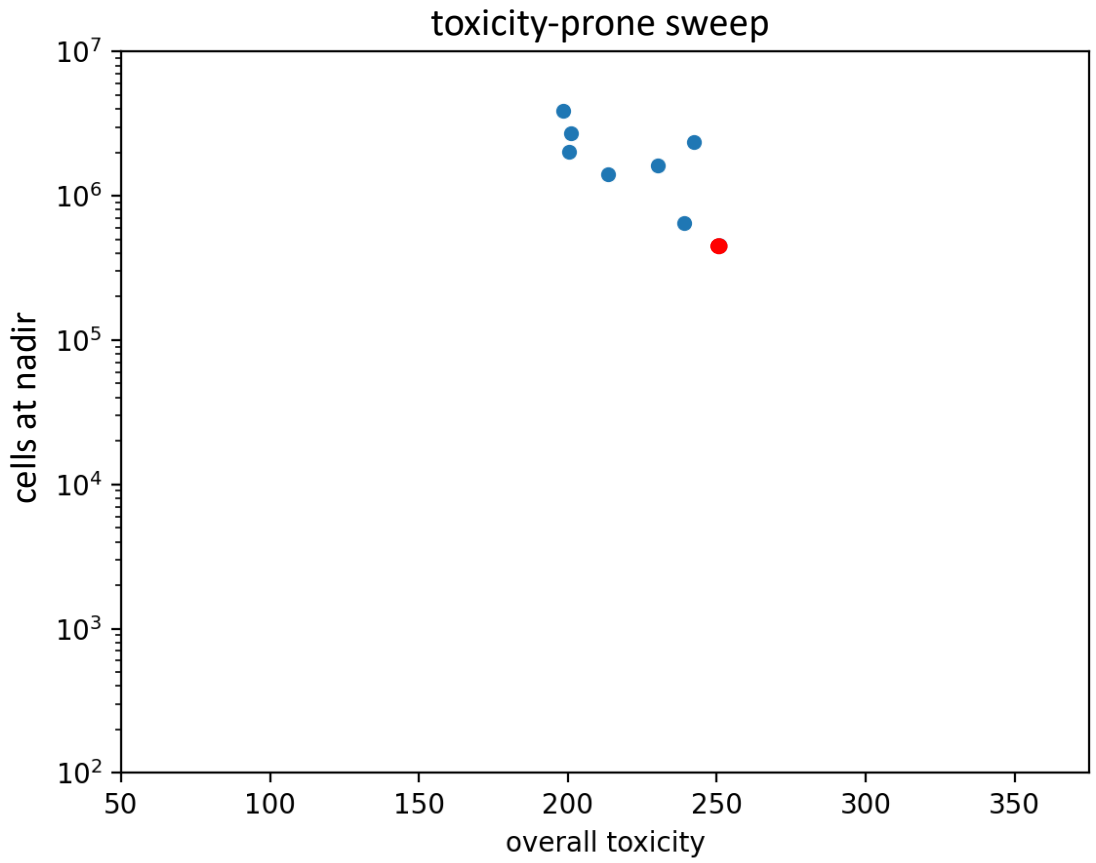
vs

d_{s1} = 100%

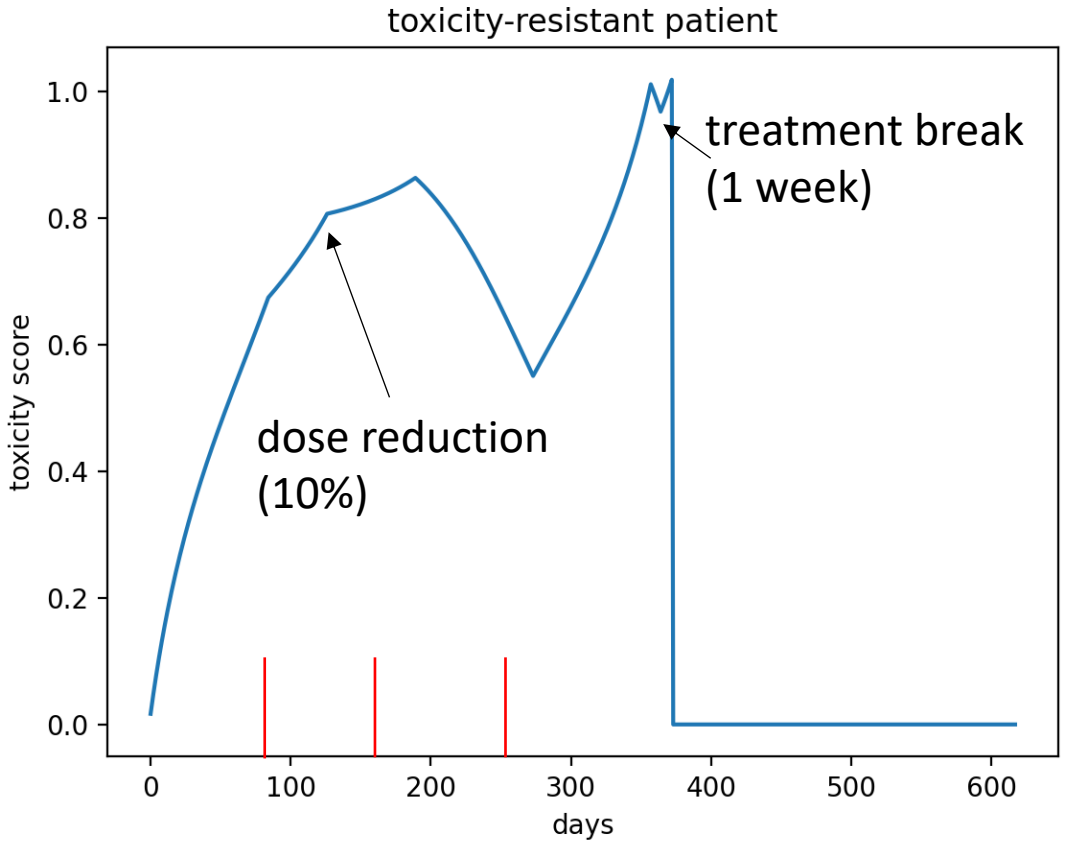


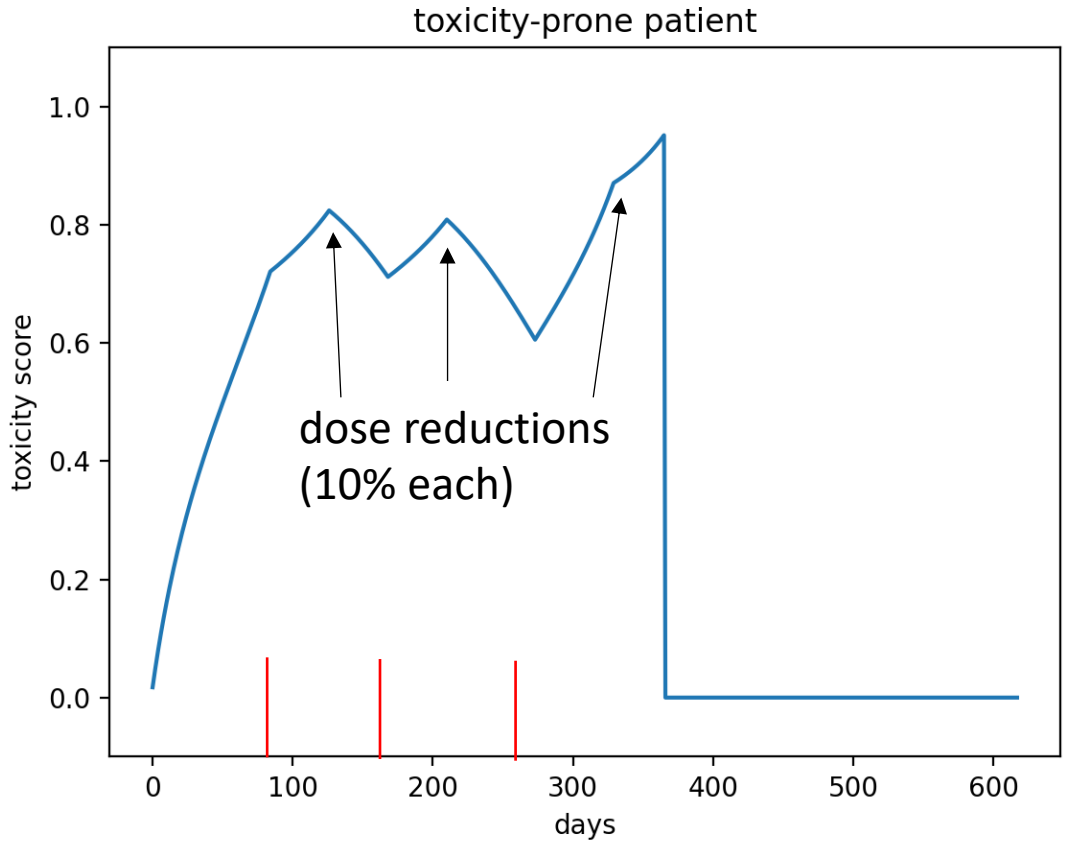
Decision tree therapy simulations





Optimal treatment strategies

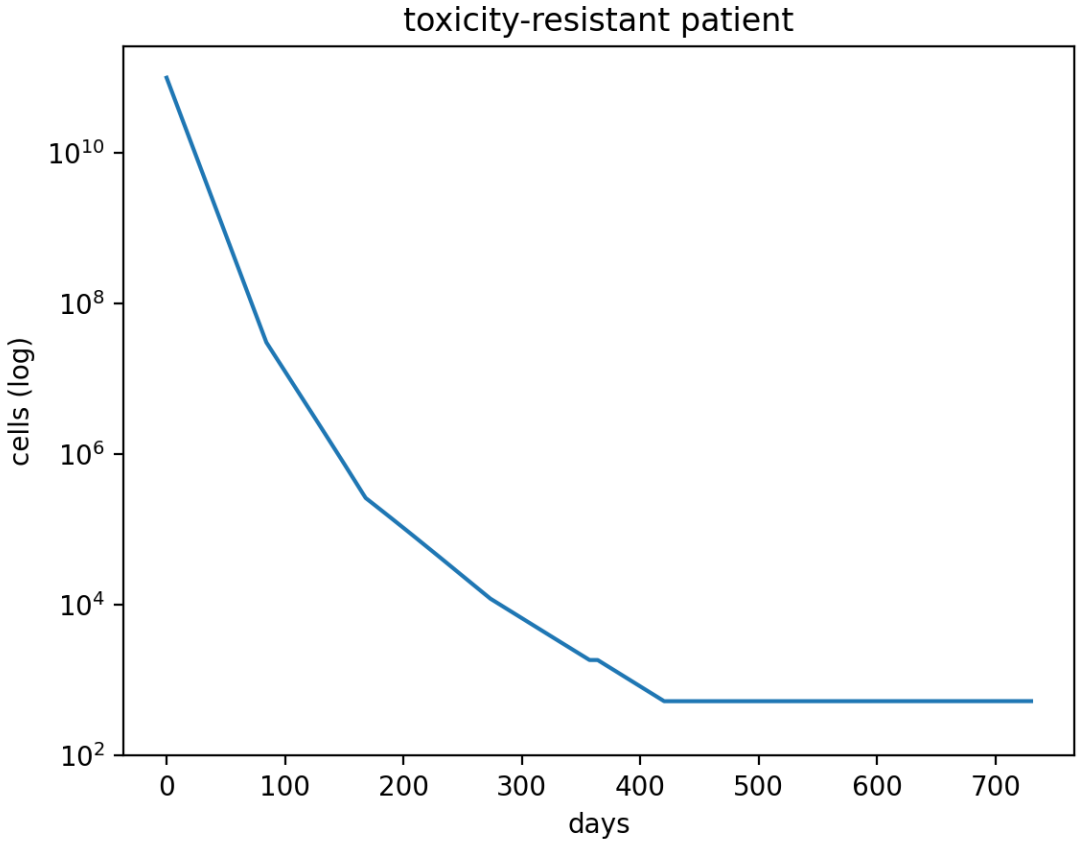


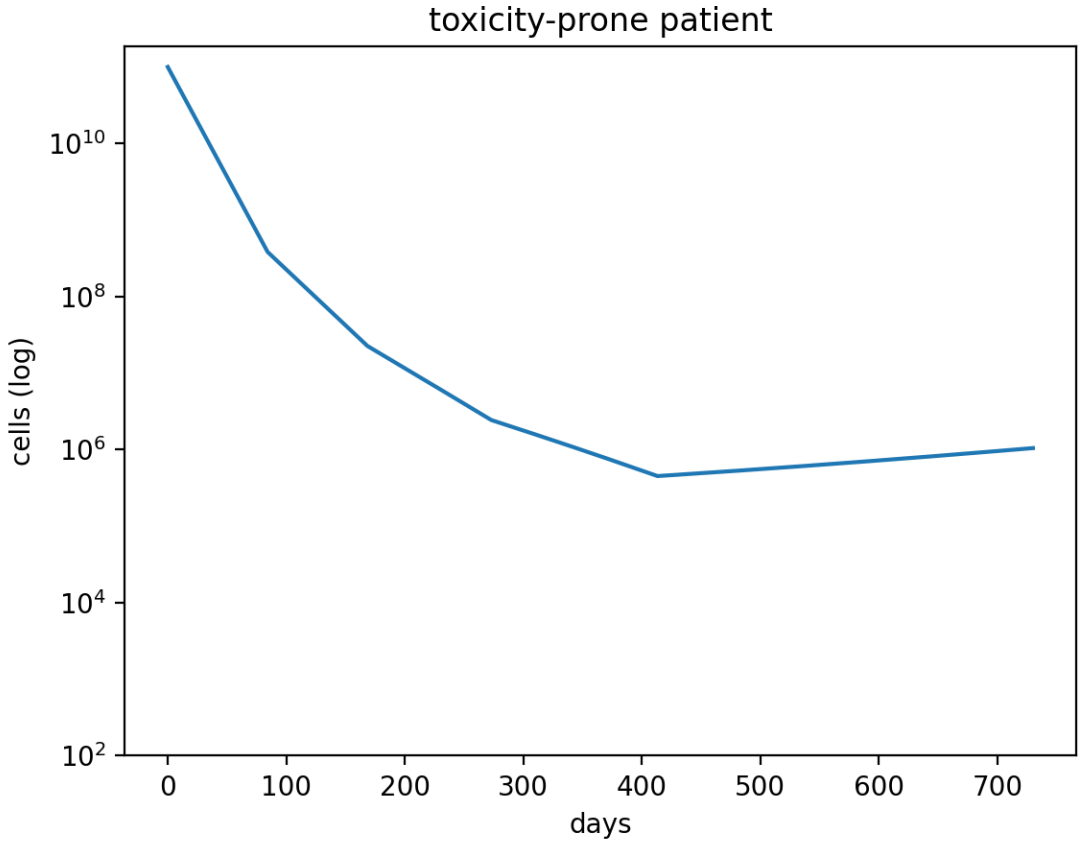


Dose 1	Dose 2	Dose 3	Dose 4
1.0	0.8	0.6	0.9

Dose 1	Dose 2	Dose 3	Dose 4
0.7	0.5	0.5	0.6

Optimal treatment strategies





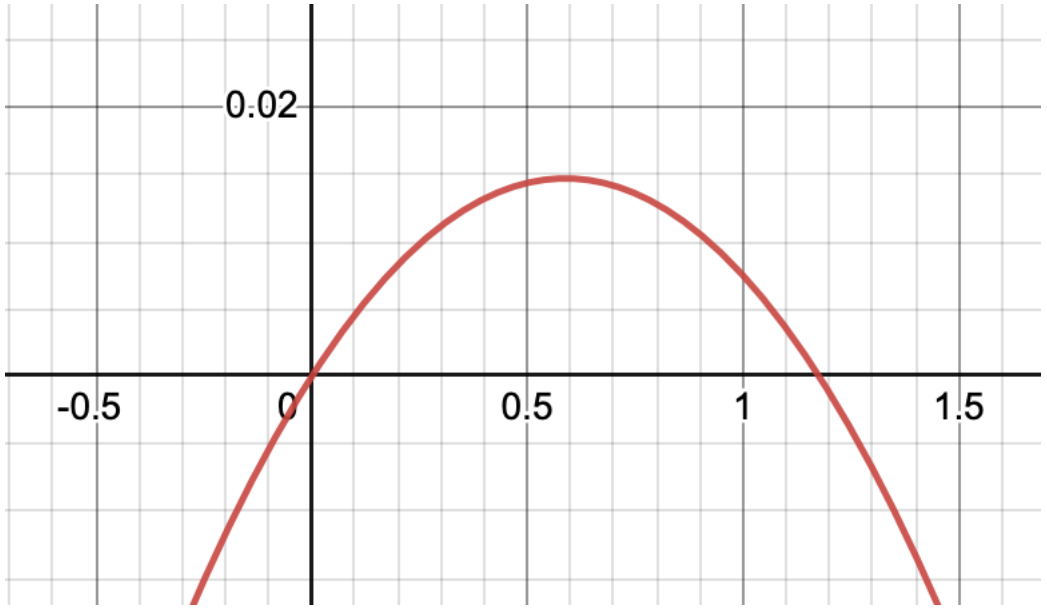
Dose 1	Dose 2	Dose 3	Dose 4
1.0	0.8	0.6	0.9

Dose 1	Dose 2	Dose 3	Dose 4
0.7	0.5	0.5	0.6

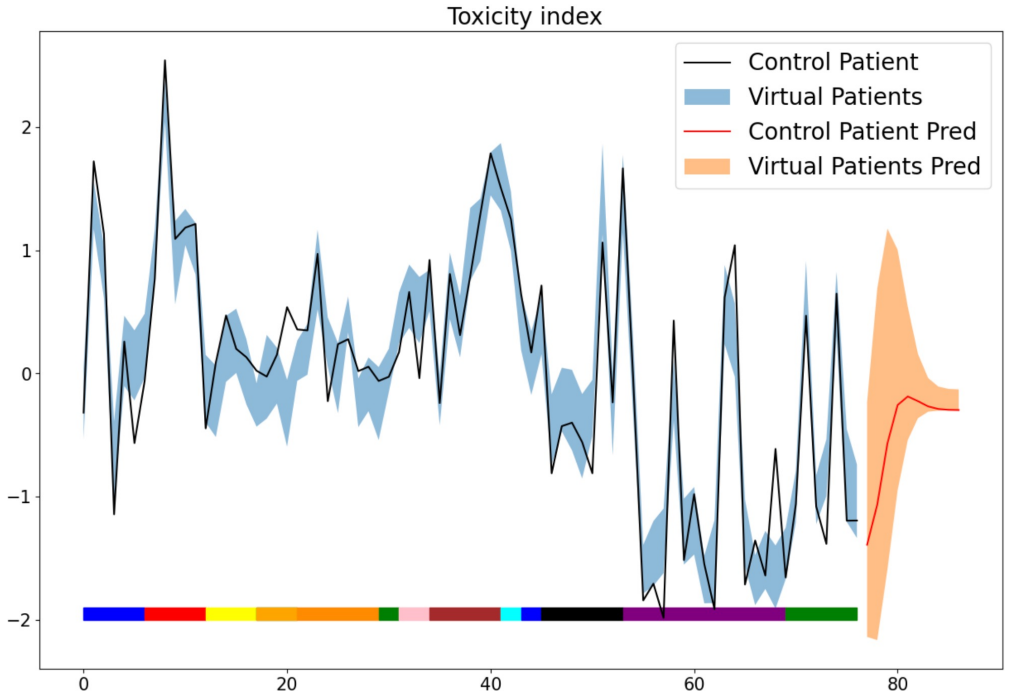
Toxicity Function

$$x_{n+1} = x_n(0.05-0.85x_n(0.05))+y_n s$$

x, toxicity
y, drug dose
s, patient sensitivity

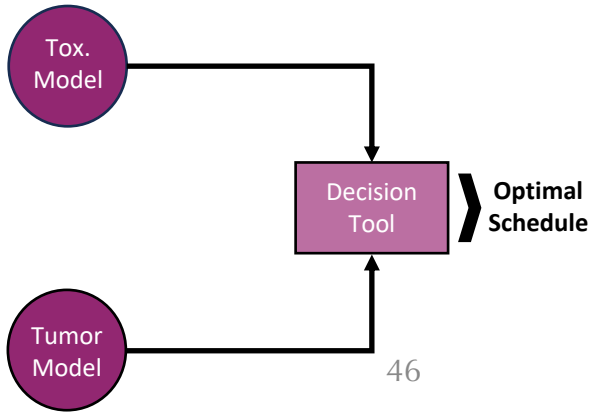


Specific Aims

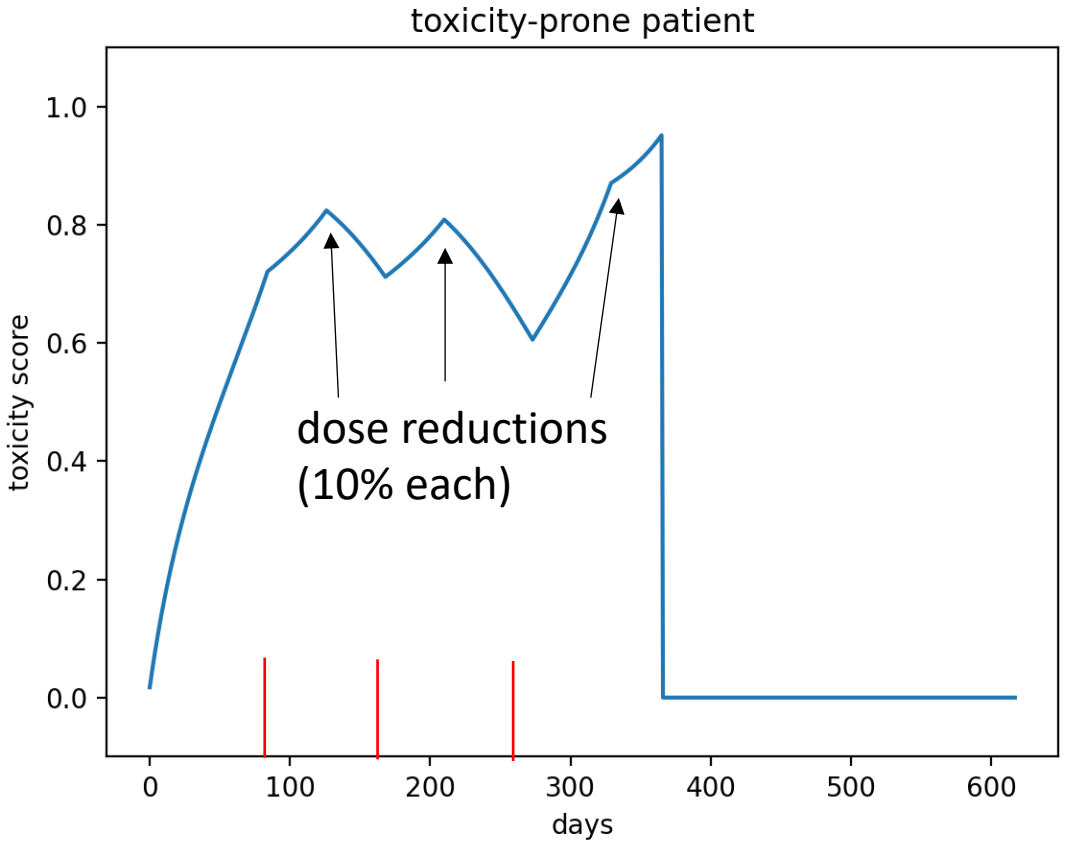


Aim 1

Define an integrative toxicity metric to monitor metastatic breast cancer patients and predict treatment response and dose adjustments.

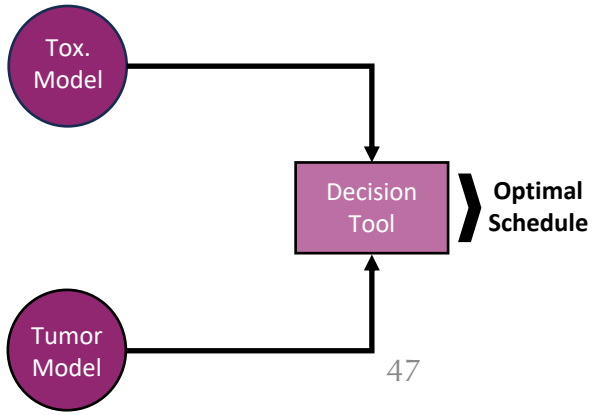


Specific Aims



Aim 2

Create a decision algorithm that adaptively integrates toxicity and treatment response metrics to determine the optimal dose and schedule for each treatment cycle during sequential therapy to maximize the probability of success for each patient.



Budget

- Storyline Health – $20,000
- Post-doc - $20,000
- Clinical Data Abstraction – $5,000
- Data analysis/math modeling – $5,000

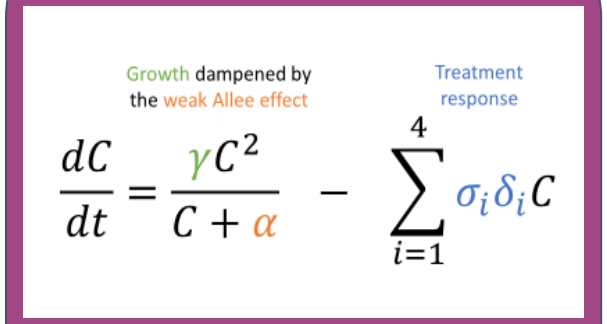
Acknowledgments

Adam Streck, PhD

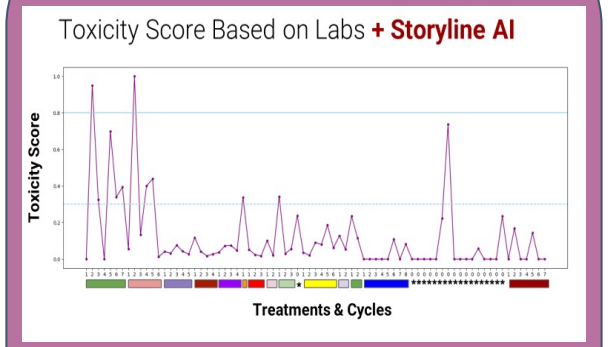
Chris Whelan, PhD

Aixa Soyano Muller, MD

Indigo Extinction Team



Tumor Modeling
Frank Bastian
Diya Upadhyaya
Tony LI



Toxicity
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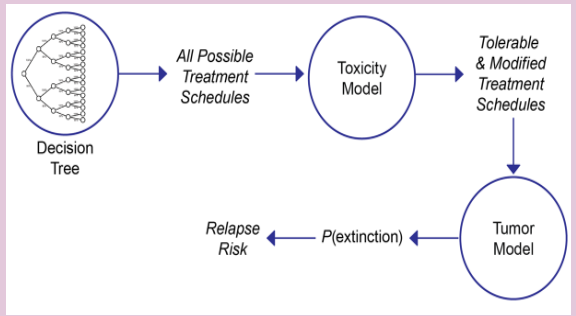
Sandhya Prabhakaran
Alexandria Johnson
Kayode Olumoyin



Decision Model
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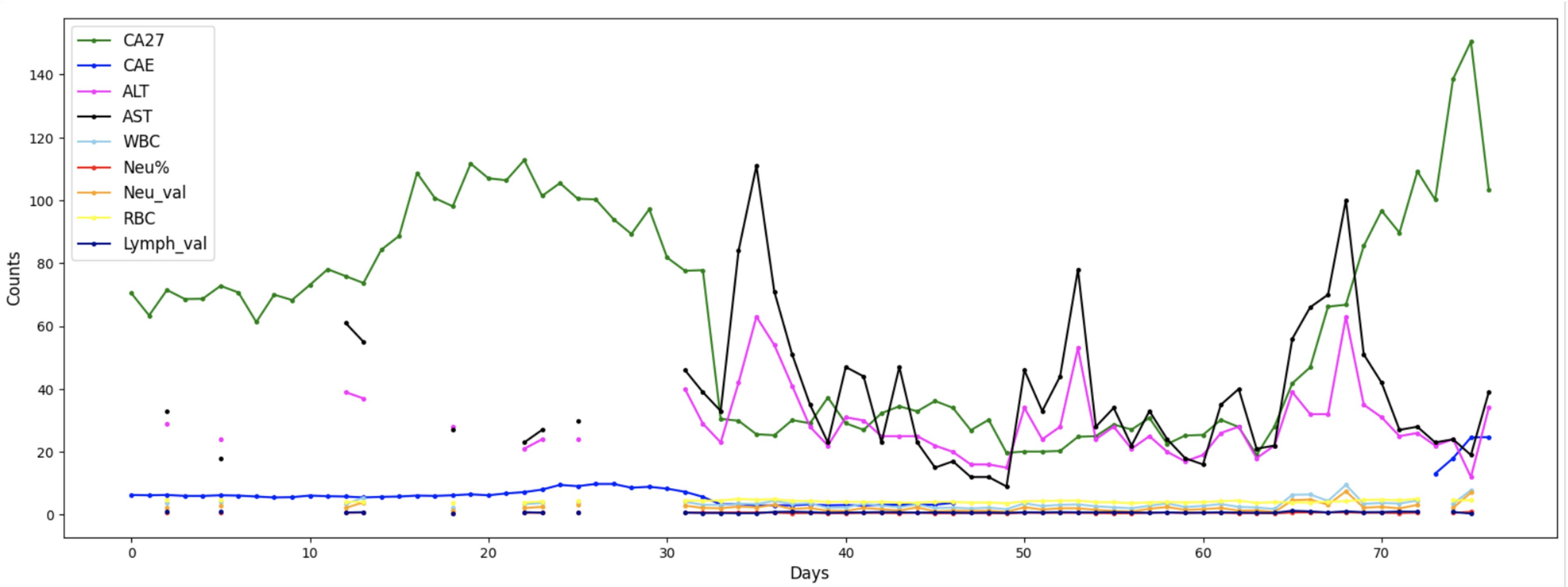
Pujan Shrestha
Marcin Kaszkowiak
Adam Streck

Dana Ataya |Renee Brady-Nicholls | Chris Sng | Chris Gregg
Aixa Soyano Muller | Chris Whelan | Mohammad Zahid | James Harris

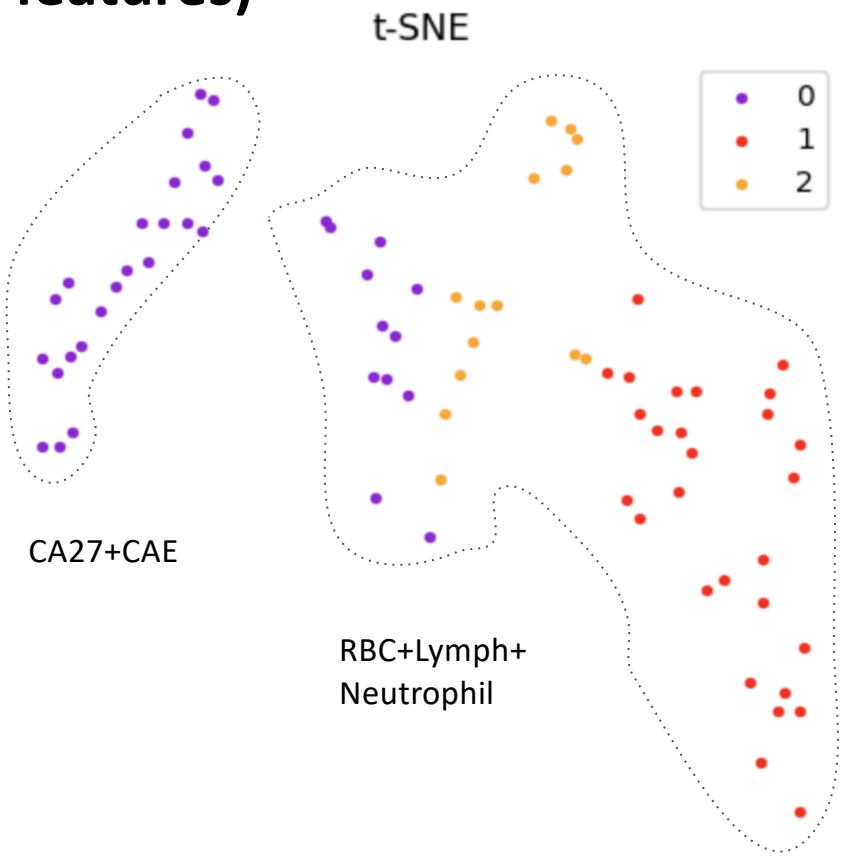
Appendix

Chris' Lab data



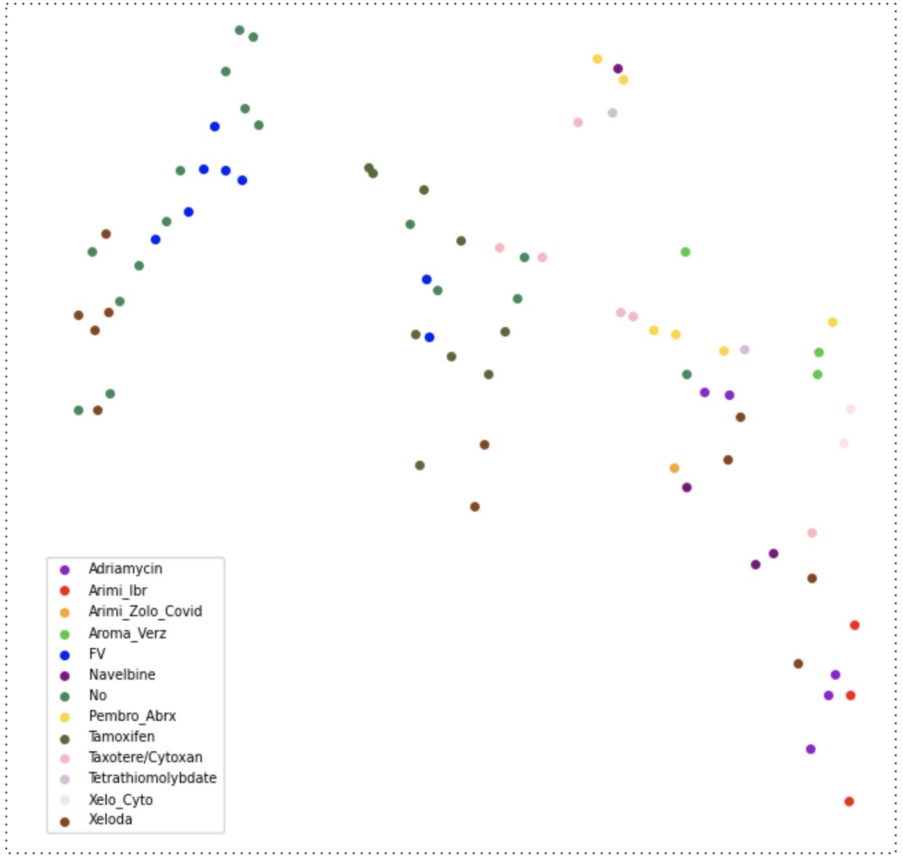
(There are missing data points; unimputed data is shown here)

Unsupervised clustering (with all lab info as features)

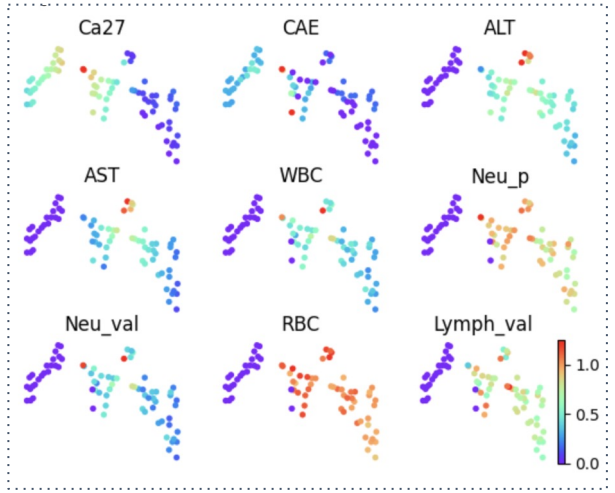


CA27+CAE

RBC+Lymph+
Neutrophil



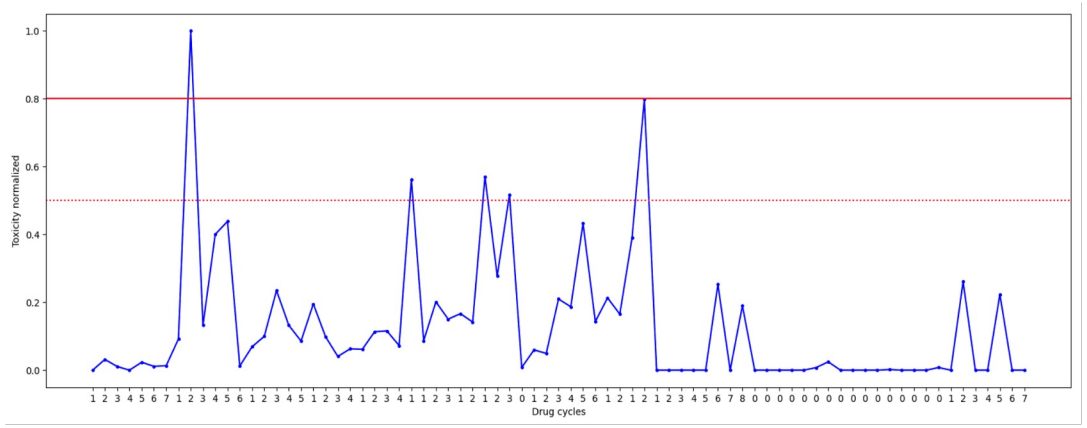
tSNE colored by Tx



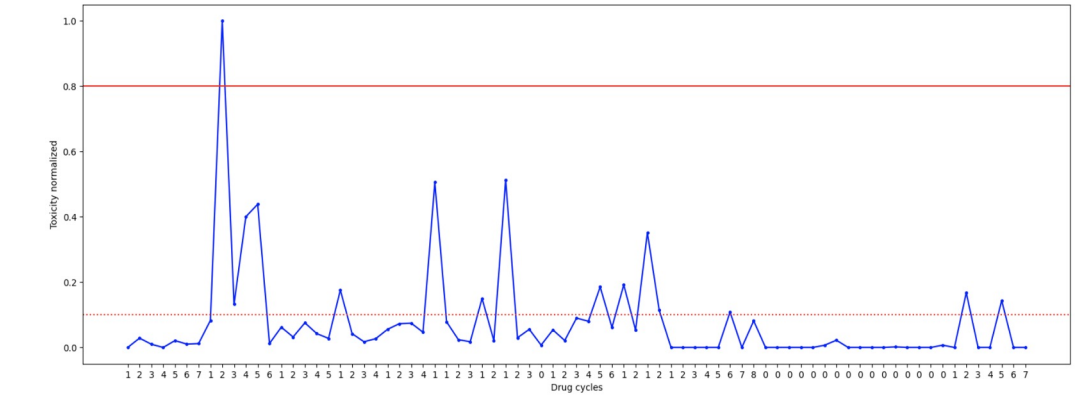
Feature spread

tSNE showing 3 clusters:
Input data had 77 days (rows), and 9 Features:
WBCs, RBCs, Neutro, Lymph, ALT, AST, CA27 and CAE

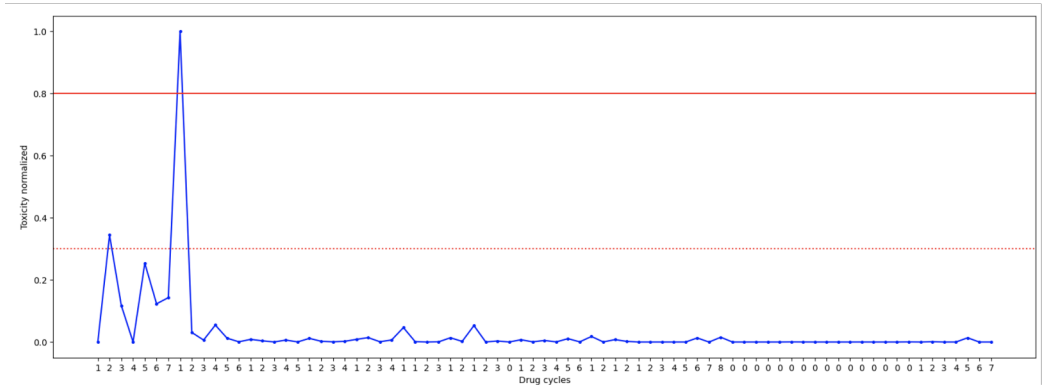
Chris’ toxicity profile



With delay per drug



With delay at each cycle set to 10 days



Prediction of toxicity based on breaks and Chris’ tx schedule