Pharmacokinetic Modeling of Fentanyl Citrate and Norfentanyl in Calves Using a Nonlinear Mixed-Effects Approach

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GOAL

Fentanyl citrate is a potent opioid agonist commonly used as an analgesic in animal studies, providing several hours of pain relief during surgical and other medical procedures [1].

Characterize the kinetics of fentanyl citrate and norfentanyl using a nonlinear mixed-effects (NLME) modeling approach
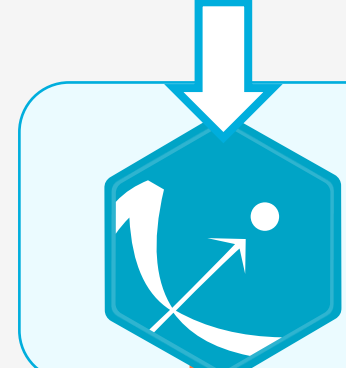
Use this model to **compare competing dosing regimens** that achieve therapeutic steady-state concentrations of fentanyl and norfentanyl, while minimizing systemic toxicity in calves.
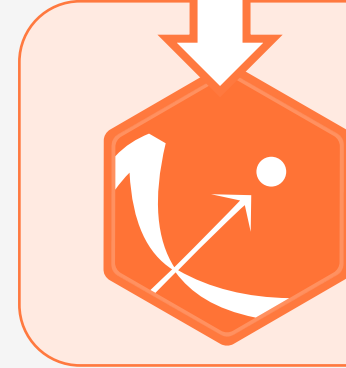
WORKFLOW

Data
- 16 calves
- Single iv dose, either 2.5 µg/kg or 5.0 µg/kg
- Parent (fentanyl) and metabolite (norfentanyl) measured for 24h after dosing

Population modeling in Monolix
- Joint model capturing parent and metabolite data and inter-individual variability
- Selection of best structural and statistical model

Compare dosing regimen in Simulx
- Predict the response to continuous infusion and intermittent boluses, with and without loading dose
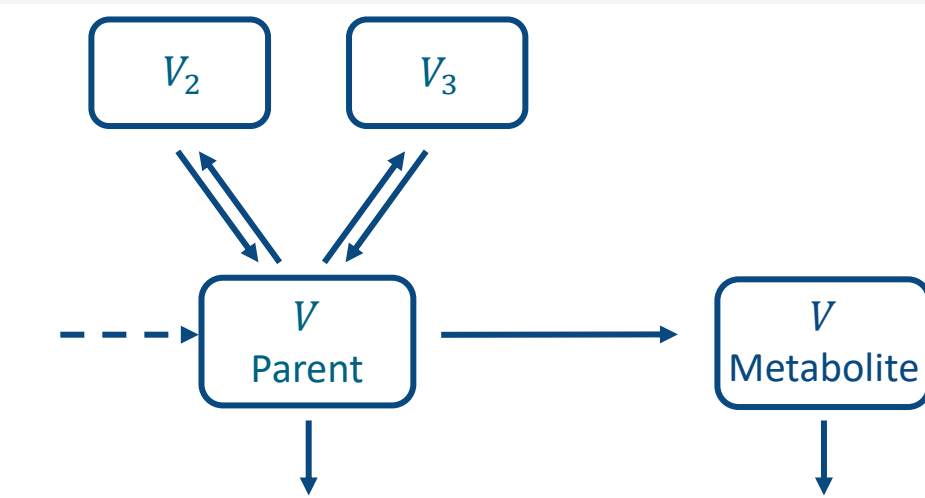- Post-process simulations to find the best regimen combining safety and efficacy

IMPORT your estimated model in one click

PARENT-METABOLITE MODEL ESTIMATED IN MONOLIX

Model selection in Sycomore

Keep track of your MODEL BUILDING steps and compare runs with Sycomore

Structural model

Statistical model

Population Parameters

	VALUE	STOCH. APPROX.	
		S.E.	R.S.E.(%)
Fixed Effects			
V1_pop	168.37	8.39	4.98
Cl_pop	0.14	0.014	10.2
Q2_pop	3.01	0.71	23.6
V2_pop	104.13	6.82	6.55
Q3_pop	2.85	0.23	8.07
V3_pop	1876.99	368.54	19.6
Clm_pop	1.19	0.0079	0.664
Kpm_pop	0.0066	0.00063	9.55
Standard Deviation of the Random Effects			
omega_V1	0.15	0.043	27.7
omega_Q2	0.63	0.17	26.9
omega_Q3	0.29	0.059	20.5
omega_V3	0.73	0.15	21.0
omega_Kpm	0.32	0.065	20.5
Correlations			
corr_Q3_Kpm	-0.82	0.11	13.6
Error Model Parameters			
bFentanyl	0.14	0.0088	6.26
aNorfentanyl	46.31	3.2	6.92

Visual Predictive Checks
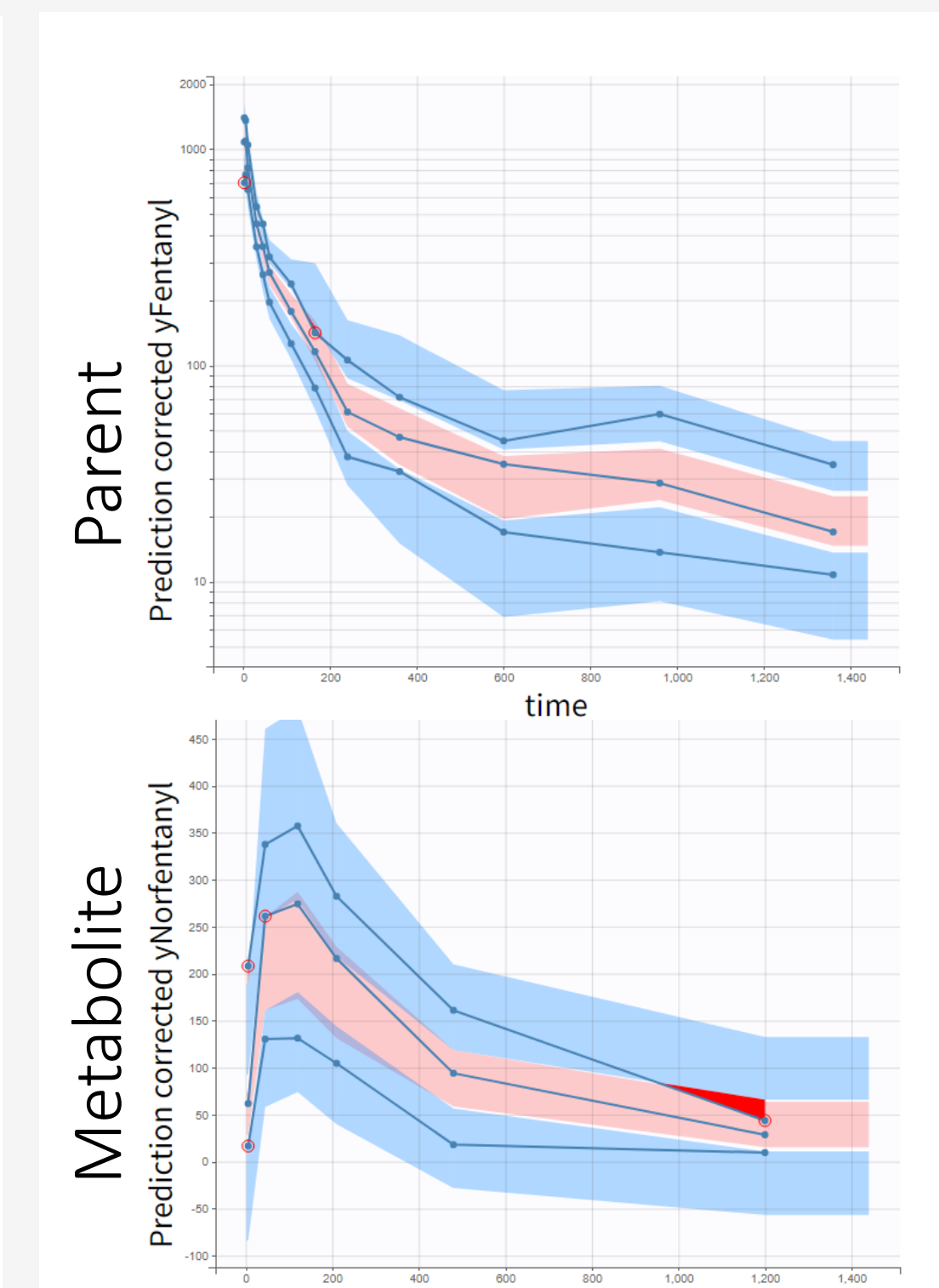
Save time and focus on the results with built-in DIAGNOSTIC PLOTS

COMPARE DOSING REGIMEN IN SIMULX

Quickly define populations and simulate them EFFICIENTLY in C++

1. How many ids stay in target after constant IV infusion (CI) vs. individual boluses (IB) of fentanyl, with or without loading dose?
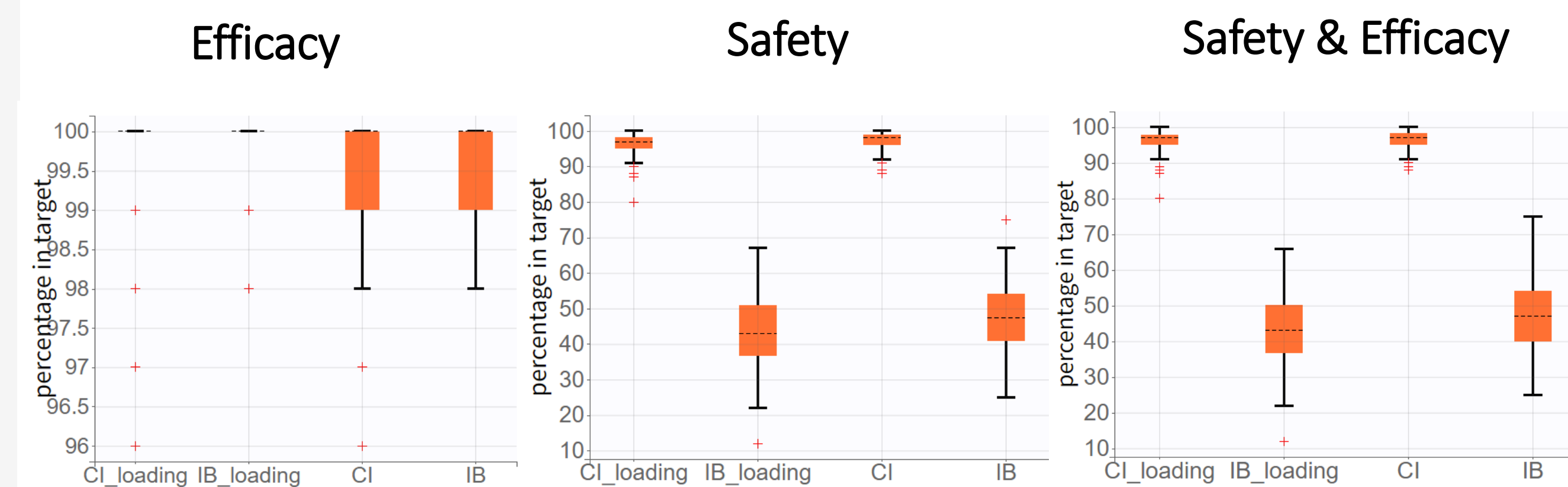
SIMULATION

Simulate 4 groups, 100 ids/group, 100 replicate studies
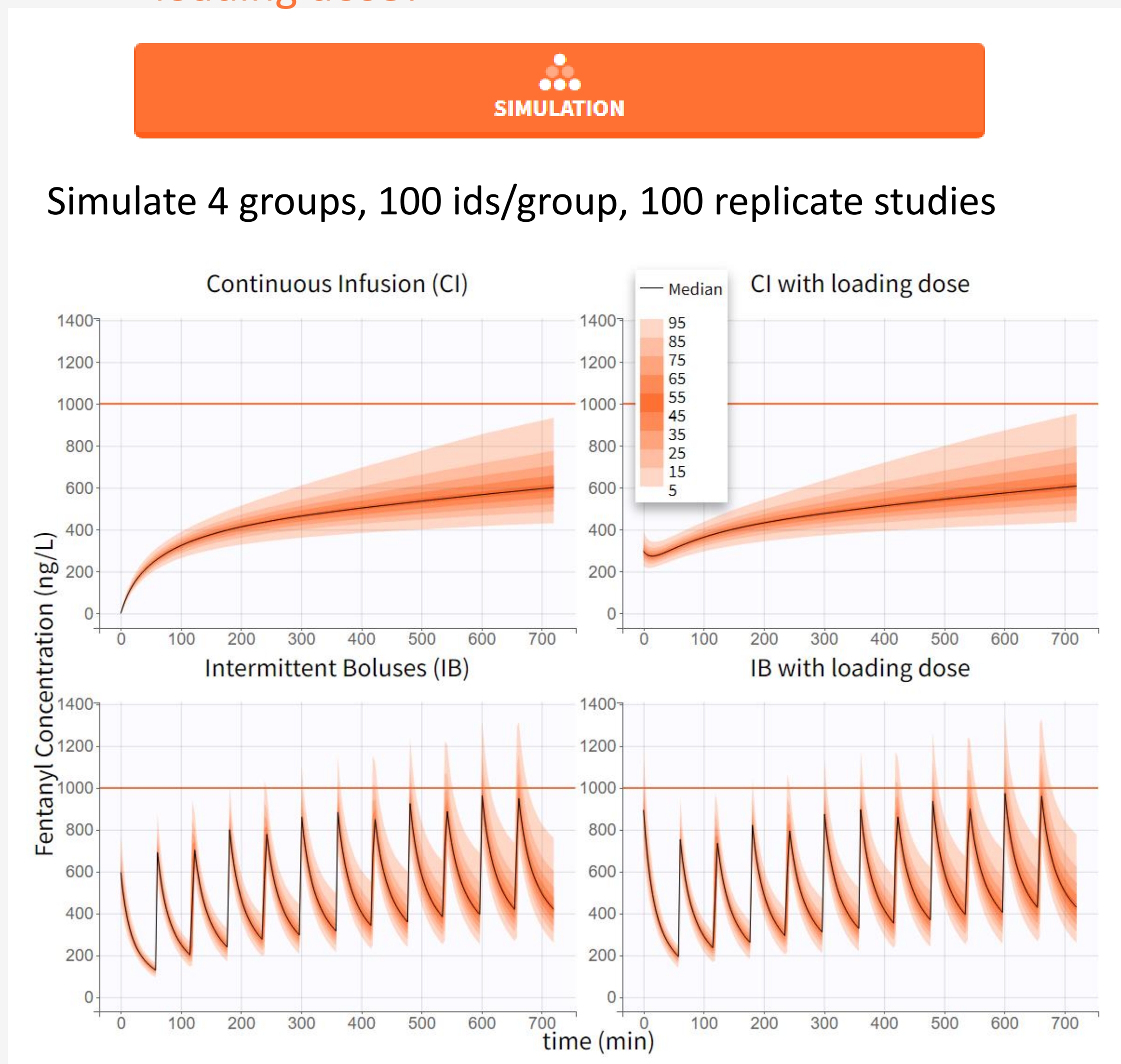
OUTCOMES & ENDPOINTS

For each replicate study:
- **For each id** in each group, compute outcomes: Cmax, AUC_12h
- **For each group**, compute endpoints:
  - % of ids with Cmax below safety target
  - % of ids with AUC above efficacy target
  - % of ids with both Cmax and AUC in target

Distribution of endpoint (%ids in target) over replicates for:

CI of 1.2mg improves safety of fentanyl compared to IB. The efficacy of fentanyl seems improved with a loading dose.

Post-process your simulations with built-in OUTCOMES & ENDPOINTS

2. In a scenario where fentanyl is given with a CI, does a loading dose improve therapeutic efficacy (characterized in terms of mean AUC at 12h)? What is the probability of technical success to reach higher systemic exposure of fentanyl with a loading dose?
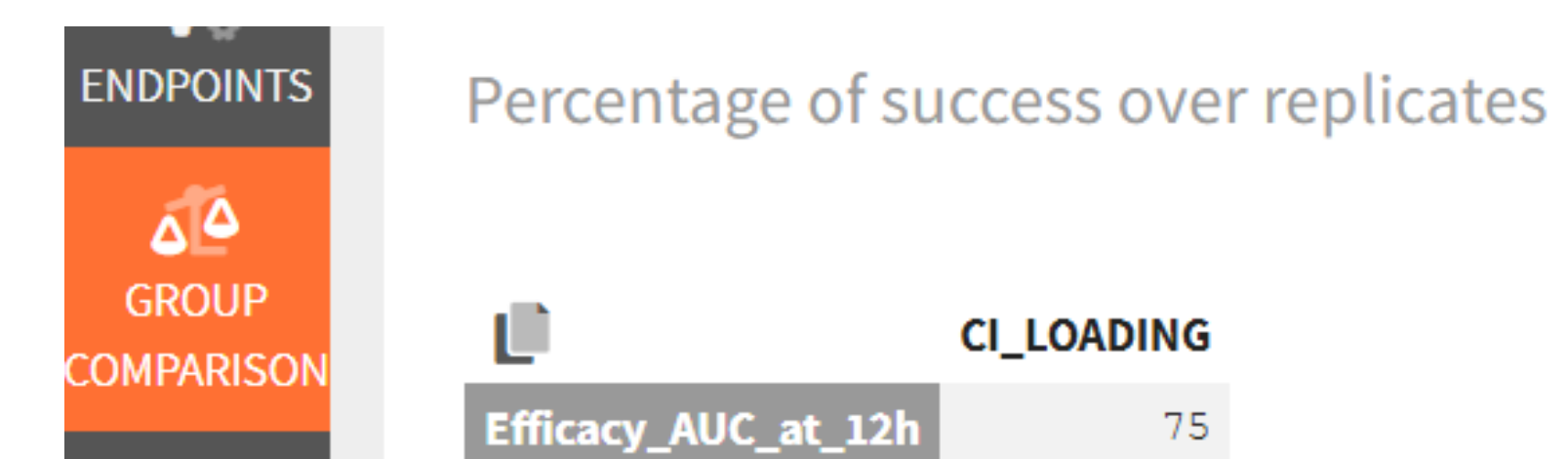
Distribution of mean(AUC) over replicates for infusion with/without loading dose
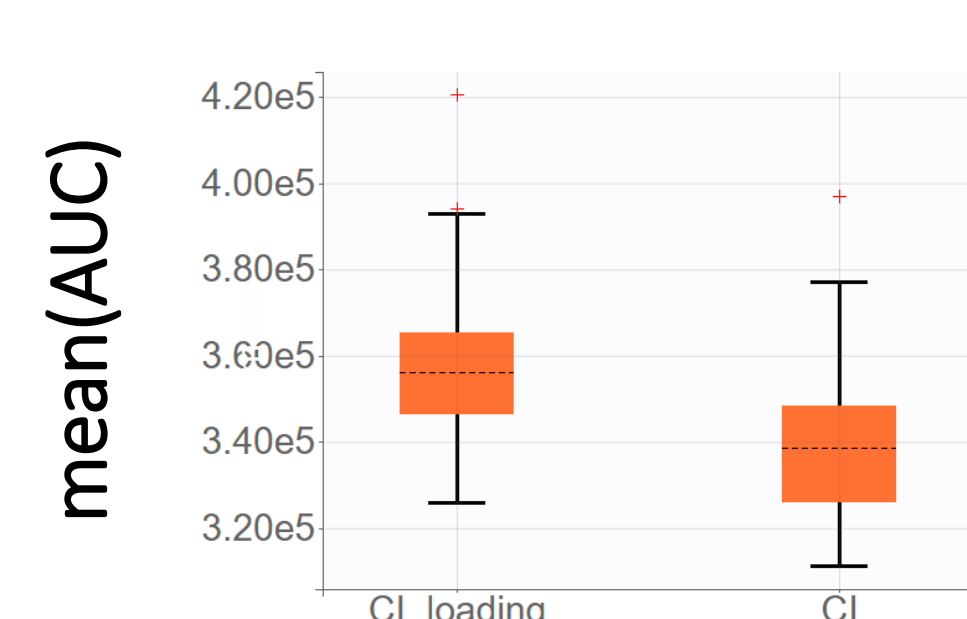
T-test to check if mean(AUC) is higher with a loading dose for each replicate study

REP	CI_LOADING		
	DIFFERENCE	P-VALUE	SUCCESS
1	28603.3	5.15e-4	✓
2	23075.9	5.15e-3	✓
3	-7028.38	7.15e-1	✗

Estimated success rate of reaching higher systemic exposure of fentanyl with a loading dose = 75%.

Percentage of success over replicates

	CI_LOADING
Efficacy_AUC_at_12h	75

STATISTICAL TESTS to check trial success in a few clicks

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These simulations assume that only the parent drug Fentanyl has an effect. The same investigation could be done for the metabolite or a combination of parent and metabolite. CI: total amount 1.2mg over 12h IB: 0.1 mg QH.
Safety target: Cmax < 1ug/L. Efficacy target: AUC_12h > 0.3ug/L*12h. Loading dose: 50ug.