Bayesian Adaptive Design for optimal irradiation dose in mice

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Objective 1

- Irradiation of animals is a technique commonly used to destroy, temporarily or permanently depending on the technical conditions, the immune system of mice (myeloablation) but there may be side effects.

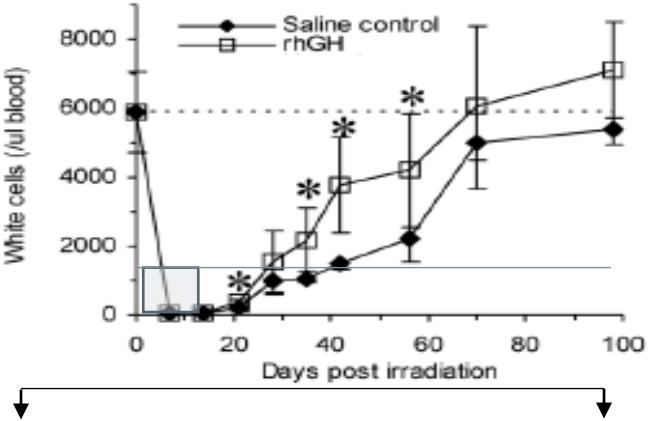
- The more the mouse strain is immunocompromised, the lower the level of irradiation will be.

- Purpose of this project: to develop the experimental conditions of irradiation for each strain in order to obtain a temporary reduction in the immune system of mice while preserving their good general condition

Objective 2

- Evaluate optimal irradiation dose for future experiments for each strain

Irradiation



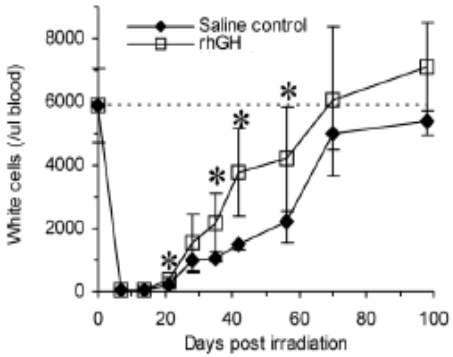
→Follow-up of general state
→ Blood Sampling

- **Binary criteria:**
  - **Safe:** yes/no
  - **Efficacy – Immune system Inhibition:** yes/no
    Decrease of at least 70% of leucocytes (white cells) of mice for 10 days

Ethics and constraints in animal studies: Xenograft development

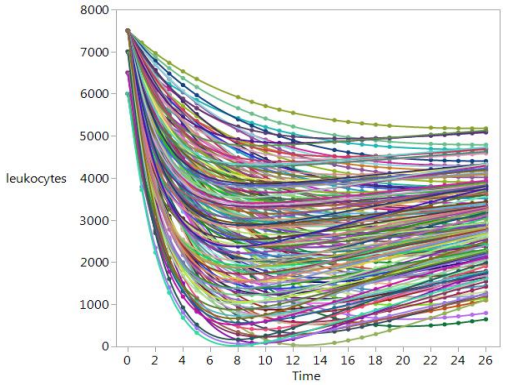
- In a irradiation immunosuppression development study, the objectives are:
  - Reduce the total number of mice
  - Reduce number of blood samples by mice to most informative ones
  - Avoid exposure to excessive dose of irradiation
  - Maximize probability that mice will stay healthy
  - Maximize probability of success for a xenograft

From literature data



Modeling

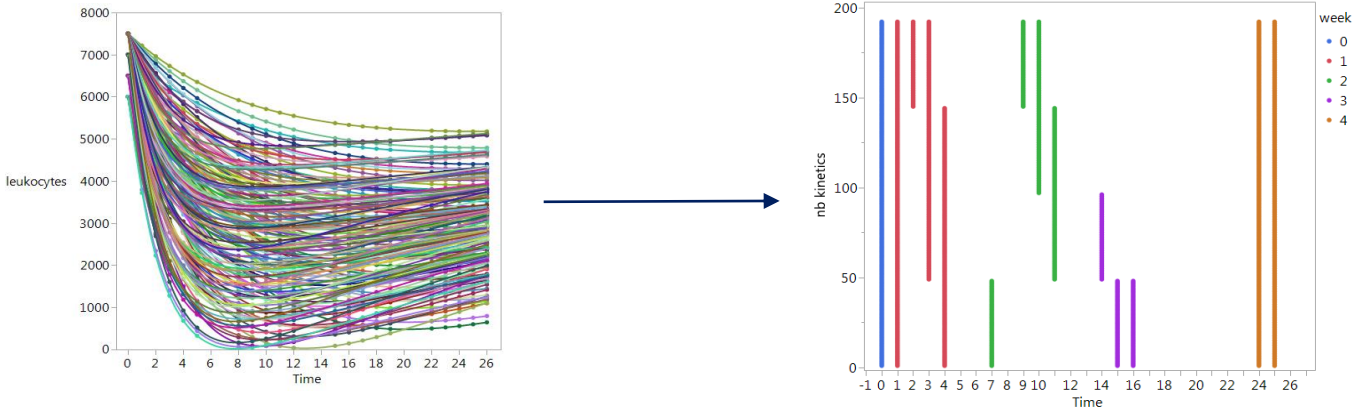
To all potential leucocyte kinetics



Reference: Chen et al, Growth hormone mitigates against lethal irradiation and enhances hematologic and immune recovery in mice and nonhuman primates, Plos One, 2015

1- “Bayesian” optimal design for sampling times

- Model and Priors on four parameters derived from literature
- Search of the most informative sampling times for “each“ scenario from prior
- 2 samples / week = 8 samples on total

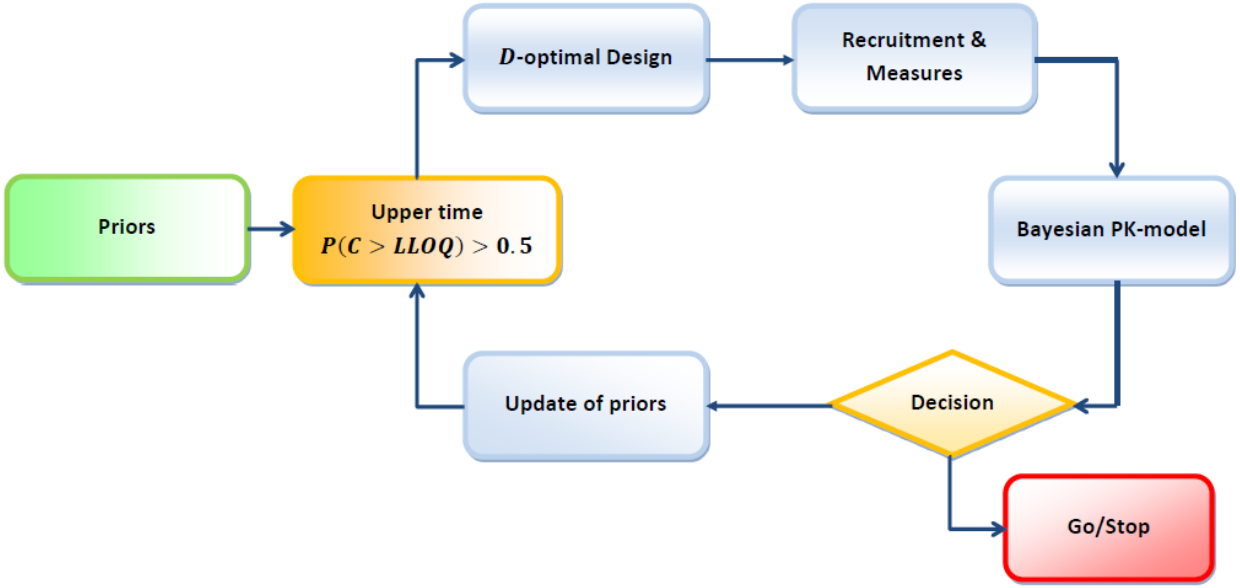


“PK” model

$$\text{number of leukocytes} = \theta_3 - \frac{\theta_4 * \theta_1 * \theta_3}{\theta_1 - \theta_2} \times \left(e^{-\theta_2 \times time} - e^{-\theta_1 \times time}\right)$$

Sampling times
week 0: baseline
week 1: Day 1 and Day 3/4
week 2: Day 7 and Day 10/11
week 3: Day 14/15/16
week 4: Day 24/25

2 - Bayesian Adaptive Sampling Times (BAST)



The PK model

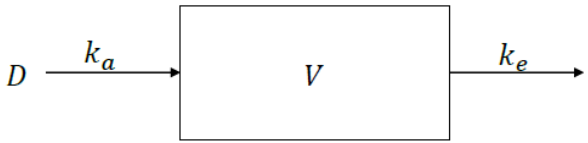
- Concentration for a one compartment model:

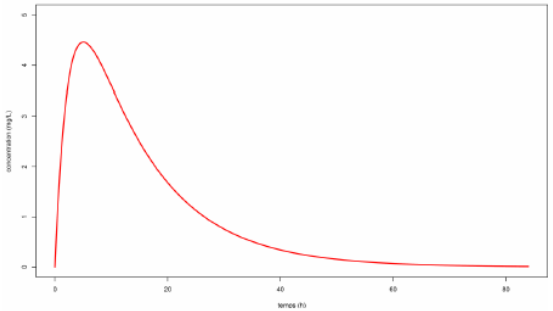
$$C(V, k_a, k_e, \xi) = \frac{D}{V} * \frac{k_a}{k_a - k_e} * \left(e^{-k_e * \xi} - e^{-k_a * \xi}\right)$$

with:

  - D, the oral dose,
  - ka and ke the absorption & elimination constant,
  - V the volume of the compartment.

- Parameterization with log(V), log(ka) and log(ke).





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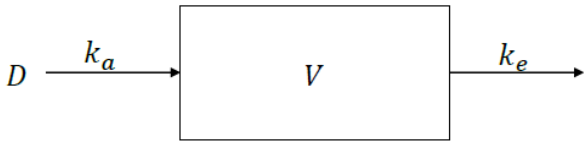
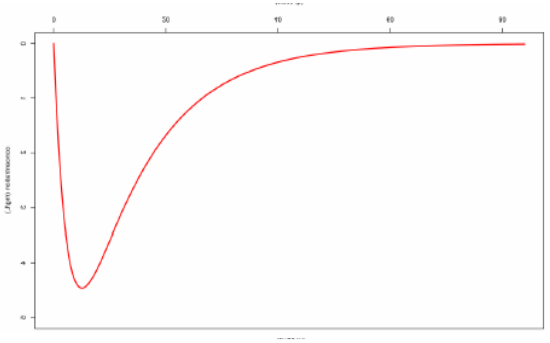
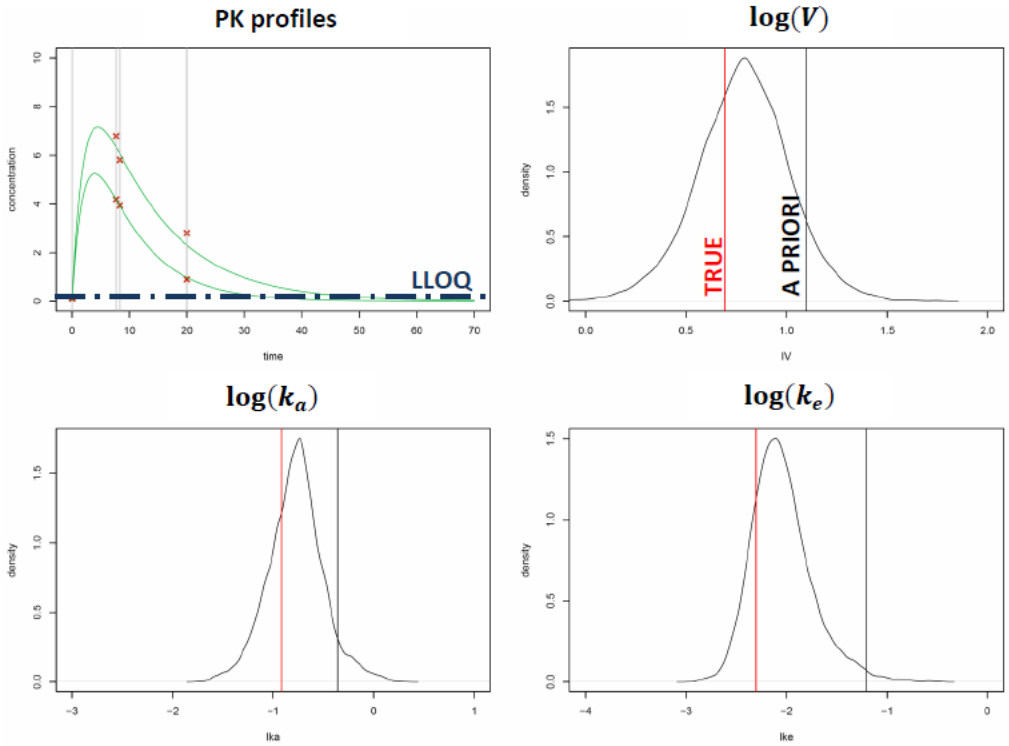
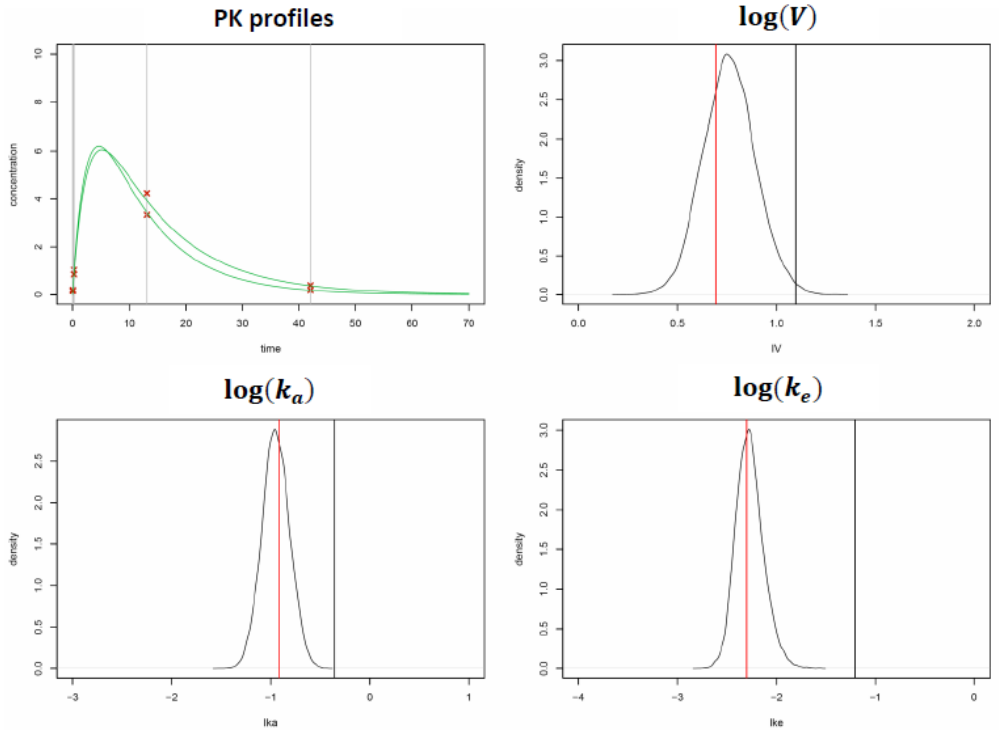




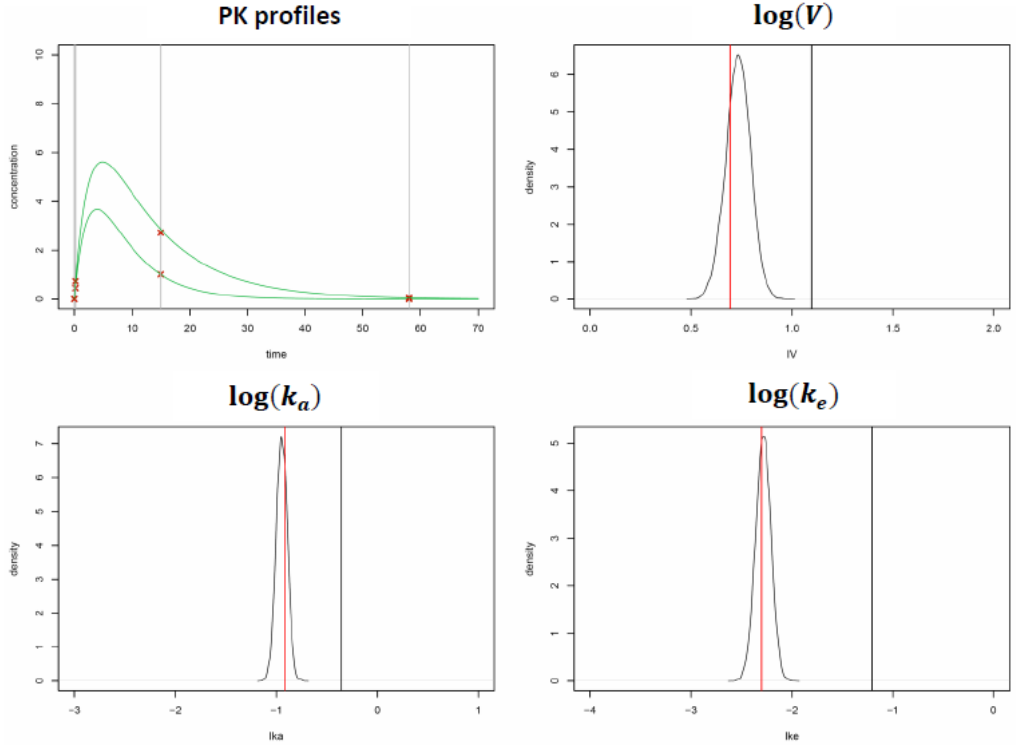
After the 1st cohort with BAST (Simulation)



After the 2nd cohort with BAST



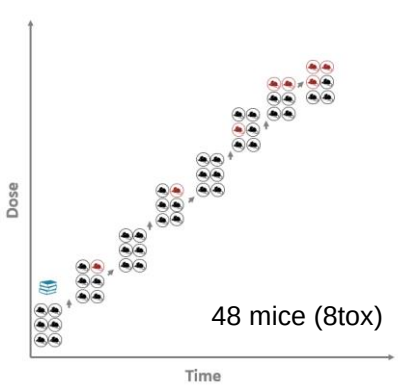
After the 6th cohort with BAST



Part 2: Dose escalation

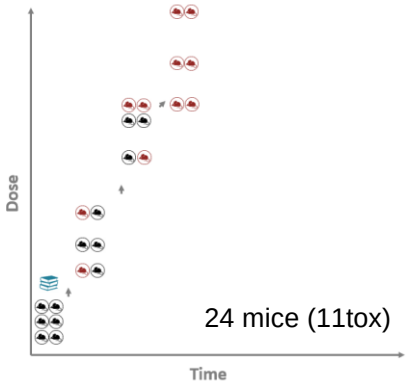
- Ethic constraints → progressive dose escalation with few mice per dose
- Calibration of dose escalation to control the number of death:

SLOW ESCALATION
Few safety issues but more cohorts



?

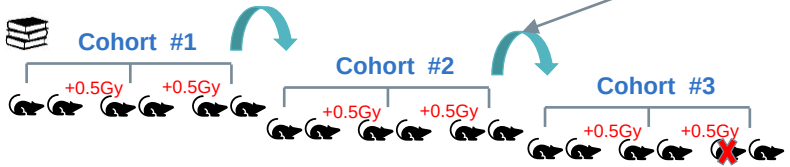
FAST ESCALATION
More safety issues but less cohorts



Adaptive dose escalation

- **Conservative approach**

How to make a decision :
- To go to the next cohort ?
- To decide doses to use ?



N=2 mice/dose

Statistical analyses

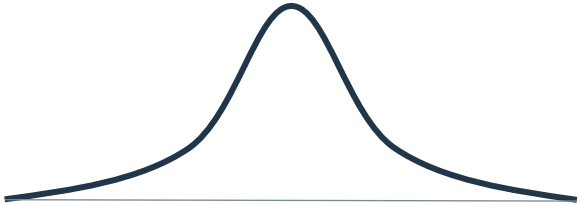
Choice of **Dose X** and confirmation

N=10 mice

→ toxicity
→ efficacy
→ inter-animal variability ➔ Joint Predictive probability of (Safety and Efficacy)

Bayesian inference is the mechanism used to update the state of knowledge

prior information
$p(\theta)$

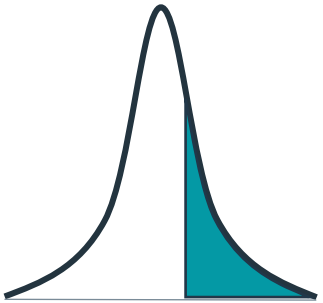


X

data information
$p(\text{data}|\theta)$

$\propto$

posterior information
$p(\theta|\text{data})$



The process to arrive at a posterior distribution makes use of Bayes' formula.

Prior elicitations for Safety and Leukocyte dynamic

For safety

- Using a Logistic model

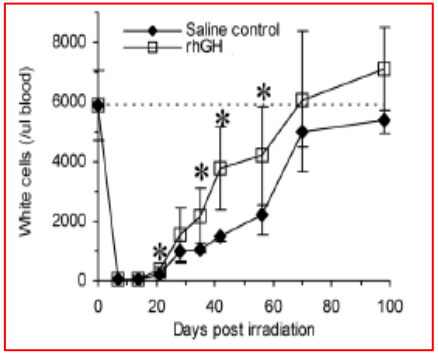
Table I. *Radiation sensitivity of NOD-scid IL2rγ^{null} mice*[a]

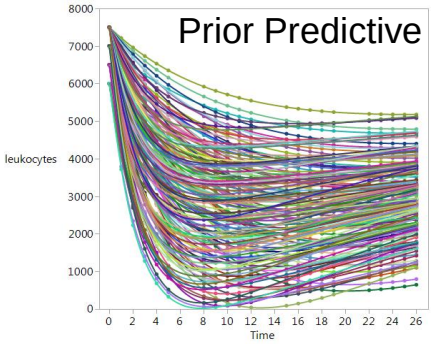
Genotype	Dose of X-irradiation (cGy)					
	200	250	300	350	400	450
scid	0	0	0	0	0	5
scid IL2rγ^{null}	0	0	0	0	5	5

[a] Data show numbers of mice that became moribund and were sacrificed within 8 wk postirradiation of five mice exposed to each radiation dose

- At dose 0 Gy, p(Tox) = 0.0005
- At dose 10 Gy, p(Tox) = 0.8
  - a = N(log(0.0005/ 0.9995), 1)
  - b = N(log(0.8/0.2) – log(0.0005/0.9995) / 10,1)
  - dose = seq(0, 20, 0.1)
  - mu = a + b*dose
  - P_Tox = 1/(1 + exp(-mu))

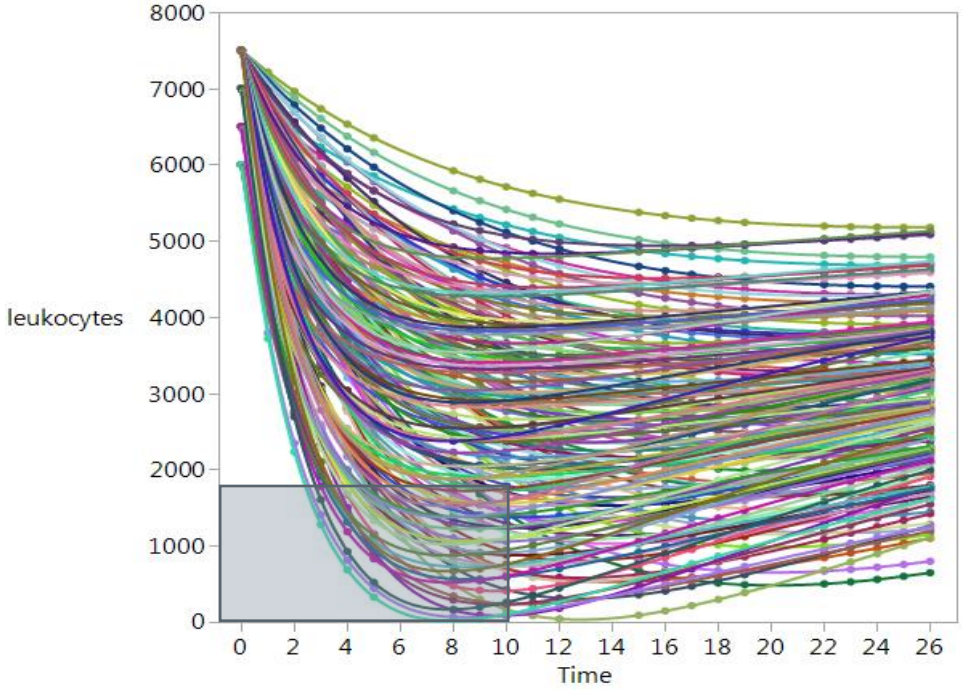
For “PD” profile





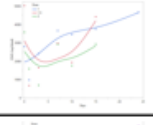
Definition of Efficacy

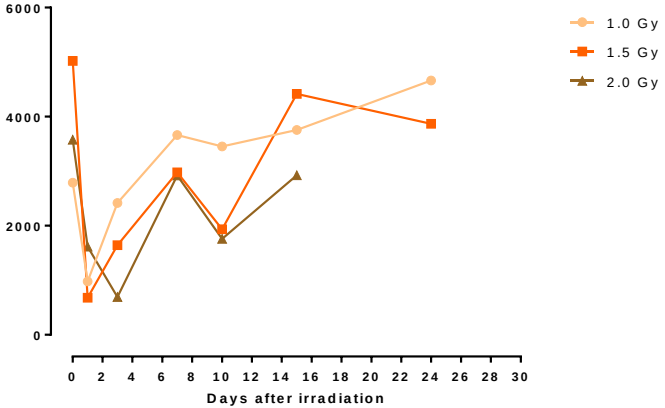
- 70% reduction leukocytes for 10 days



Choice of Optimal Dose

Dose (Gy)	Toxicity	Efficacy
1	0	0
1.5	0	0
2	1	0





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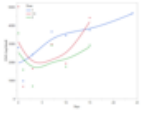
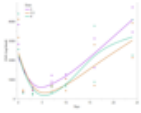
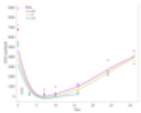
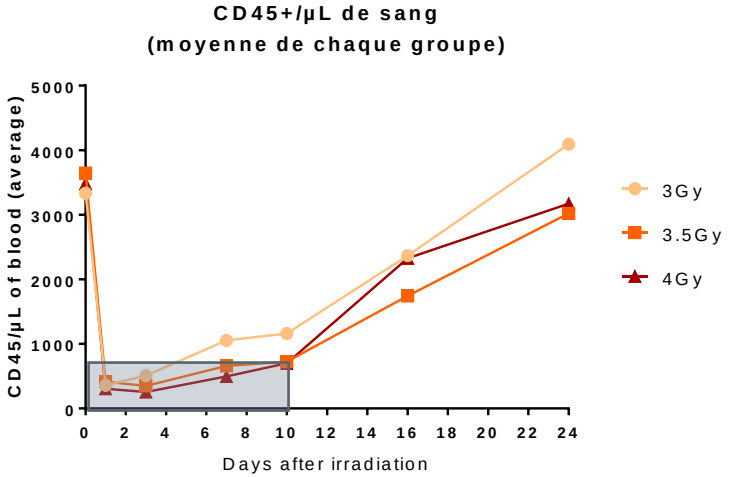
1	0	0	
1.5	0	0	
2	1	0	
3	0	0	
3.5	0	1	
4	0	2	
4.5	0	3	
5	**0**	**3**	
5.5	3	3	

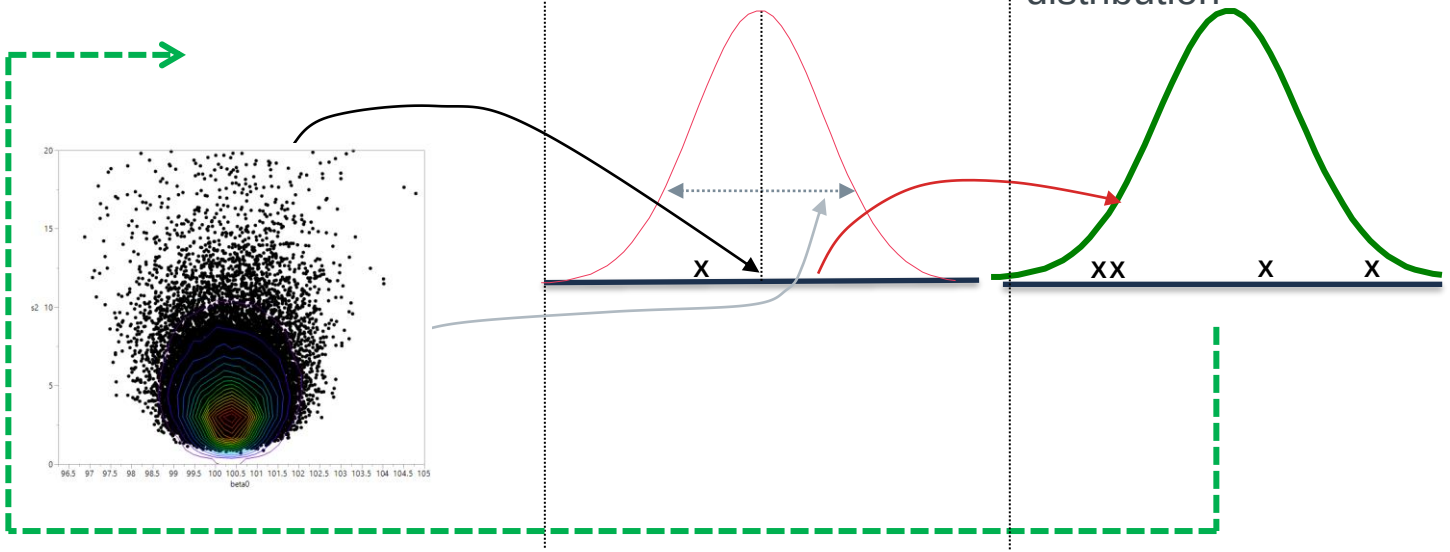


Practically, how to make predictions

1st , draw a mean μi and a variance $\sigma^2 i$ from joint distribution:

2nd , draw an observation from the resulting distribution Y~ Normal(μi, $\sigma^2 i$)

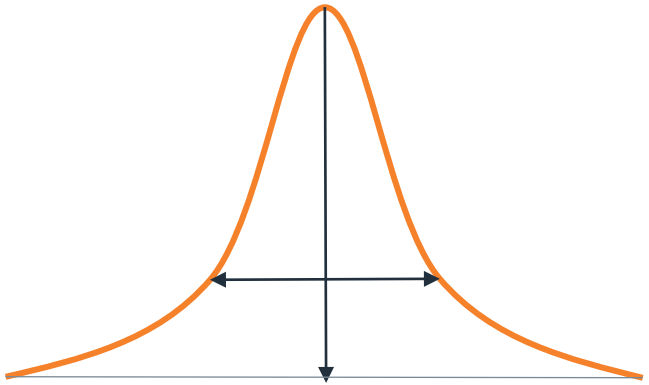
3rd , repeat this operation a large number of time to obtain the predictive distribution



Difference Simulations/Predictions

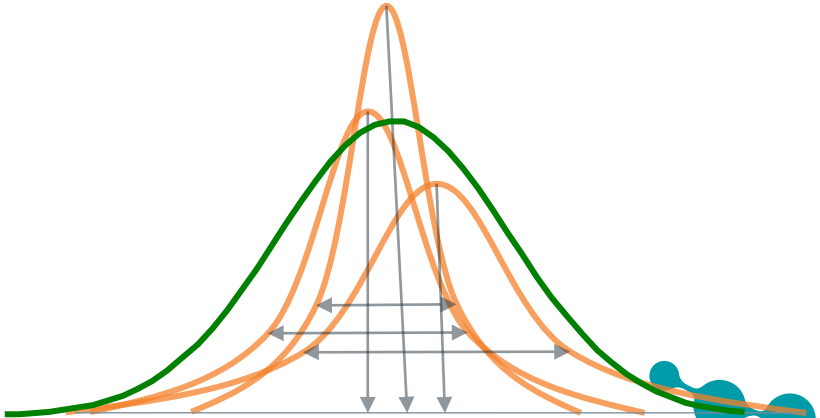
Simulations

the “new observations” are drawn from distribution “centered” on estimated location and dispersion parameters (treated as “true values”).



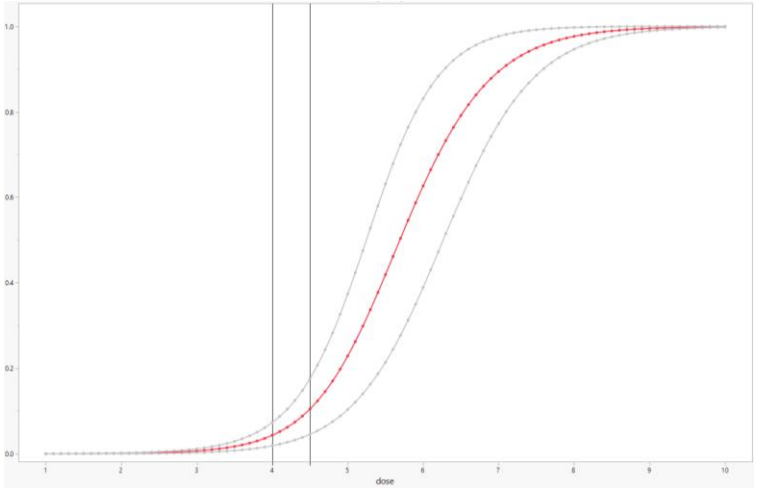
Predictions

the uncertainty of parameter estimates (location and dispersion) is taken into account before drawing “new observations” from relevant distribution



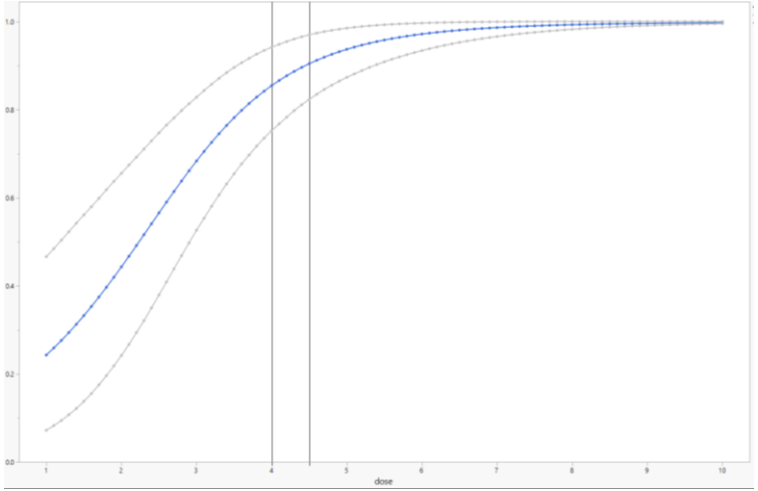
Predictive Probabilities Toxicity and Efficacy

Predictive Probability of Toxicity



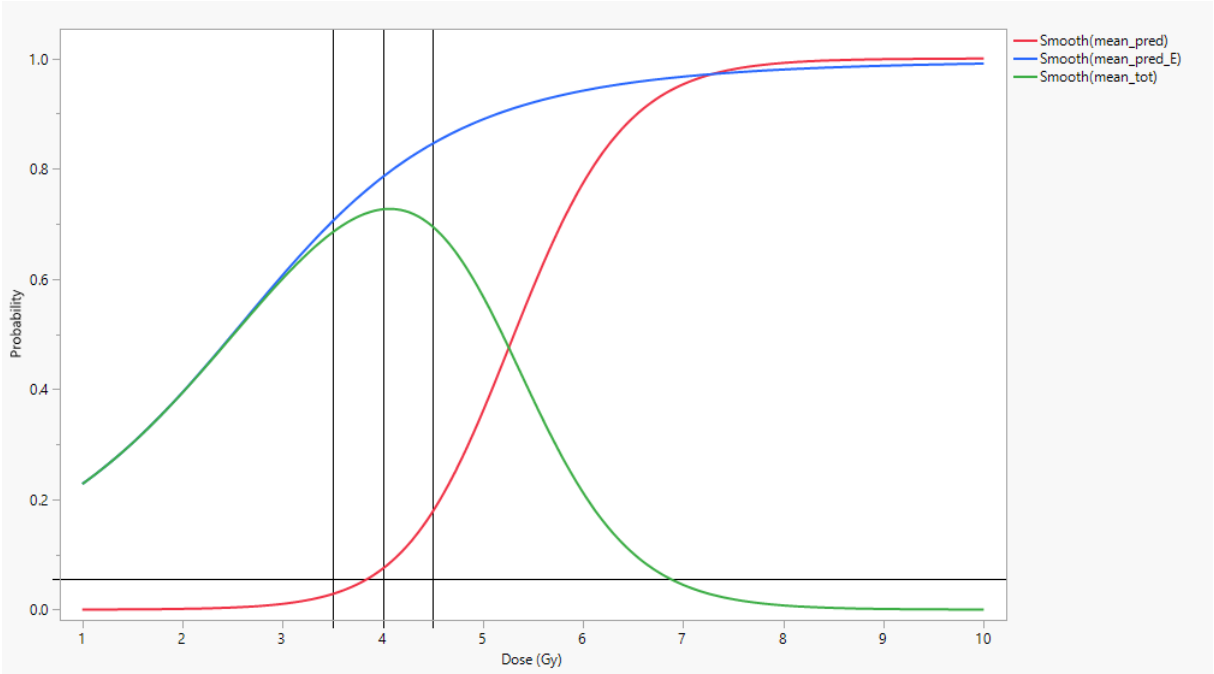
Dose (Gy)

Predictive Probability of Safety



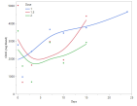
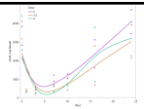
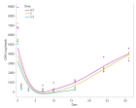
Dose (Gy)

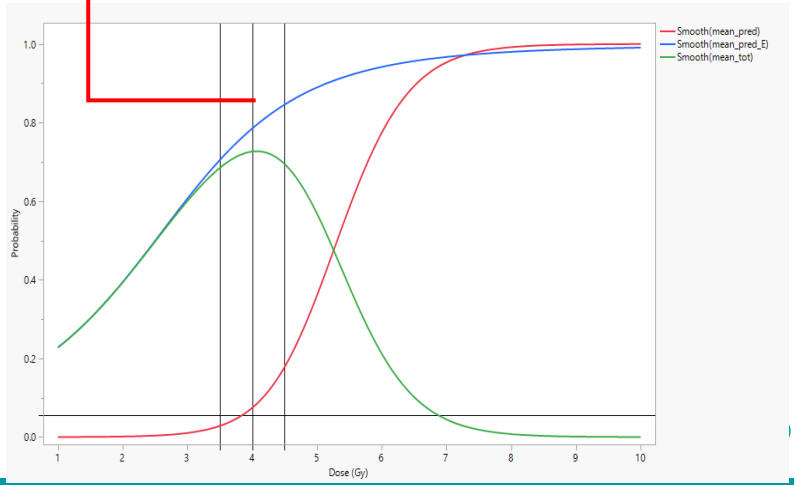
Joint Predictive Probabilities of (Toxicity and Efficacy)



Dose (Gy)

Choice of Optimal Dose

	Dose (Gy)	Nb with Toxicity	Nb with Efficacy	
N=2/dose	1	0	0	
	1.5	0	0	
	2	1	0	
N=2/dose	3	0	0	
	3.5	0	1	
	4	0	2	
N=3/dose	4.5	0	3	
	5	**0**	**3**	
	5.5	3	3	

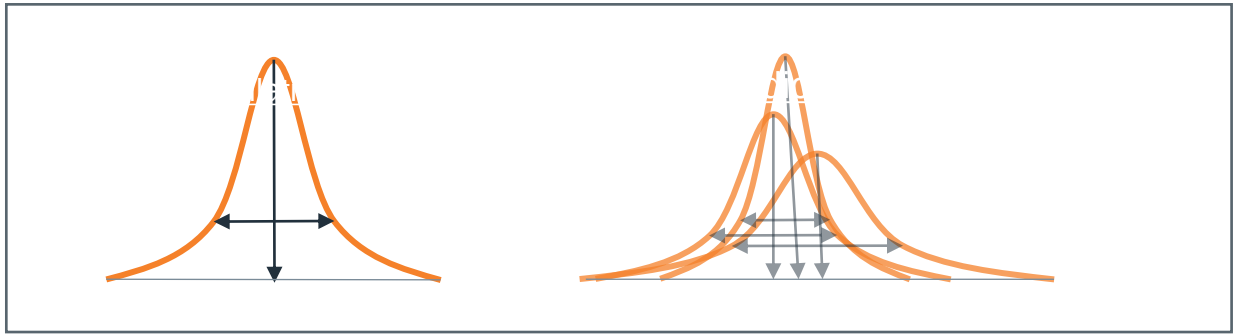


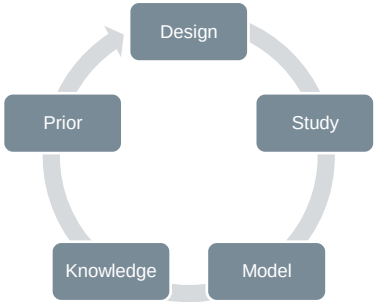
Last cohort on most promising doses to confirm

Dose (Gy)	Toxicity	Efficacy*
1	0/2	0/2
1.5	0/2	0/2
2	1/2	0/2
3	0/2	0/2
3.5	0/2	1/2
4	**0/5**	**5/5**
4.5	**0/6**	**6/6**
5	**0/6**	**6/6**
5.5	3/3	3/3

Added value of Bayesian Statistics

- Use the posterior distribution to compute probability for decision making
- Simulations VS predictions: Predictions take into account the uncertainty of the model parameters.





- Prior knowledge is also used to make the study design more effective and informative ➔ Compute Probability of Success.
- Using Prior Predictive Distribution

Conclusions

- What's the question ?
- In discovery the prior probability of success is low
- Broad use of Bayesian statistics in discovery and preclinical research will help to tackle the replicability crisis
- ….combined with better design of experiments as well
- Consider Bayesian (optimal) designs
  - Ethics (#animals, #samples, ….)
  - Lower risk wrong decisions
  - Adaptive designs
- Assurance instead of Power

Contacts

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