PharmacoMetrica

PK/PD modeling

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Definitions

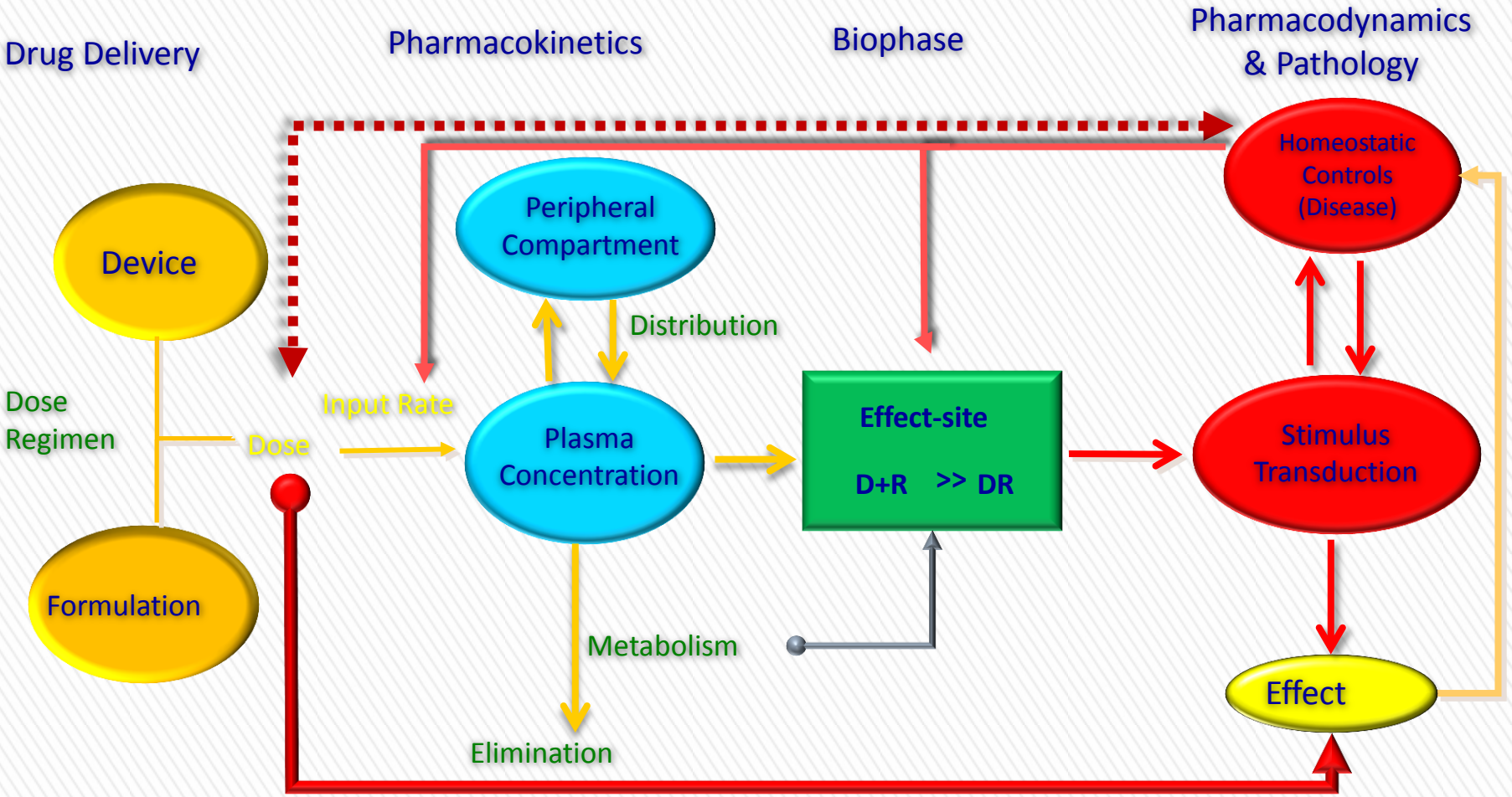
- **Pharmacokinetics** (PK) describes the time course of drug concentrations resulting from a particular dosing regimen
- **Pharmacodynamics** (PD) expresses the relationship between drug concentrations and the resulting pharmacological effects in term of safety and efficacy

Population PK/PD Model

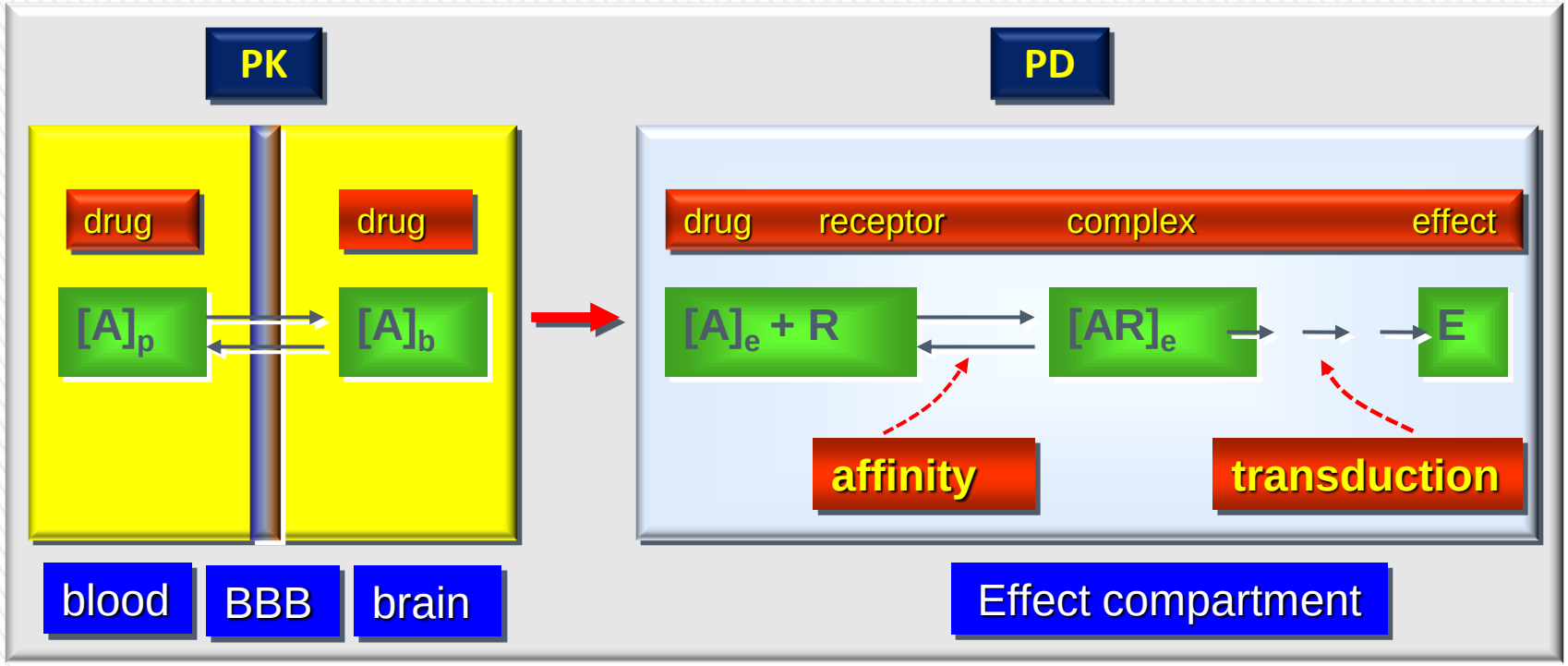
A Population PK/PD Model is an integrated model including:

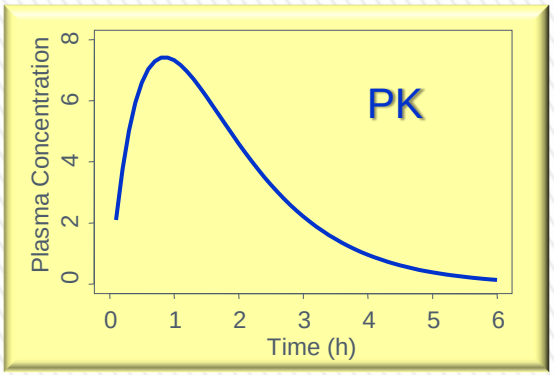
- A model describing the time course of drug concentrations vs. time (PK)
- A model describing the relationship of effect vs. concentration (PD)
- A model linking the PK measurements to the PD observations
- A statistical model describing variability on individual response (inter and intra subjects) and on measurements

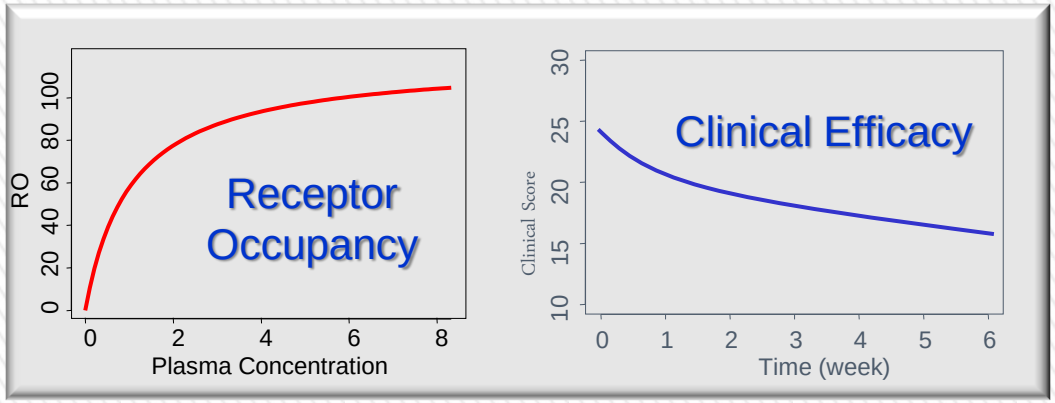
Understanding Drug Response & Variability



From empirical to mechanistic models

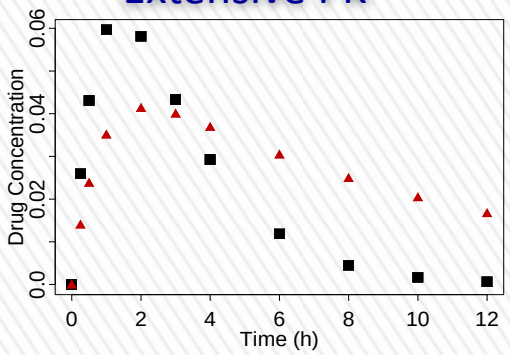




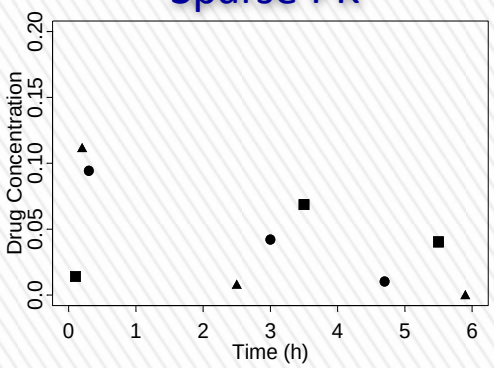


Dose Selection: Modeling Exposure-Response

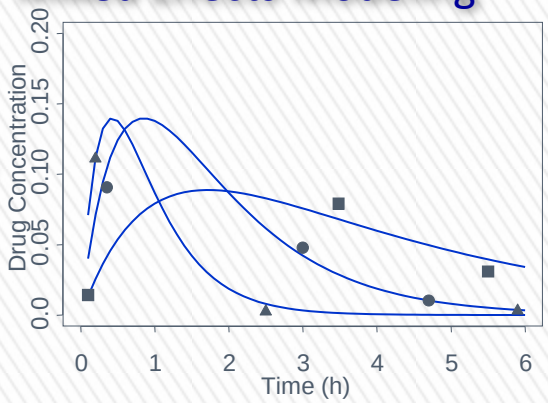
Extensive PK



Sparse PK



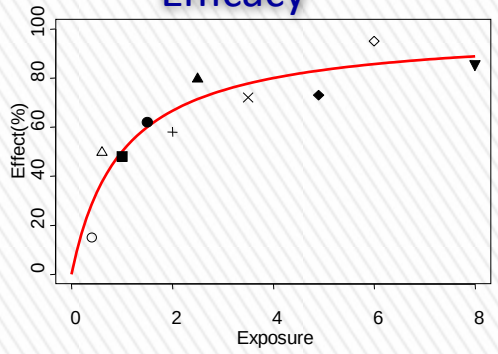
Mixed Effects Modeling



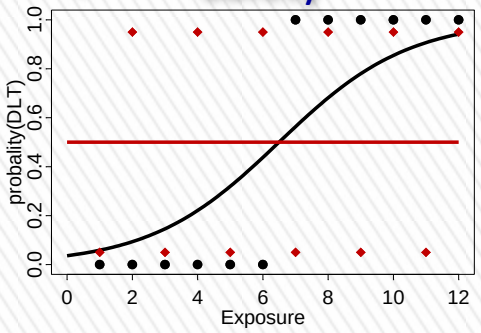
Exposure

Exposure

Efficacy

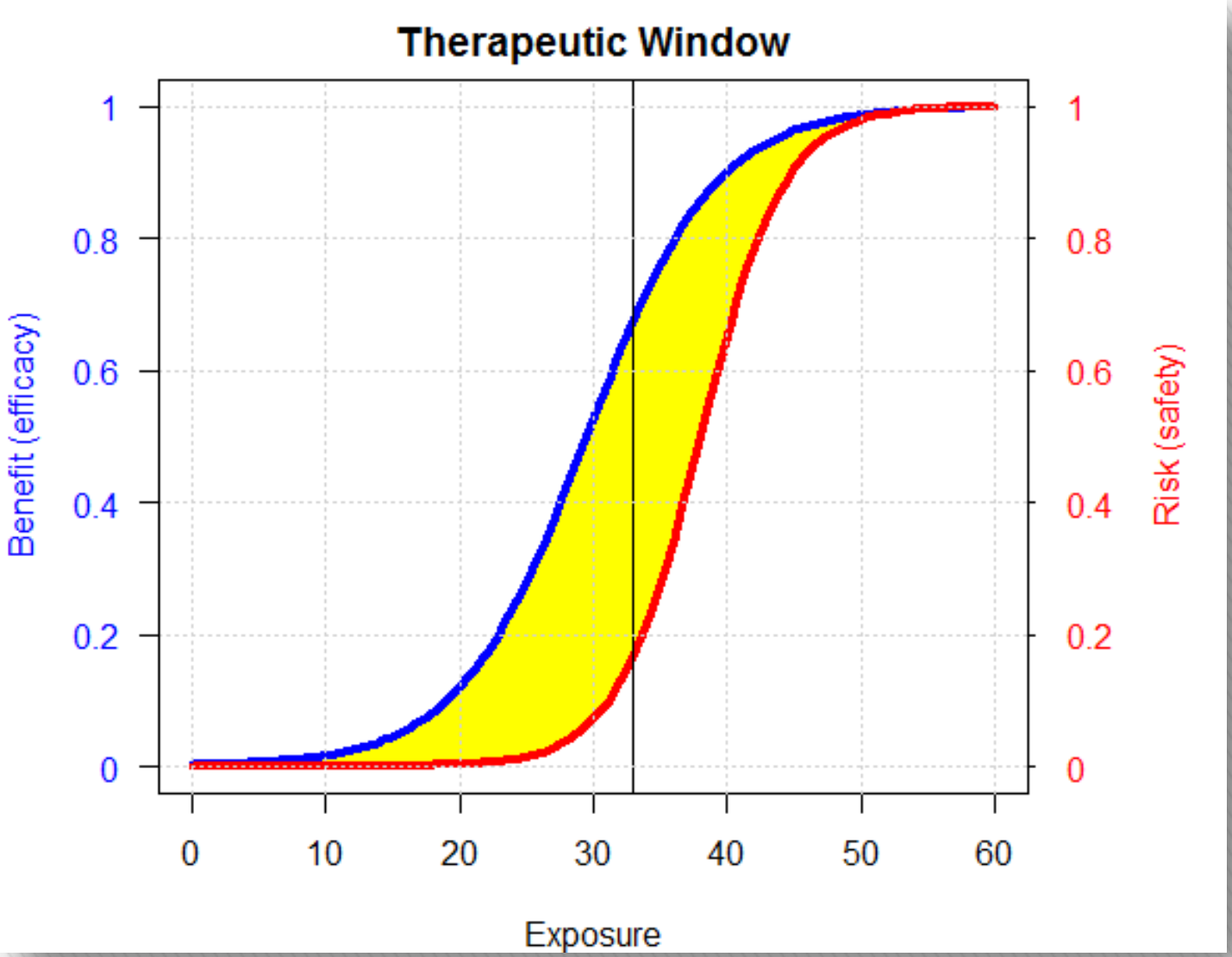


Safety

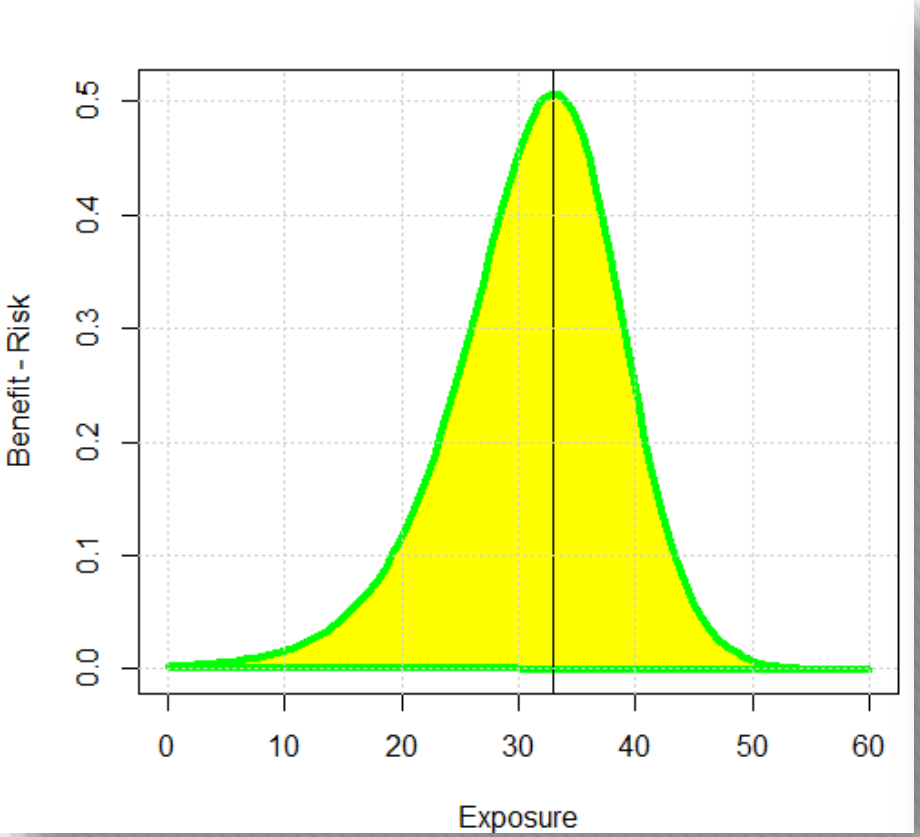


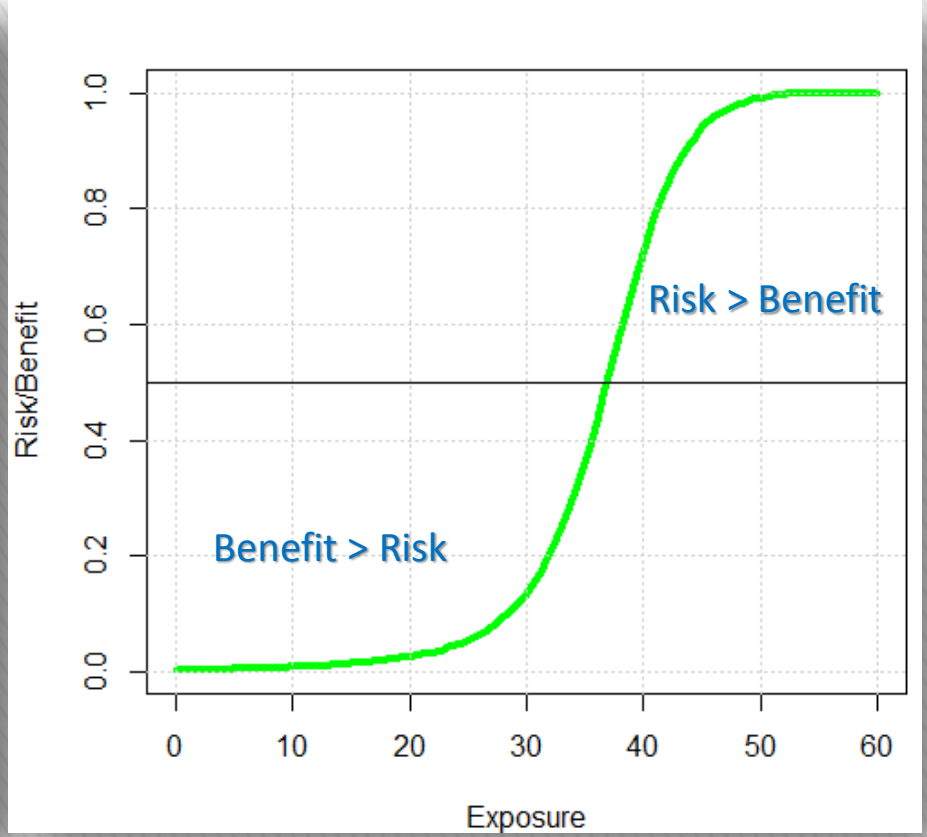
Rational dose selection

Defining a Therapeutic Window

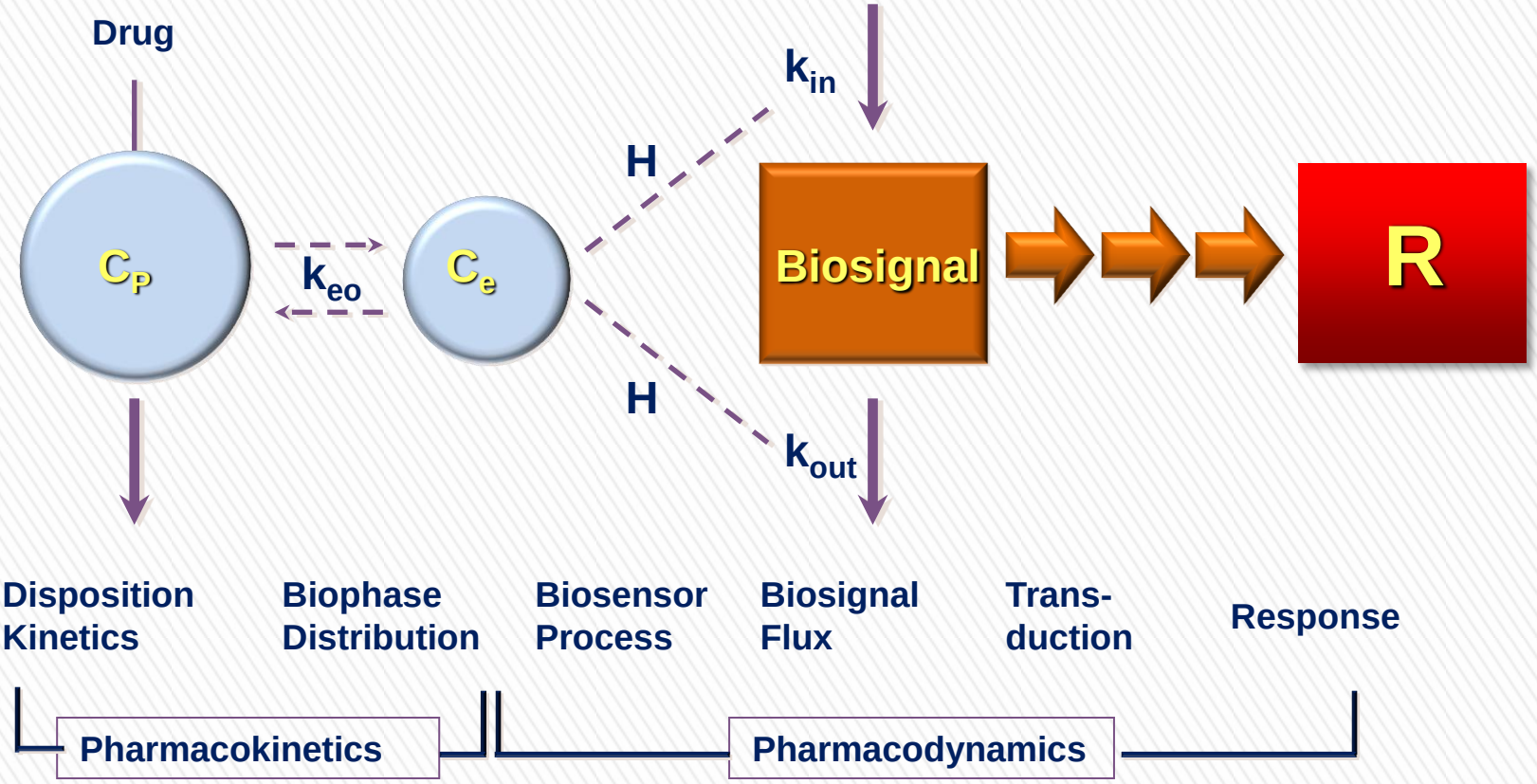


Defining Risk Benefit



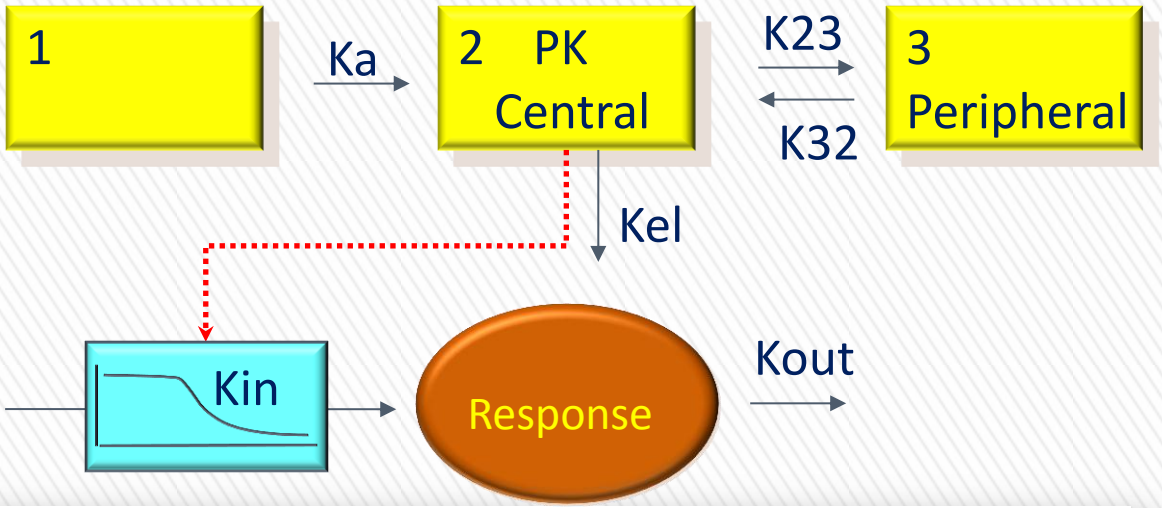


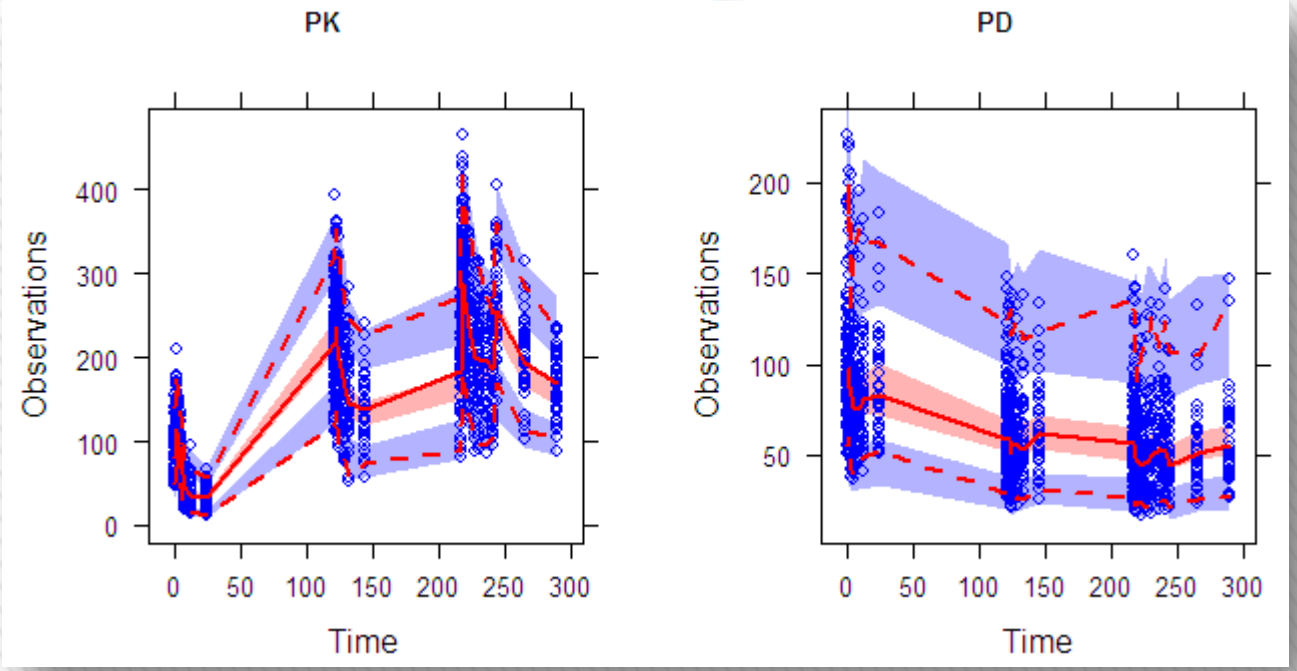
Continuous models: Triggers of the pharmacological response



Jusko et. al., JPB 1995

Indirect response PK/PD model





Basic Models of Indirect Response

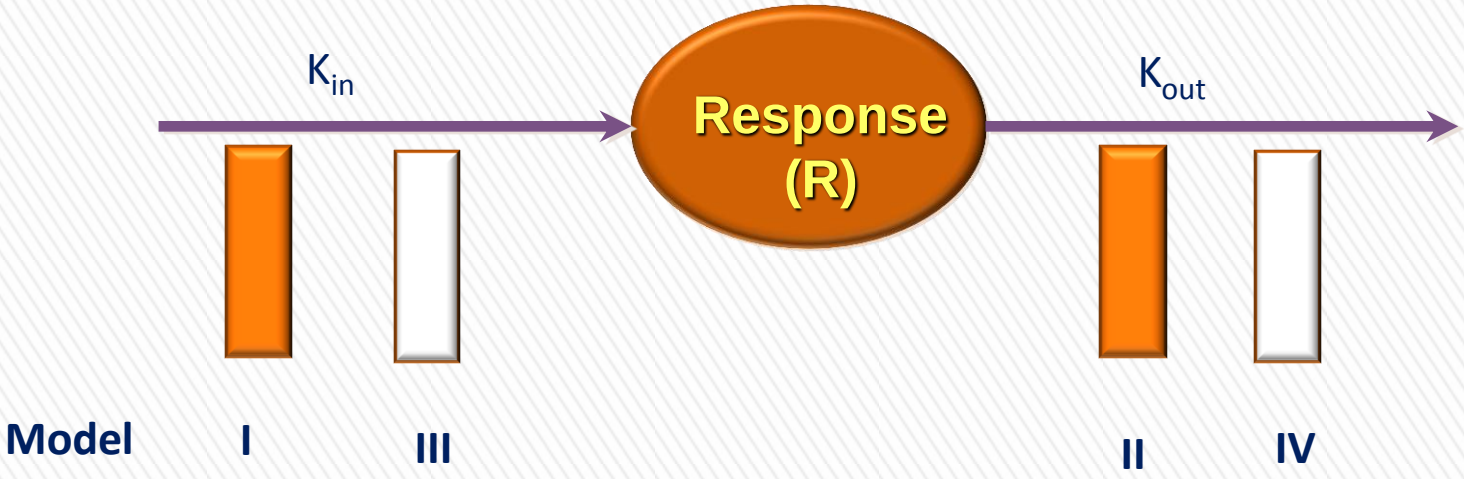
In the simplest scheme, the rate of change of the response when no drug is present is described by

$$\frac{dR}{dt} = k_{in} - k_{out}R$$

where k_{in} represents the zero-order rate constant for production of response, R, and k_{out} is the first-order rate constant for the loss of response variable. The response variable R may be a directly measured entity or an observed response, which is immediately proportional to the concentration of R

As the system is assumed to be stationary for these models, the response variable (R) begins at a predetermined baseline value ($R0$), changes with time following drug administration, and eventually returns back to $R0$. Thus, $k_{in} = k_{out}R0$

Schematic of the four basic models of indirect response



The solid bars represent inhibition and the open bars represent stimulation of the input and output functions

The inhibitory function, $I(t)$, and the stimulatory function, $S(t)$, can be described as

$$I(t) = 1 - \frac{C}{C + IC_{50}} \qquad S(t) = 1 + \frac{E_{max} C}{C + EC_{50}}$$

Categorical Data

- Data from clinical trial may be available as discrete or categorical data
  - cure or symptom relief – yes/no
  - adverse event – yes/no
  - Pain relief or adverse event - normal, mild , moderate, severe
- With only two categories, the outcome is called binary outcome
- With multiple categories, the data may be
  - nominal (no order) data – e.g. race, sleep stage
  - ordinal (ordered categorical data) – mild moderate, severe

Binary or Ordered Categorical Data

- There may be only one observation per subject e.g. cure/no cure *or* multiple observations e.g. Nausea/Rash
- The underlying theory for modeling such data is same
- One observation per individual – most severe observation – link summary/average PK parameter eg. C_{avg} or AUC (0-t)
- Loss of information – specifically information over time
- Easier or simpler model
- Logistic regression or proportional odds model

Binary Data

- Aim is to develop the model where the P(y) can be explained by some covariate or predictor variable (x_i)
- This refers to the conditional mean of Y given the independent variable (x) E(Y|x)
- For linear regression we have something like

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots$$

- With binary data (0/1) we need to ***transform*** the data to allow for the estimation of the probability (with values ranging from 0 to 1)

Modeling the Probability of AE (Somlolence)

A logistic model was used to describe the probability (p) of observing a somnolence event as function of the maximal individual plasma concentration (Cmax)

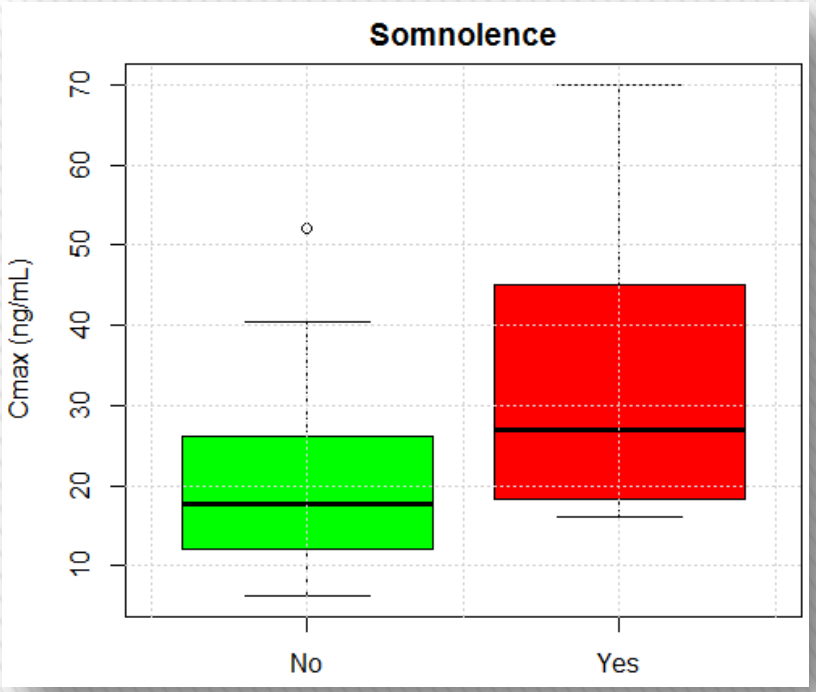
The probability p was estimated by :

$$\lambda = \text{intercept} + \text{slope} \cdot C_{max}$$

$$p = \frac{e^{\lambda}}{1+e^{\lambda}}$$

Where: λ is the logit function, 'intercept' is the intercept of the logistic function and 'slope' is the coefficient of the predictor variable

Exposure/AE model




```
Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -2.58538    0.79402  -3.256  0.00113 **
cmax         0.06542    0.02657   2.462  0.01381 *
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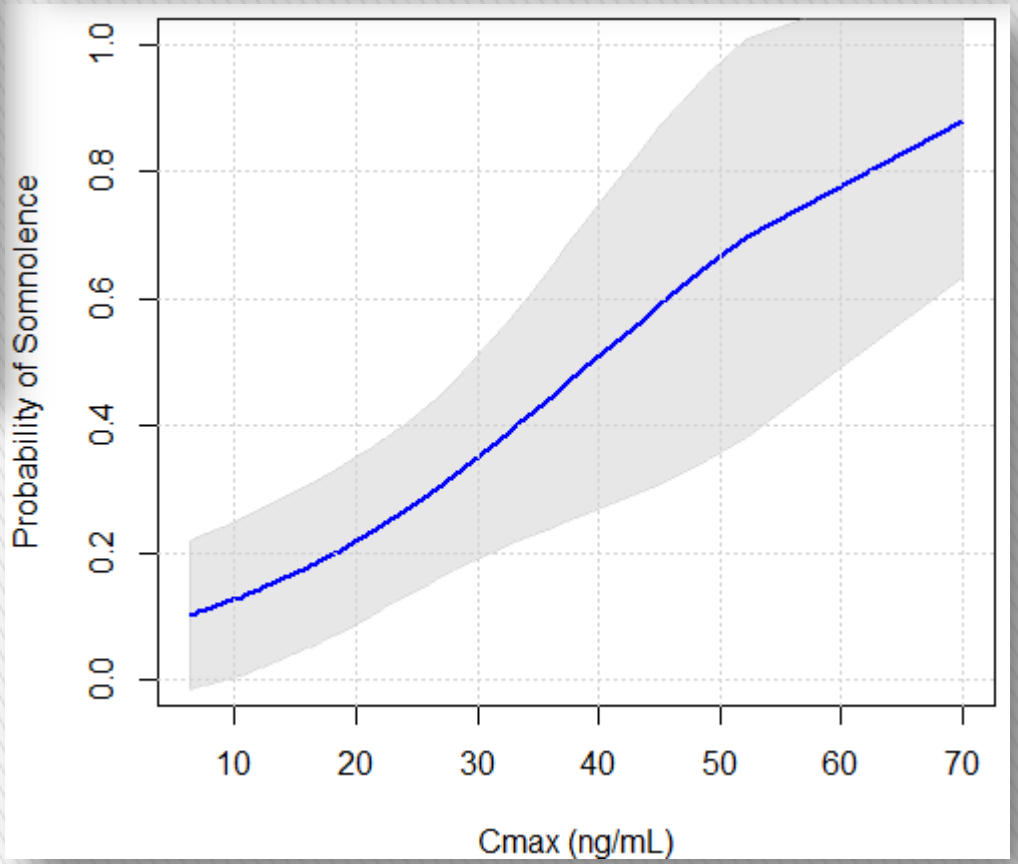
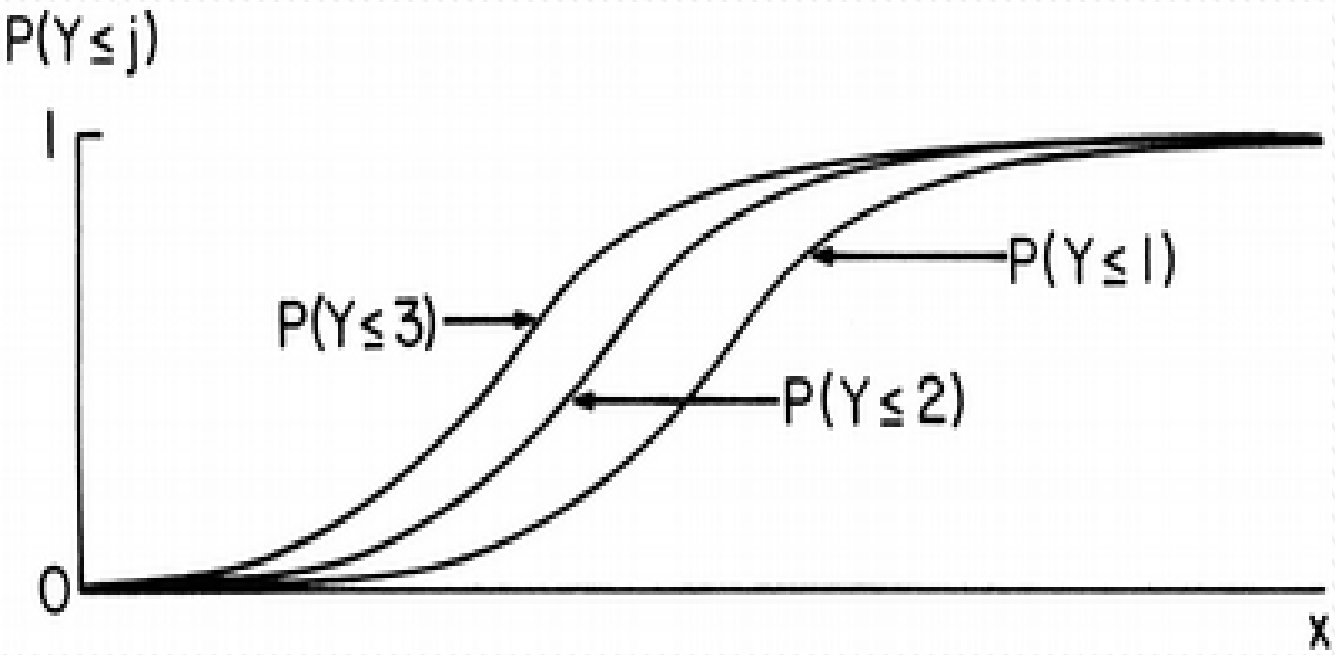


Ordered Categorical data

- This is extension of the binary data model
- Multiple logits are defined
- Cumulative probability is estimated



What is time-to-event (TTE) analysis?

- Often called survival analysis
- Events may include a PD effect (vomiting, experiencing pain, et…), death, injury, onset of illness, recovery from illness, DROPOUT, …
- Goal is to:
  - > Estimate TTE for a group or groups of individuals
  - > To assess the relationship of covariates to TTE
  - > To be able to predict TTE

Concentration-to-event

- Terms:
  - > Concentration-to-event: The drug concentration from entry into a study until an event occurs
  - > (Right) Censoring: Occurs if study ends before a subject has an event
    - + We know that the subject did not experienced the event at least at the maximal Cp measured
- Data Structure:
  - > Cp_i = Maximal concentration observed or concentration at event
  - > *Censoring data value:*

    c_i =1 if Cp_i is associated with an event;

    c_i =0 if Cp_i indicates the maximal concentration observed (no event)

Concentration-to-event analysis

Concentration-to-event analysis is a collection of statistical procedures for data analysis for which the outcome variable is

the drug concentration at which an event occurs

The concentrations (Cp) at which an event occurs is considered as

a random variable having a probability distribution

The distribution of Cp is characterised by the:

- **Probability Density Function** f(Cp)
- **Cumulative Probability Density Function** F(Cp)=Prob(CP<=Cp)
- **Concentration-to-event function** S(Cp) = Prob(CP>Cp) =1-F(Cp): the probability that the event occurs at a concentration lower than c
- **Hazard function** h(Cp)=(dF(Cp)/dCp)/S(Cp) : the probability that an individual who has not yet experienced the event, will have it at the concentration c

With the Hazard we can compute the rest …

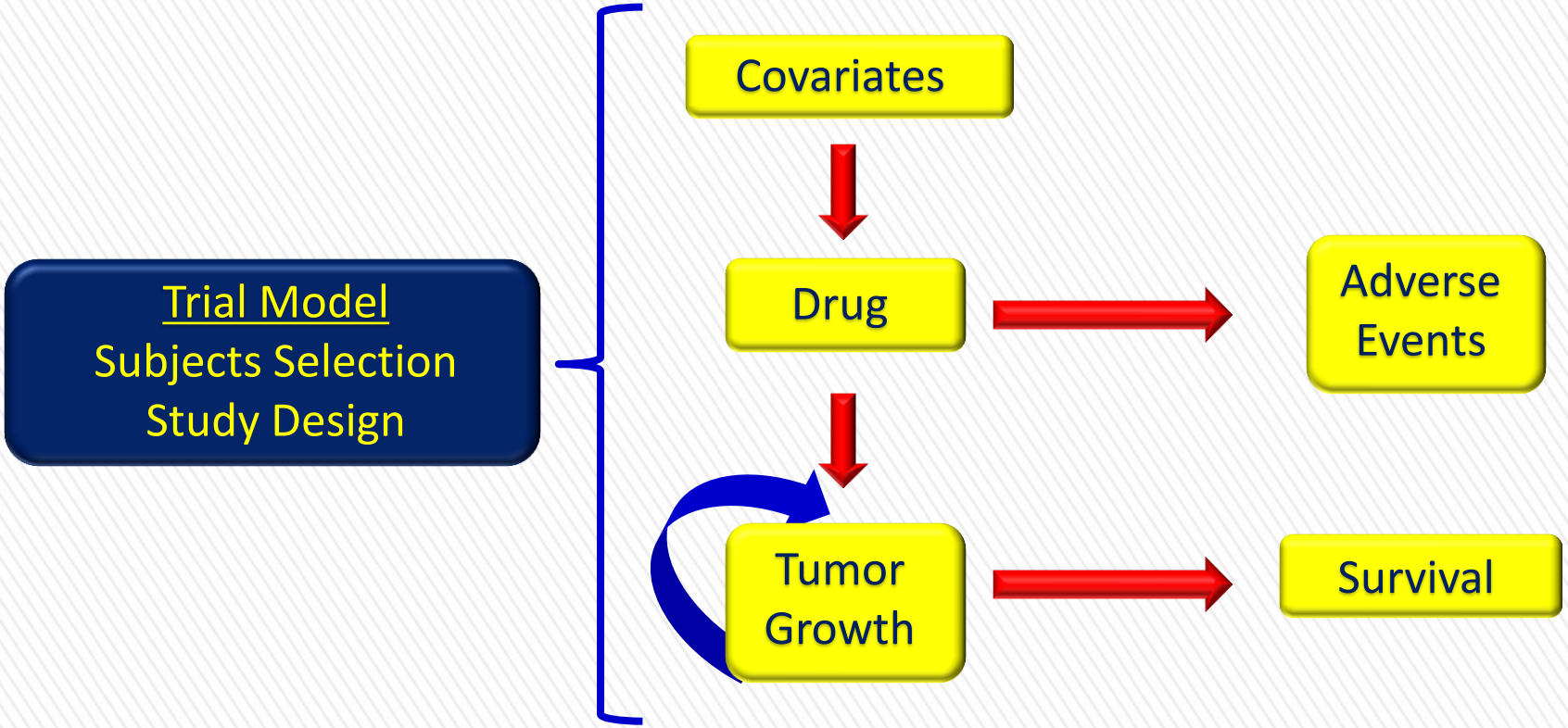
The Hazard is a function of Cp defining the instantaneous rate of an event:

$$h(Cp) = \lambda(Cp)$$

S() is the probability of not having an event within that concentration interval (a-b) (survival):

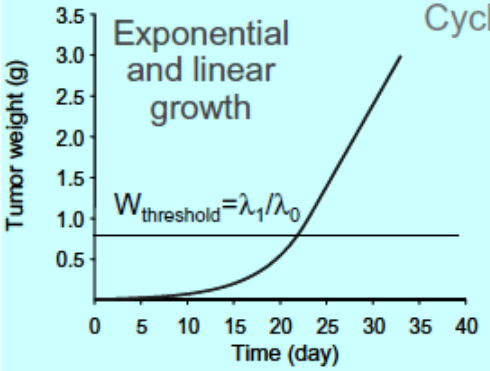
$$S(Cp) = e^{-\int_a^b h(Cp)}$$

Drug-Disease-Trial Model



Integrated model

Tumour growth in control animals



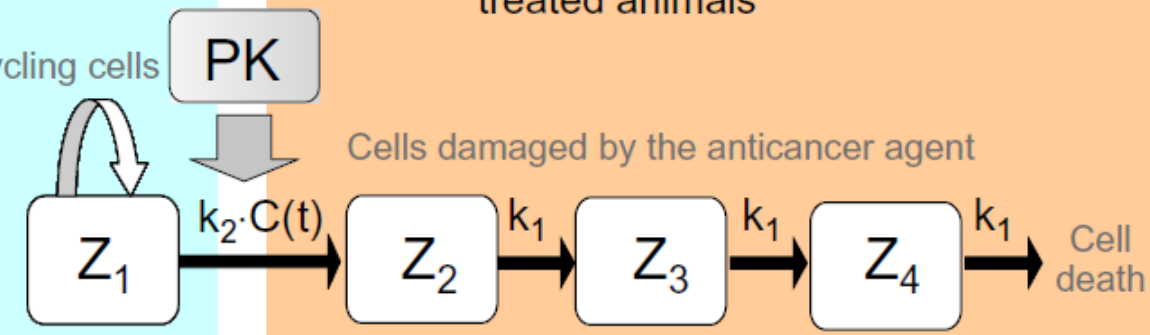
Differential equations for controls:

$$\frac{dW}{dt} = \lambda_0 \cdot W(t) \qquad W(t) < W_{threshold}$$

$$\frac{dW}{dt} = \lambda_1 \qquad W(t) \geq W_{threshold}$$

$$\frac{dW}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[\left(1+\frac{\lambda_0}{\lambda_1}\cdot W_1(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} \qquad W(0) = W_0$$

Tumour growth in treated animals



Overall system of differential equations:

$$\frac{dZ_1(t)}{dt} = \frac{\lambda_0 \cdot Z_1(t)}{\left[\left(1+\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} - k_2 \cdot C(t) \cdot Z_1(t)$$

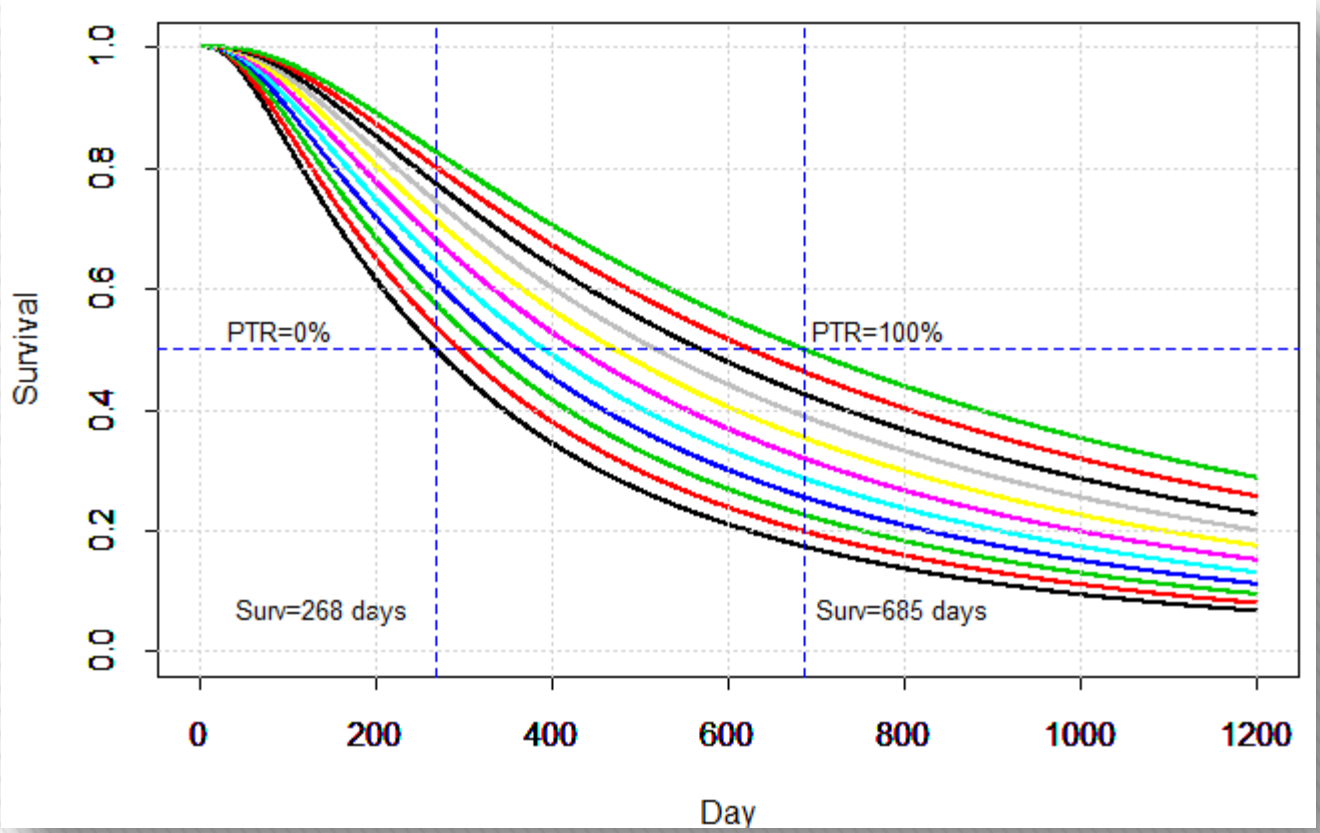
$$\frac{dZ_2(t)}{dt} = k_2 \cdot C(t) \cdot Z_1(t) - k_1 \cdot Z_2(t)$$

$$\frac{dZ_3(t)}{dt} = k_1 \cdot Z_2(t) - k_1 \cdot Z_3(t) \qquad Z_1(0) = w_0$$

$$\frac{dZ_4(t)}{dt} = k_1 \cdot Z_3(t) - k_1 \cdot Z_4(t) \qquad Z_{2,3,4}(0) = 0$$

$$W(t) = Z_1(t) + Z_2(t) + Z_3(t) + Z_4(t)$$

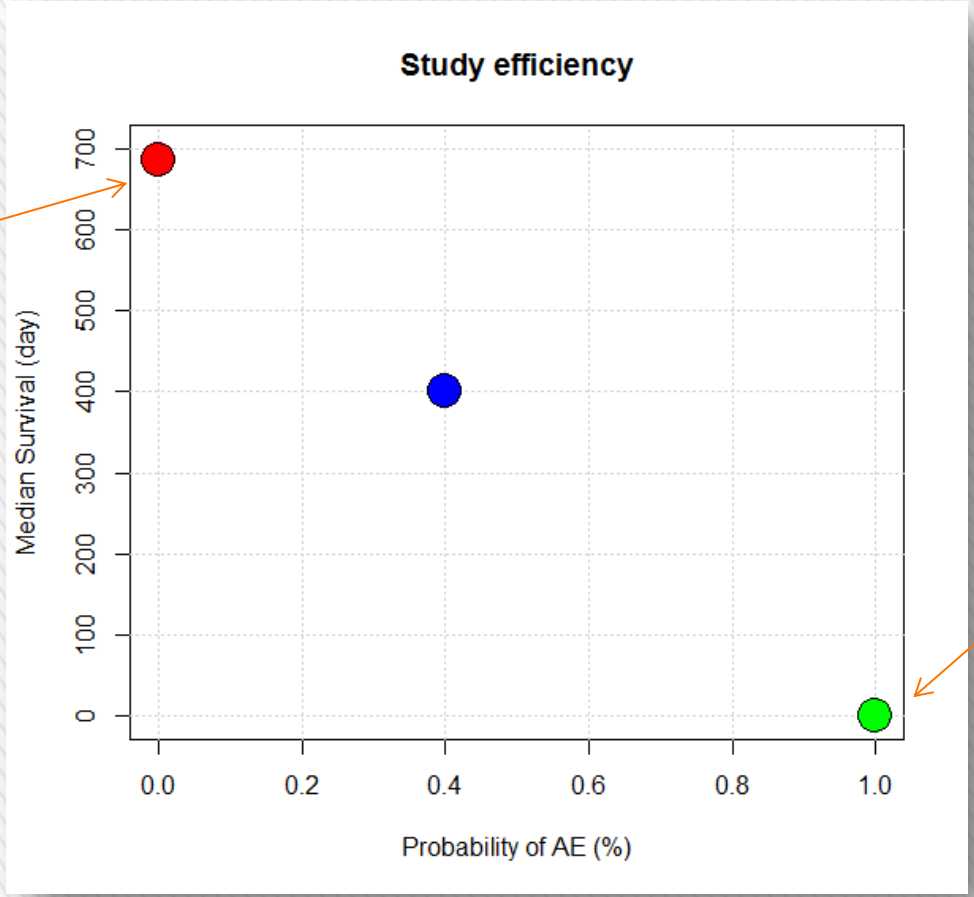
Survival as a function of Tumor Size reduction



Wang Y., Sung C., Dartois C., Ramchandani R., Booth B.P., Rock E., and Gobburu J. (2009) Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin. Pharmacol. Ther. 86, 167-174.

Definition of Study Efficiency

An ideal treatment would provide complete response (max median survival time) for all subjects in the trial without AE



An ineffective treatment is characterized by a poor medial survival and a high incidence of AEs

Clinical Trial Simulation