Integrative modelling of experimental Medicine clinical data

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Outline

- From translational Science to translational Medicine through **Experimental Medicine** (EM)
  - EM studies: what they are and what they are not
- **Statistical Learning for EM**:
  - methods
  - role of pharmacology
    - ★ pharmacokinetics (PK) and target engagement (TE) models
    - ★ estimation of the probability of pharmacological success (POPS)
  - from biomarkers to clinical endpoints
    - ★ assumptions needed to leverage FTH results in Phase II planning
    - ★ prediction of the probability of clinical success

From translational Science to translational Medicine

- **The problem** (Wehling, M. [2008]): *"Despite increased [...] investments into R&D, the output of novel medicines has been declining dramatically"*
- **What is needed**: *"Improvement of translation is thought to become a remedy as one of the reasons for this widening gap [...] is the difficult transition between preclinical and clinical stages in R&D"*
- **A solution**: *"This goal [...] relates to biomarker development and predictivity assessment, biostatistical methods, [...] accelerated early human study designs and decision algorithms"*

EM studies: what they are and what they are not

- **Experimental Medicine** (MRC): is *"Investigations undertaken in humans [...] to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments"*
- A clinical study will be defined as EM *iff* it demonstrates all the following principles:
  i. A small study answering focussed and specific questions about the MOA and potential links to efficacy,
  ii. Man as the experimental model,
  iii. Biomarker rich including biomarker endpoints,
  iv. Study has clear, pre-defined go/no go criteria.
- EM applies **abductive reasoning** to clinical trial design and analysis (Peirce [1878], Popper and Miller [1987], Ward et al [1999])

Statistical learning for EM: methods

- **Evidence against null hypotheses is not sufficient** because "go/no-go" decisions require magnitude, precision and estimated relations among multiple endpoints.
- **Assumptions**:
  - priors for model and population structure require pharmacological and epidemiological bases to ensure interpretable results.
  - priors for model parameters require meta-analysis, elicitation or shrinkage mechanisms improving the study operational characteristics
- **Estimation**: we use MCMC to approximate posterior inferences.
- **Model assessment**: comprise biological plausibility and weigh model fit and predictive power against model complexity (Occam's razor).

Statistical learning for EM: role of pharmacology

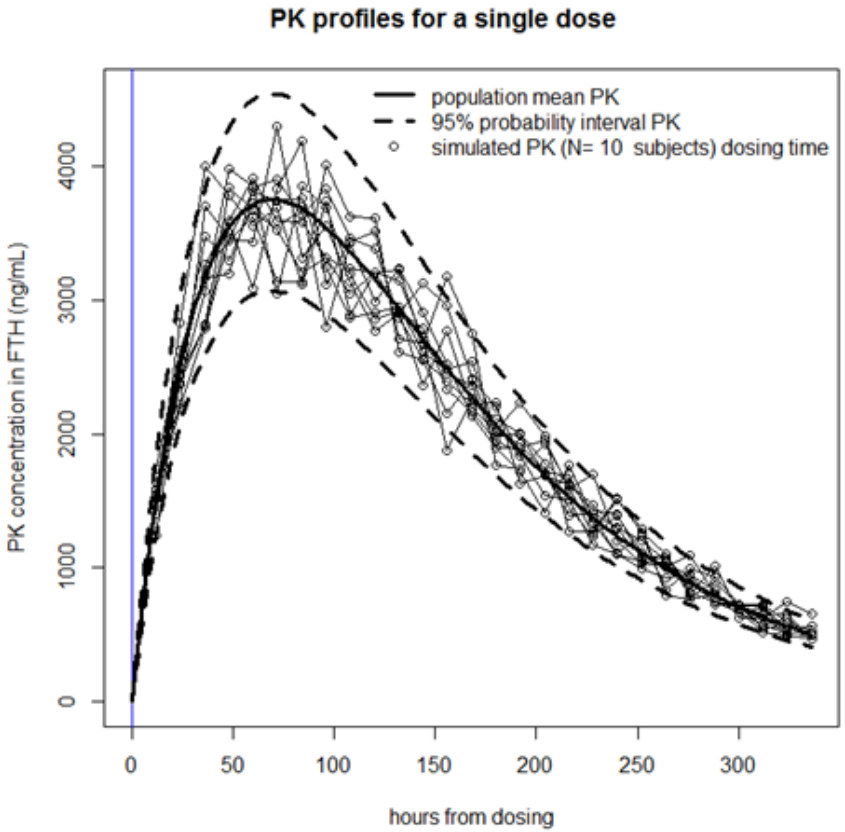
A necessary condition for EM trial success is **pharmacological success** (Morgan, P. [2012]), i.e.:

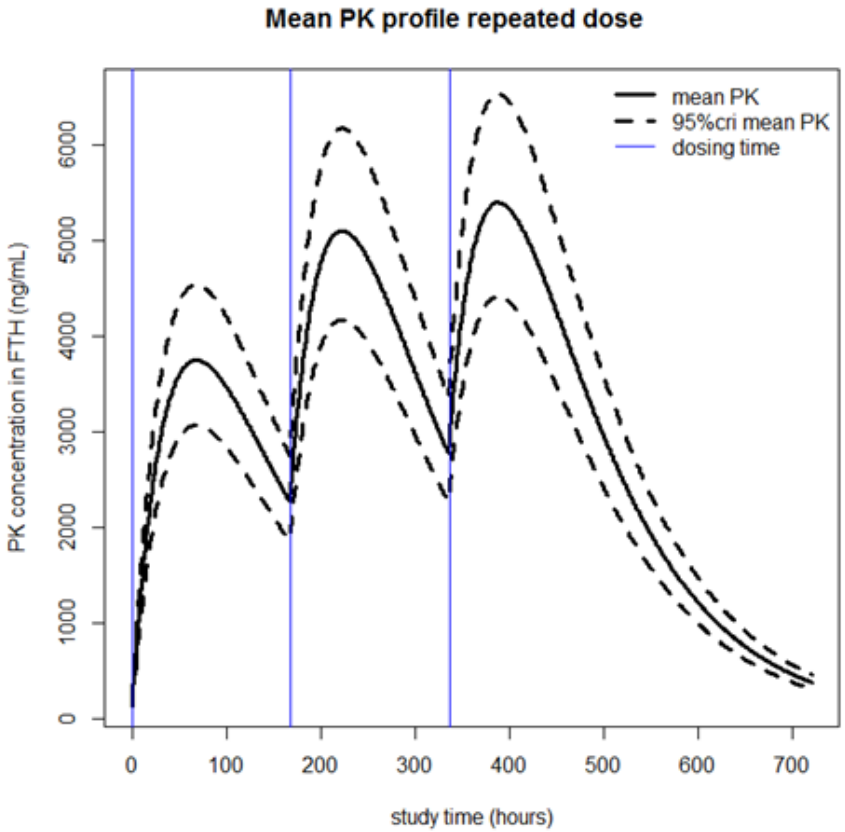
- exposure at site of action (PK) and
- target binding and engagement (TE) and
- expression of *functional* pharmacological activity (biomarkers)

- Statistical models are needed to quantify the links between:
  - *i)* treatment and PK,
  - *ii)* PK and TE,
  - *iii)* TE and biomarkers and
  - *iv)* biomarkers and clinical efficacy.

Statistical learning for EM: two-compartments PK

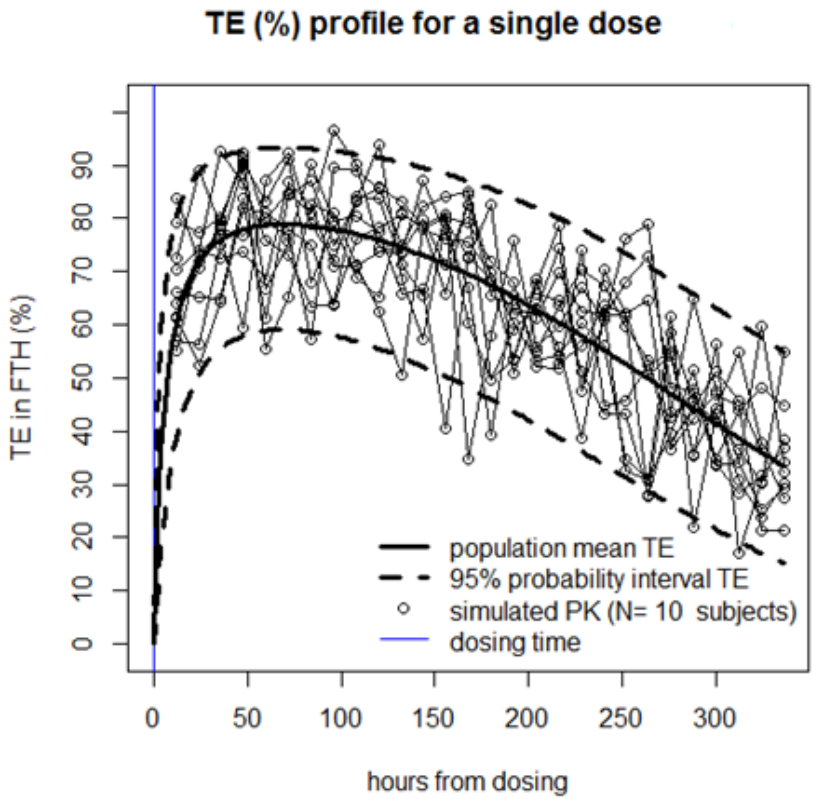
- $PK(t) \sim LogNormal(mean = \log(\mu_{PK}(t)) - \sigma^2/2, SD = \sigma)$ (1)
  with $\mu_{PK}(t) := dose(0)/V \times Ka/(Ka-Kel) \times (e^{-Ka \times t} - e^{-Kel \times t})$

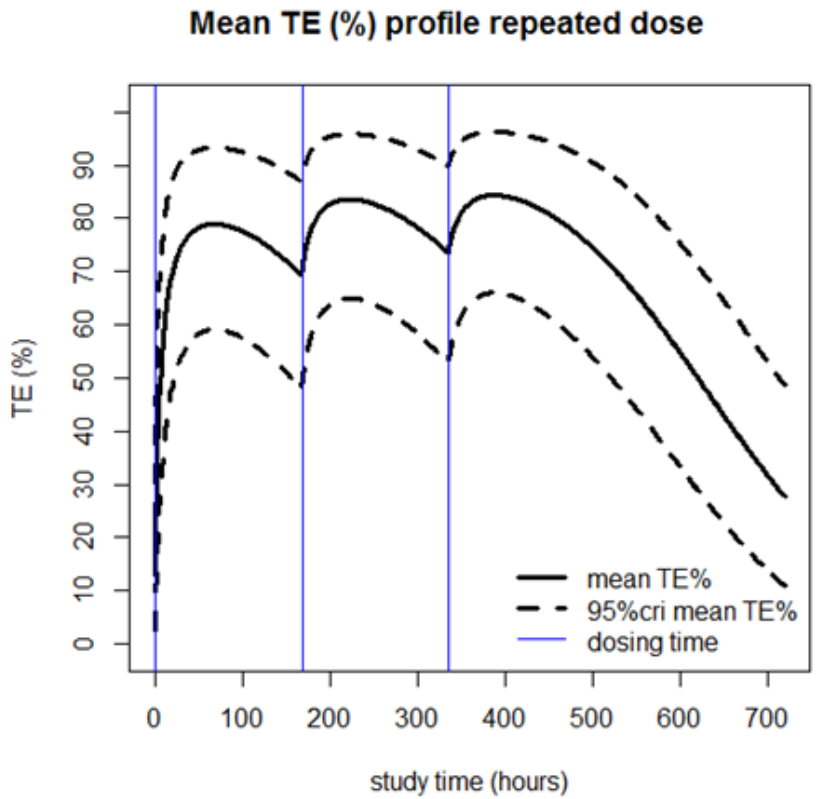




Statistical learning for EM: TE prediction model

- $\mathrm{TE}_{\mathrm{FTH}}(t) \sim \mathrm{Beta}(\mathrm{mean} = 1/(1+EC50/\mu_{\mathrm{PK}}(t)), \mathrm{variance} = \nu)$ (2)
- $\mathrm{TE}_{\mathrm{Patient}}(t) := \gamma \times \mathrm{TE}_{\mathrm{FTH}}(t)$ with conversion factor $\gamma \in (0,1)$





Example: POPS definition and estimation for a phase II repeated dose clinical trial

- Pharmacological success of one trial is defined here for any combination of **sample size (N), dose (D) and dosing times (t_k)** for k=1,...,K as:

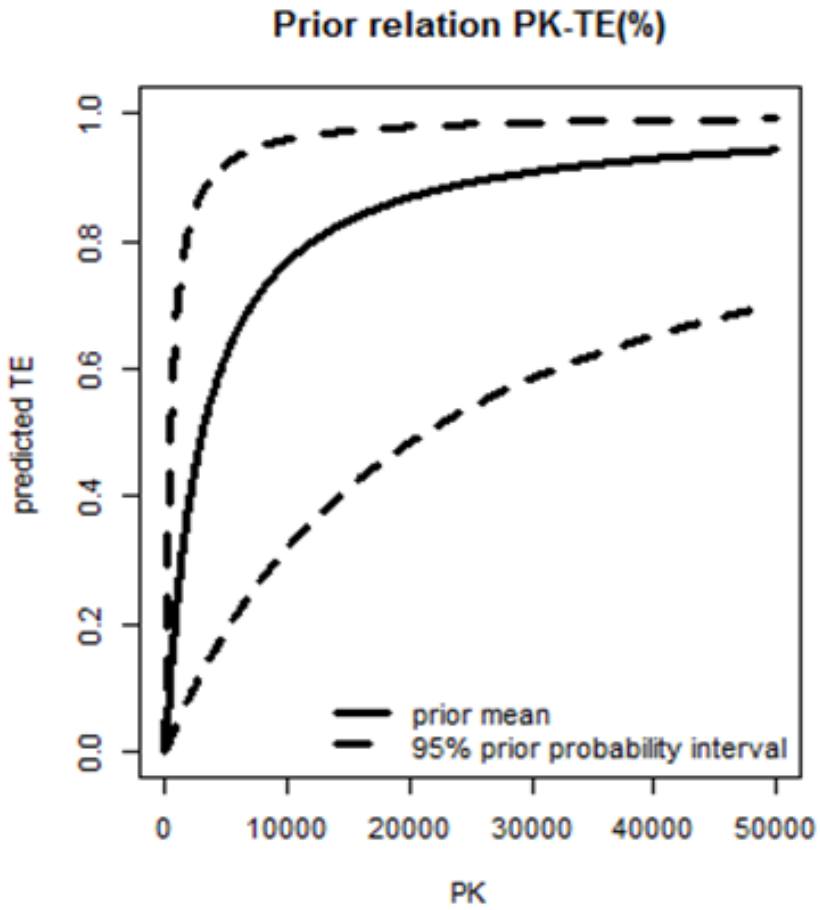
$$PS(N,D,t_{1:K}) := 1_{\{(\%\text{ subjects with PK} < \tau_{PK} \textit{ and } TE\% > \tau_{TE}) > \pi\}}$$

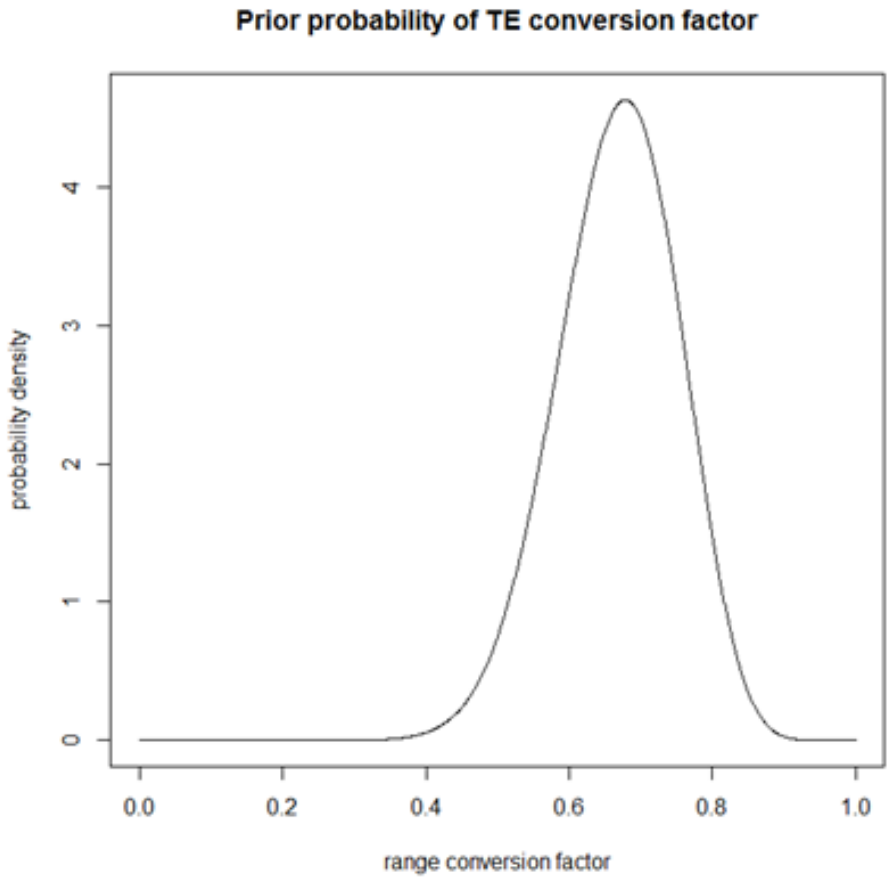
- The corresponding probability of pharmacological success is:

$$POPS(N,D,t_{1:K}) := \%\text{ trials achieving } PS(N,D,t_{1:K})$$

- $POPS(N,D,t_{1:K})$ is estimated by *clinical trial simulation*
  - When relying only on FTH PK data, simulation of TE% data needs priors for the parameters relating
    - ★ PK to TE% in healthy subjects and
    - ★ TE% in healthy subjects to that in patients

Statistical learning for EM: TE priors





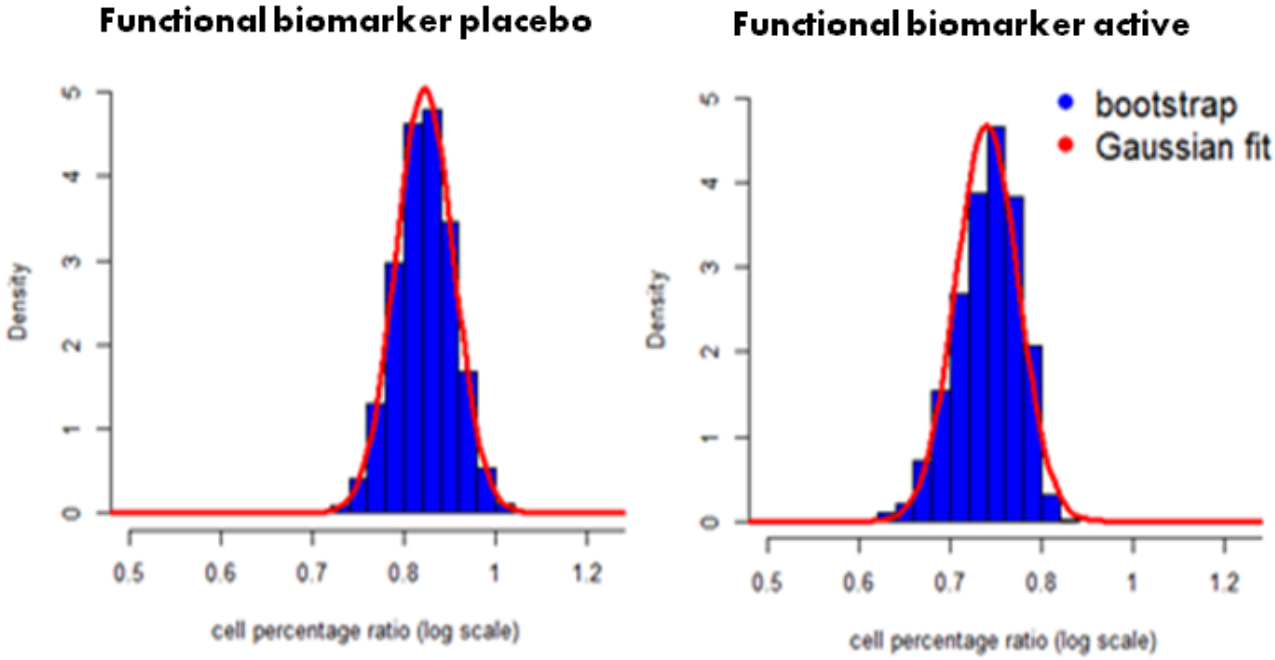
Estimated POPS from FTH PK data for two designs

Low dose at 0,14,28 days				High dose at 0,14,28 days			
Sample Size	%<τ_{PK}	%>τ_{TE}	POPS	Sample Size	%<τ_{PK}	%>τ_{TE}	POPS
20	100%	31%	31%	20	88%	71%	61%
30	100%	31%	31%	30	93%	71%	66%
40	100%	31%	31%	40	97%	71%	69%
100	100%	31%	31%	100	100%	71%	71%

- Low dose: all PK Cmax$< \tau_{PK}$ and few mean(TE%) $> \tau_{TE}$
- High dose:
  - the proportion of PK Cmax$< \tau_{PK}$ increases in sample size
  - the proportion of subjects achieving sufficient TE% is constant in sample size due to the high uncertainty in the TE priors used here

Measurement of functional biological activity

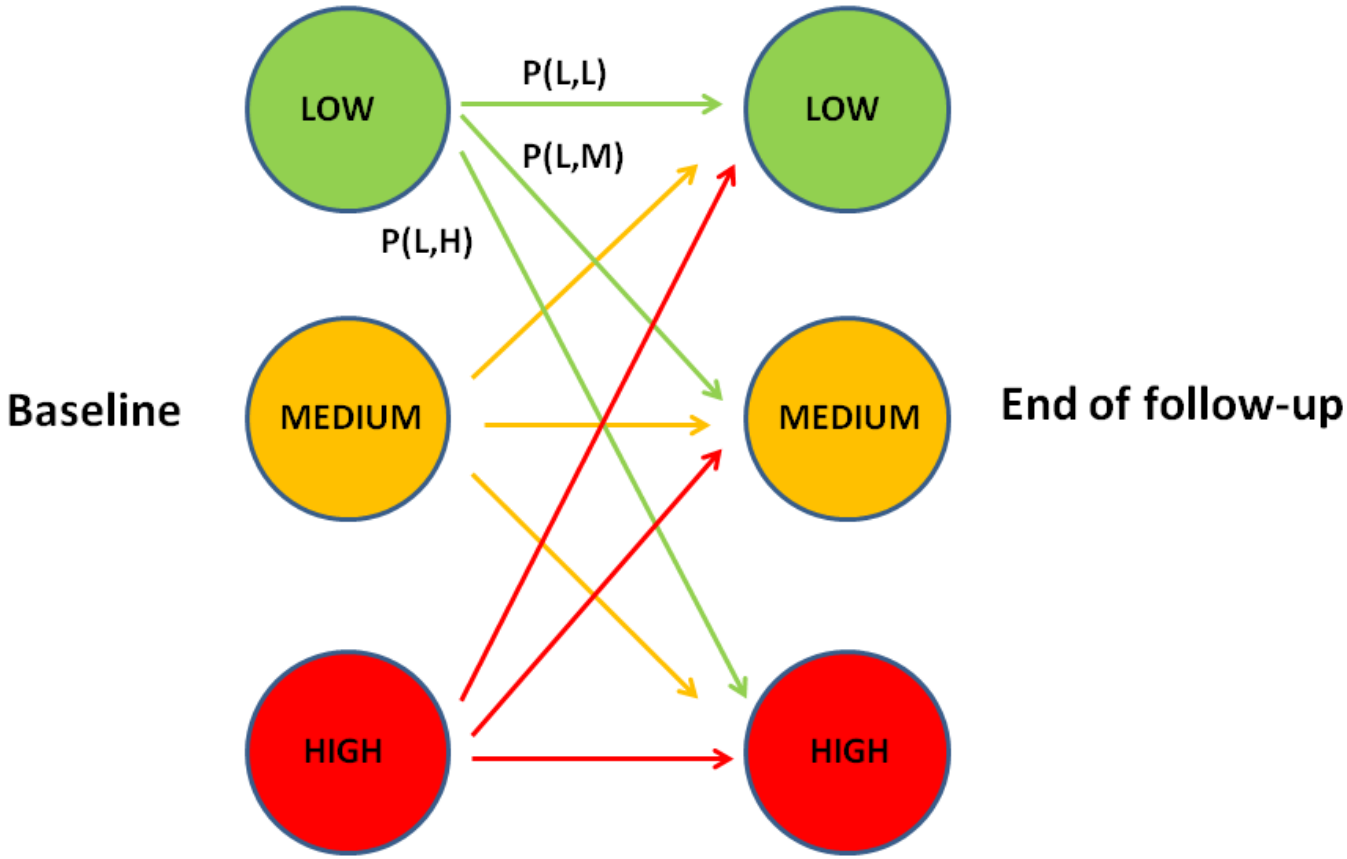
- Treatment with an investigational molecule causes a decrease in a biomarker mediating infammation at the site of action in a FTH study



- This evidence can be leveraged when planning a Phase II study if
  - biomarker changes in FTH predict those to be measured in patients,
  - the biomarker is a correlate of the clinical endpoint of interest.

An ordinal-valued Phase II clinical endpoint

- Consider a clinical endpoint measured on a three-rungs ordinal scale (e.g. a validated clinical score)



Simulation of clinical outcomes in patients from correlate biomarker results in FTH

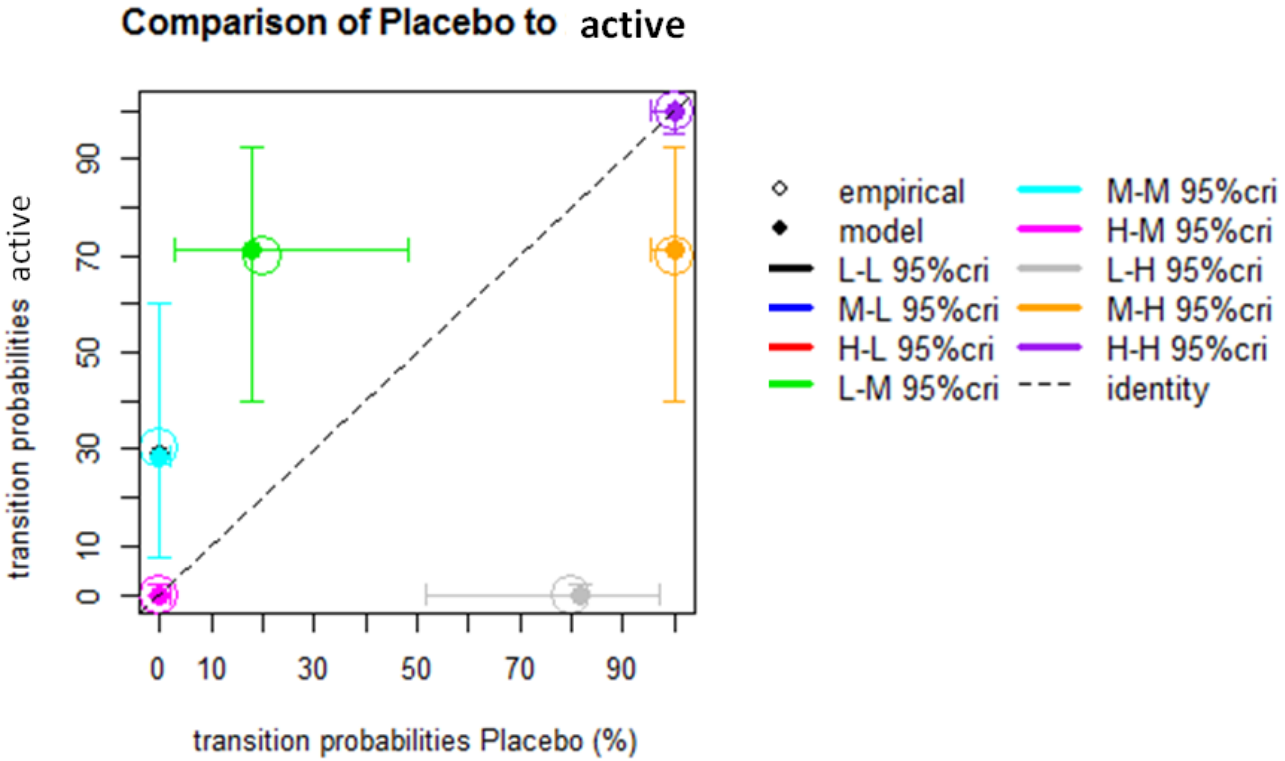
- The FTH study shows the frequencies of healthy subjects exhibiting a low, medium or high biomarker ratios

Treatment group	Proportion of subjects with biomarker ratios falling within each class		
	$< \tau_R$	$\geq \tau_R$ and $< \tau_M$	$\geq \tau_M$
Placebo	0%	25%	75%
Active	12%	84%	4%

- Clinical trial simulation: these frequencies are taken as estimates of individual Multinomial transition probabilities from *any* baseline value and towards each of their end of follow-up values

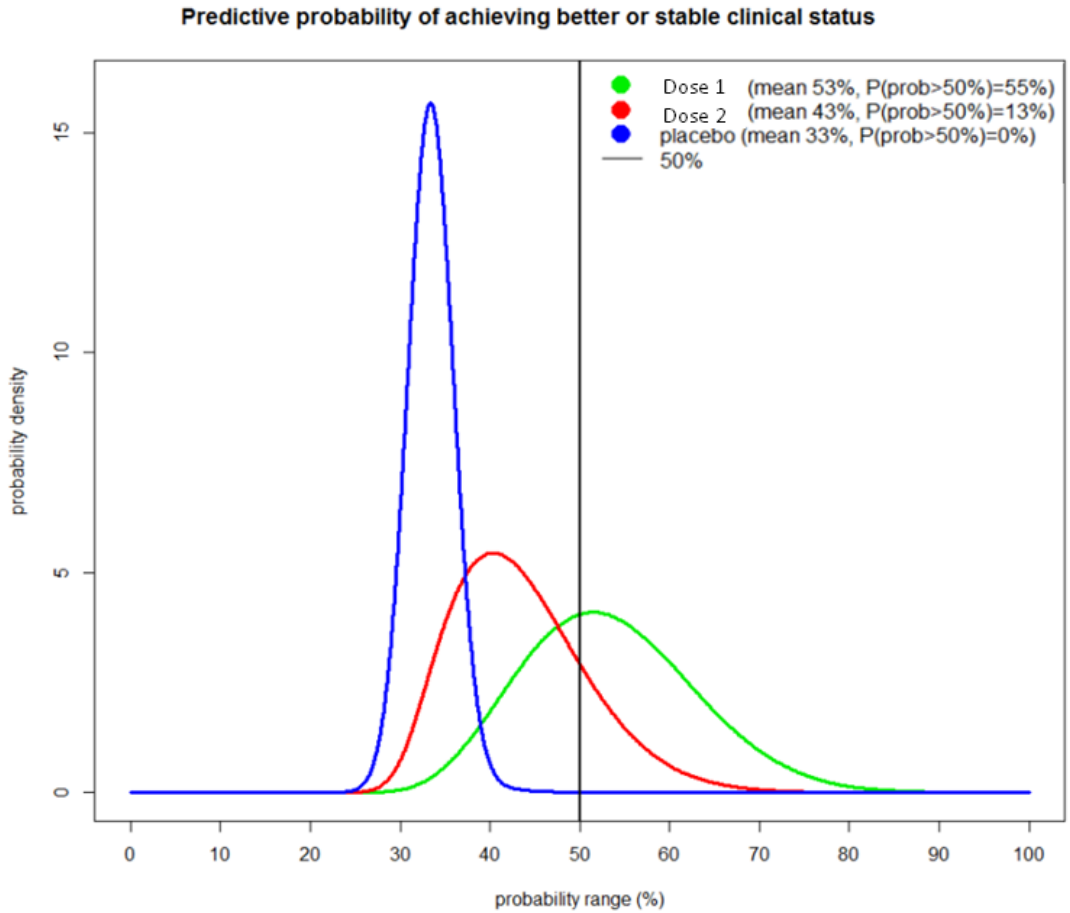
Bayesian inference from simulation results

- Sufficient statistics of the simulated data within arm: number of patients whose clinical status changes between each pair of rungs
- Data analysis
  - within arm: Multinomial-Dirichlet estimates of transition probabilities,
  - between arms: compare posterior distributions of transition rates.



Marginal predictive distributions of transition rates

- The probability that patients will achieve stable or better clinical states is 33% for placebo, 43% for the low dose and 53% for the high dose



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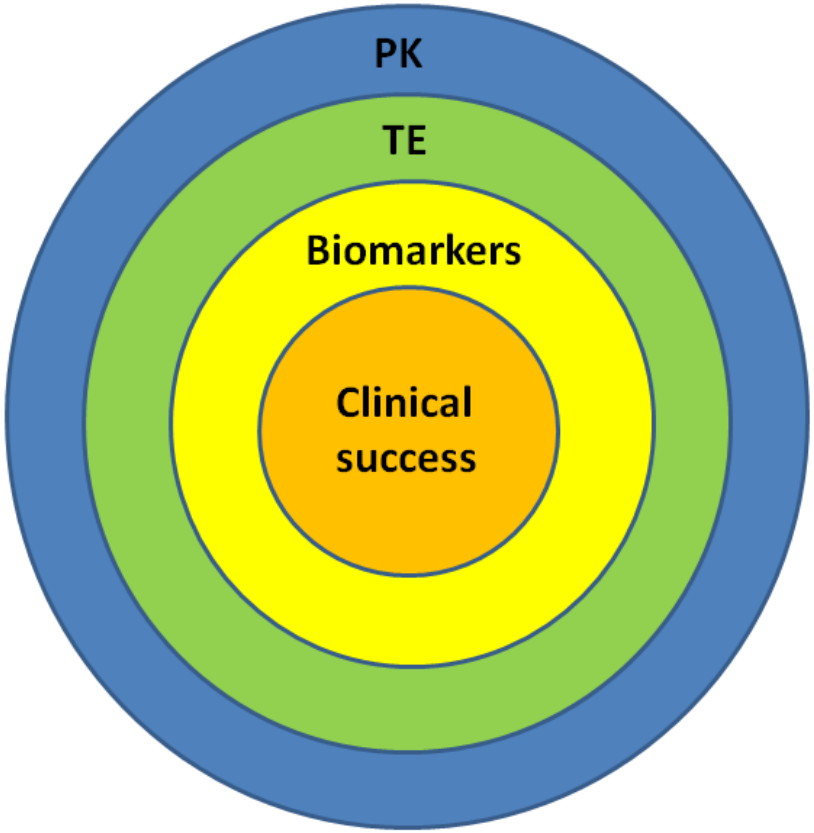

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