How many bits of information did my study provide?
Kullback-Leibler information gain, standard errors and shrinkage

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Background and Objectives

Information theory concerns the quantification, storage, and communication of information. The key measure in information theory is entropy which can be expressed in the units of ***bits***. The Kullback-Leibler divergence D_{KL} is a widely used measure in information theory. Many other quantities can be interpreted in terms of D_{KL} and it is often referred to as "information gain". **Our objective was to explore measures of information gain from model estimation.**

We evaluated the following properties for a information measure:
1) Units of ***bits***, the natural unit of information
2) Increase proportionally with number of individuals
3) Increase with the number of observations per individual
4) Unchanged by non-informative individuals
5) Increase with decreasing observation error
6) Increase with decreasing parameter relative standard-error

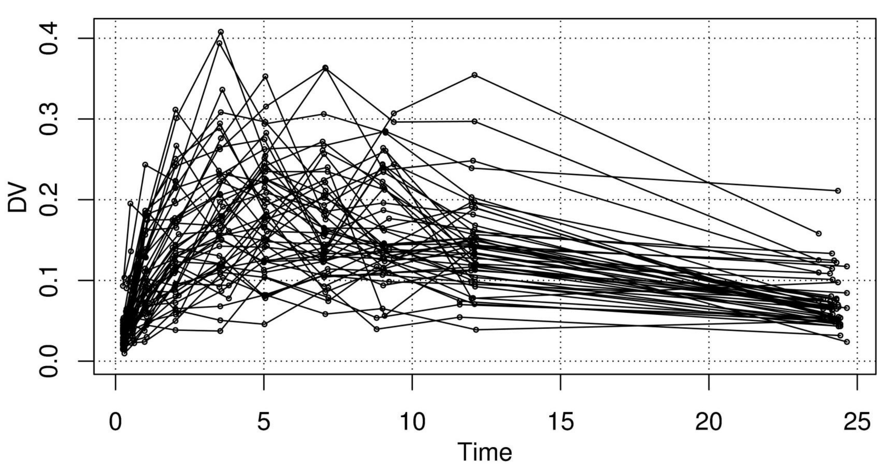
Methods and Results

Methods

Simulations were performed using a one-compartment PK model with absorption:

$$KA = 0.6 \cdot (WGT/70kg)^{-0.25} \cdot \exp(\eta 1)$$
$$V1 = 20 \cdot (WGT/70kg) \cdot \exp(\eta 2)$$
$$CL = 1 \cdot (WGT/70kg)^{0.75} \cdot \exp(\eta 3)$$
$$IPRED = C_{V1} \cdot (1+\varepsilon)$$

η1, η2, η3 inter-individual variance 0.05
ε observation error standard deviation 0.2236
Simulated WGT varied from 54.6-86.4 kg and there were 10-11 samples per individual



Kullback-Leibler divergence

For multivariate normal distribution the $D_{KL}(N0||N1)$ of $N0(\mu 0,\Sigma 0)$ from $N1(\mu 1,\Sigma 1)$ is:

$$= \frac{1}{2}\left\{ tr\left(\Sigma_1^{-1}\cdot\Sigma_0\right) + (\mu_1-\mu_0)^T \Sigma_1^{-1}(\mu_1-\mu_0) - k + \ln\left(\frac{|\Sigma_1|}{|\Sigma_0|}\right)\right\}$$

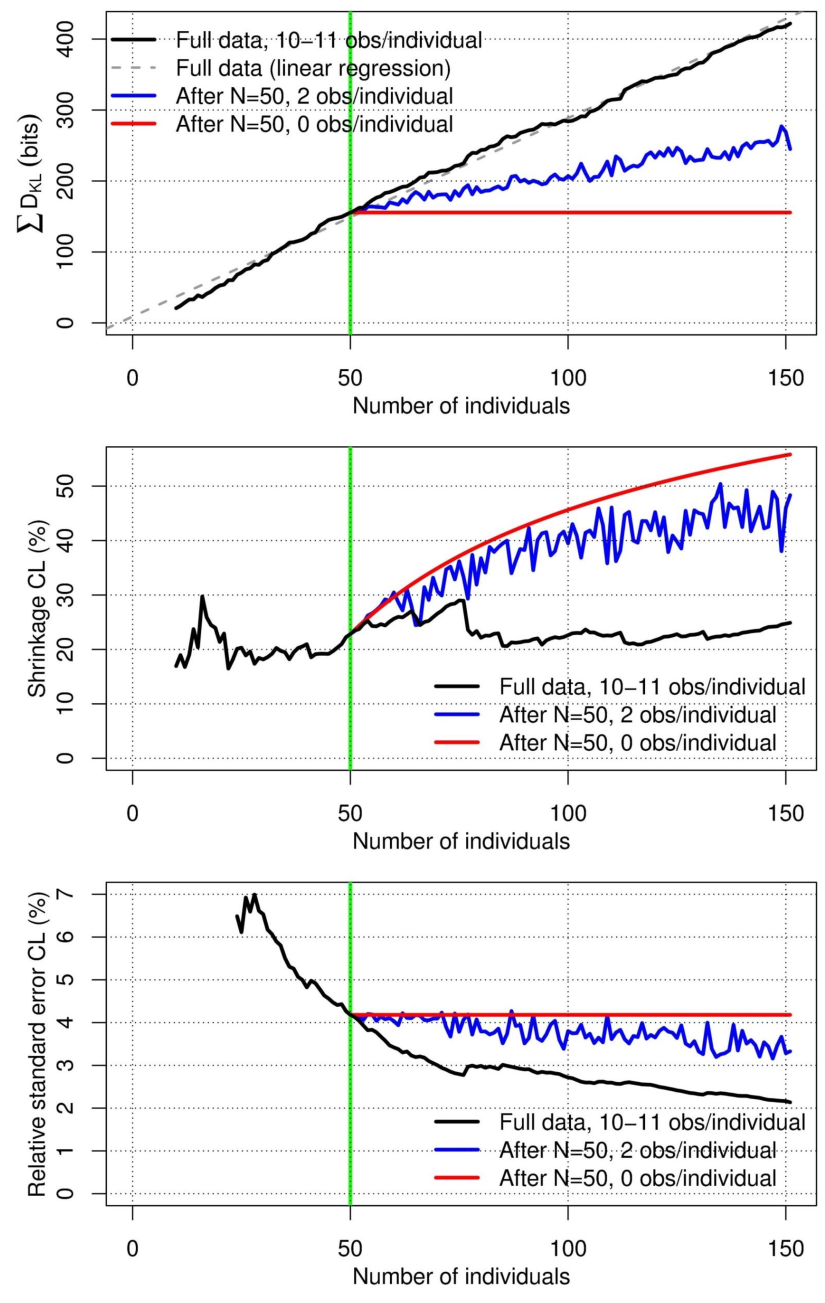
where *N0* to is the individual estimated distribution and *N1* to represent the estimated population distribution. D_{KL} represents the information gained when one revises one's beliefs from the prior *N1* to posterior *N0*. We sum D_{KL} over the individuals to obtain ΣD_{KL}. Dividing the equation above by *ln(2)* results in units of ***bits***.

Simulations

- The number of individuals was N=10-150. Mixed data-richness was simulated by limiting the number of observations to 2 when N>50. Non-informative individuals had 0 observations
- Observation error ε was varied from 0.02-0.4.

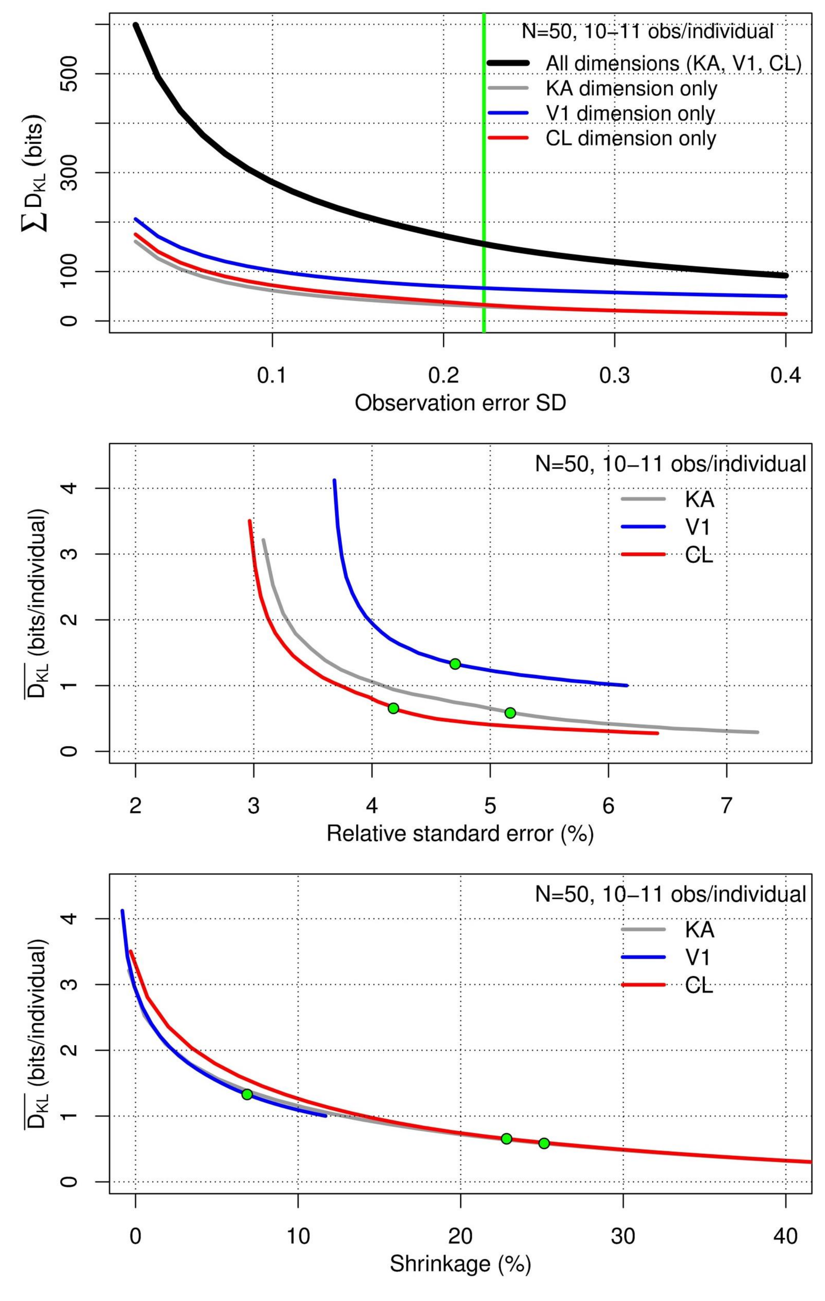
Varying number of individuals and data richness

- For constant observations/individual, ΣD_{KL} is proportional to the number of individuals
- ΣD_{KL} increased with number of observations/individual
- ΣD_{KL} constant with non-informative individuals
- Shrinkage reflects average information content and creating interpretation difficulties with unequal-data-richness across individuals



Varying observation error

For N=50 and 10-11 observation/individual
- ΣD_{KL}, and each dimension, decreases with observation error
- Relative standard error decreases with $\overline{D_{KL}}$ for each dimension
- In this equal-data-richness case, $\overline{D_{KL}}$ for each dimension seems related to *η*-shrinkage



Conclusions

Evaluating ΣD_{KL} satisfies the properties expected of a information measure. This allows a new quantification of information obtained by model estimation. For the reference PK model:

Parameter	η1 (KA)	η2 (V1)	η2 (CL)	Total
Estimated variance	0.0616	0.0793	0.0414	
Relative standard error (%)	5.17	4.70	4.18	
Shrinkage (%)	25.1	6.86	22.8	
ΣD_{KL}(bits)	**29.2**	**66.4**	**32.7**	**155.5**

Questions for future work

- How do we interpret the physical meaning of ***bits***?
- How is the information obtained related to non-eta parameters?
- Does maximizing ΣD_{KL} lead to optimal study design?
- Is there a relationship (possibly approximate) between ΣD_{KL} and parameter certainty (i.e. standard errors)?
- Are ΣD_{KL} summaries useful to combine multiple studies of varying quality?