Special Cases for the Statistical Evaluation of Bioequivalence: An Example of In-Vitro, Skin Permeation Test Data

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Topical dermatological products

- Creams, ointments and gels
- Drug is intended to act locally near the site of application of the skin
- Typically, it cannot be monitored through systemic circulation

Clinical Endpoint Studies

- Gold standard for safety and efficacy studies
- In the case of BE studies, a way is sought in order to make direct comparisons

- For such a direct comparison, a clinical endpoint study may require a very large number subjects to be adequately powered

Clinical endpoint studies

For topical products, different issues arise during BE assessment:

- the altered permeability barrier of diseased skin across a range of severity is associated with inter-patient variability, adding a burden of complexity to BE study design
- Variability between and within subjects
- Placebo effects can be very high
- Patient compliance can be an issue

Alternative: Dermal-PK studies

Skin-Stripping, Microdialysis, dOFM, IVPT

They monitor local BA, which reflects the rate and extent to which the drug becomes available at the site of action

Limitation

There have been no accepted statistical analyses or endpoints with which BE could be established using these alternative approaches

The lack of statistical methodology

Reasons

- The inherently high variability in the barrier properties of human skin, and
- the associated variability in the results from BE studies with topical products, has limited the establishment of statistical approaches to evaluate BE using Dermal PK approaches
- The high variability observed within studies involving topical products arises from both, inter-subject and within-subject (within-reference) variability

The lack of statistical methodology

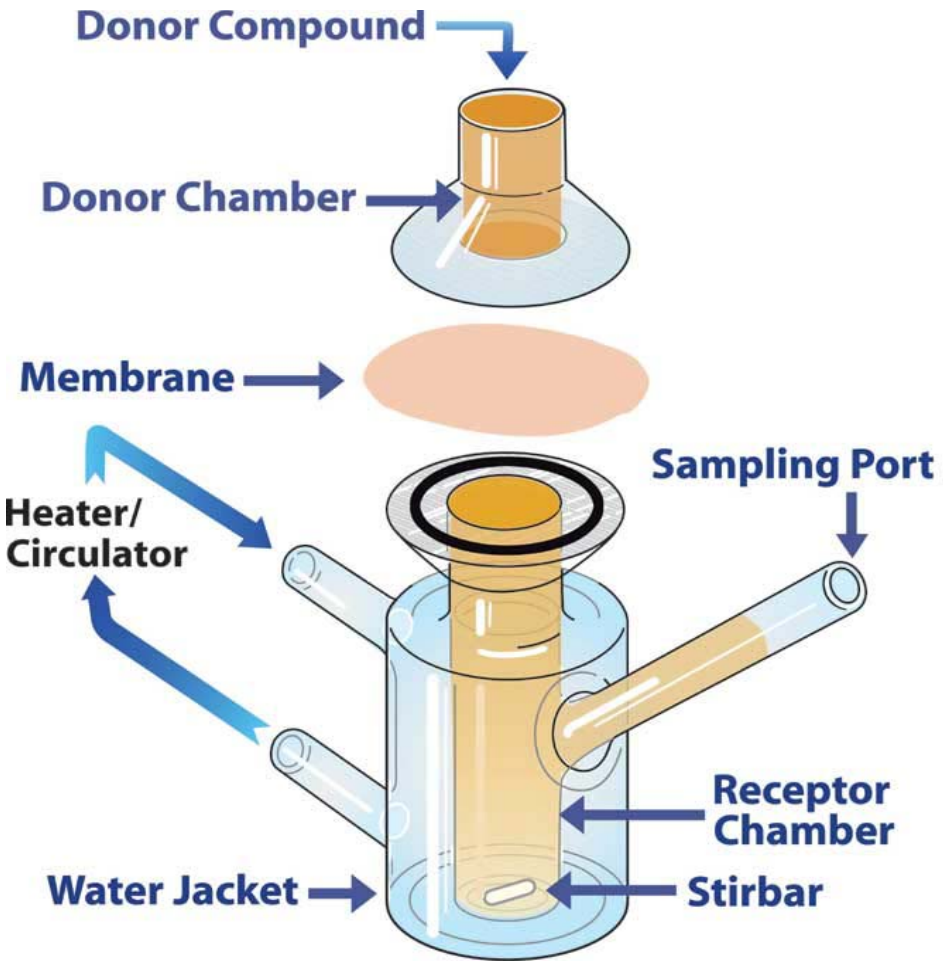
Consequences

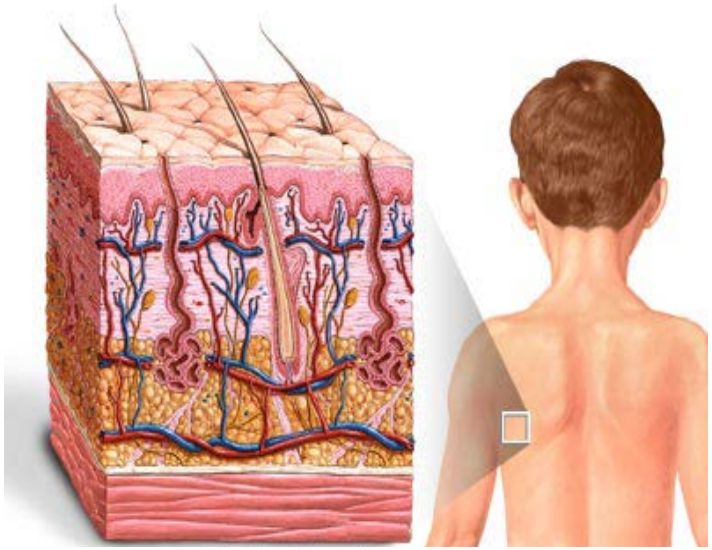
- Most generic versions of most topical drug products, utilize clinical endpoint studies to establish BE.
- There is a gap between the scientifically sound PK approaches and the development of regulatory standards that are appropriate for these topical products

In-Vitro Permeation Test (IVPT)

- Uses excised human skin
- Measures drug concentration
- The rate of drug delivery (flux) is measured by sampling at specific, pre-selected time-points in a way analogous to that used in blood (or plasma) concentration sampling in PK studies

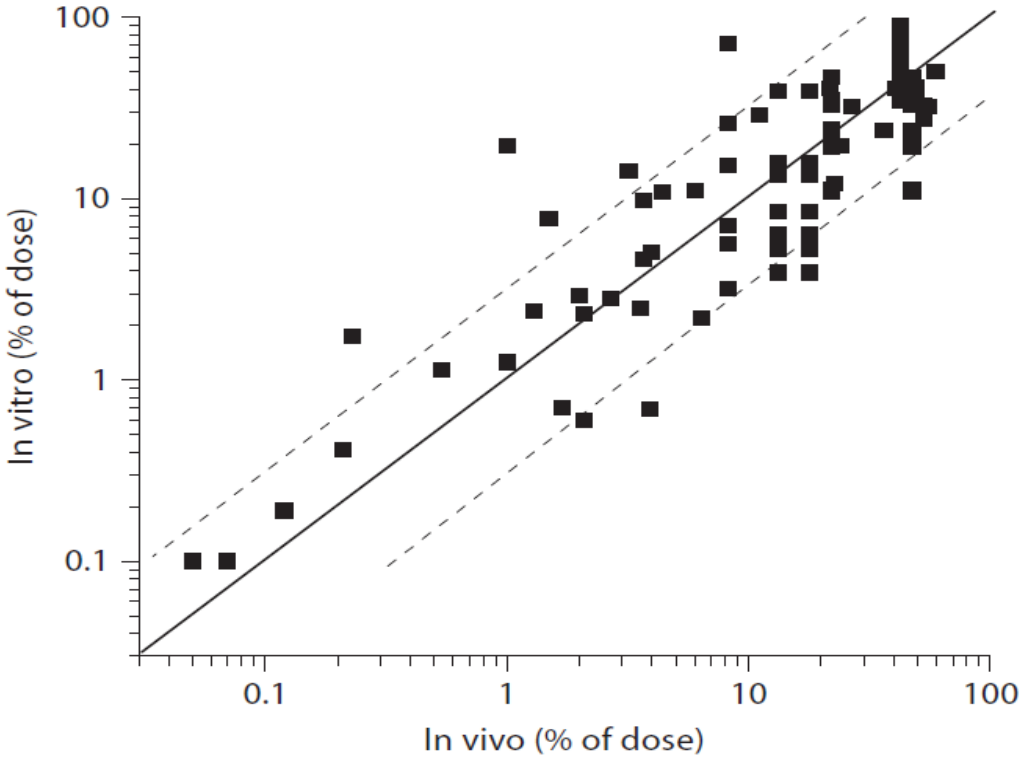
In-Vitro Permeation Test (IVPT)





Validating IVPT: IVIVC

- Franz et al., 2011 (92 IVIVC Data Sets)



Study design

The response considered is the log-transformed

- total penetration (AUC)
- max flux rate (Jmax)

We consider a sample of

***n: donors*,**

r: replicate skin sections from each one of the n donors

2 treatment formulations: test (generic: T) and reference (R)

Study design

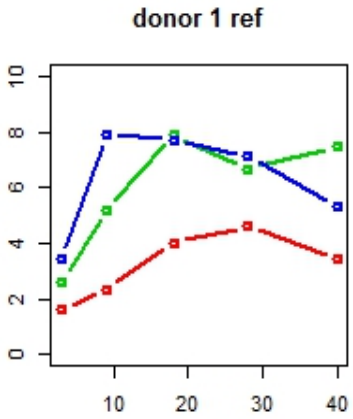
Test:

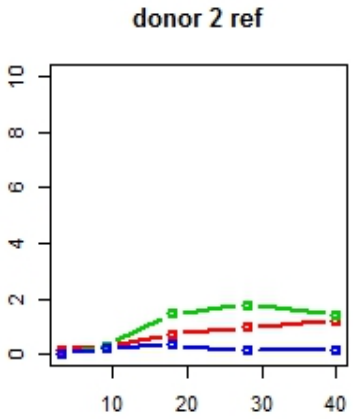
$$T_{11}, T_{12}, \ldots, T_{1r}$$
$$T_{21}, T_{22}, \ldots, T_{2r}$$
$$\vdots$$
$$T_{n1}, T_{n2}, \ldots, T_{nr}$$

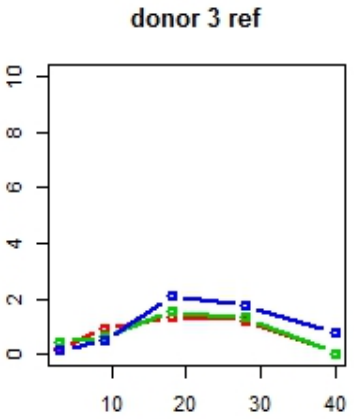
Reference:

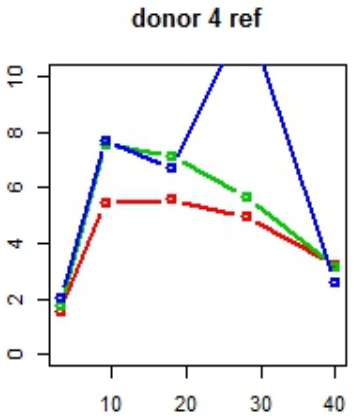
$$R_{11}, R_{12}, \ldots, R_{1r}$$
$$R_{21}, R_{22}, \ldots, R_{2r}$$
$$\vdots$$
$$R_{n1}, R_{n2}, \ldots, R_{nr}$$

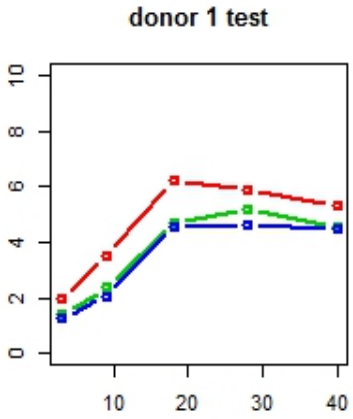
An example of flux curves

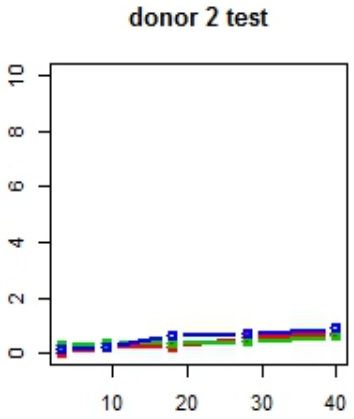


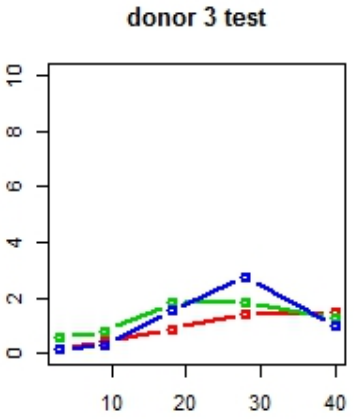


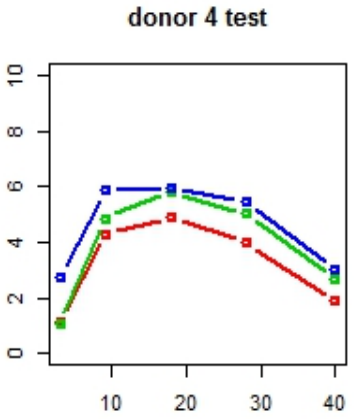












Novel statistical approach

- It is based on the mixed scaled criterion used by CDER for Highly Variable Drugs (HVD)
- It has been adapted to dermal PK methods
- It can be adequately powered by 6-36 donors
- It is among the most accurate and reproducible ways to establishing BE

Mixed scaled criterion:

- Cutoff point: Within-reference standard deviation (σ_{WR})
- For $\sigma_{WR} \leq 0.294$, the test and reference formulations are declared bioequivalent if the (1-α) *100% confidence interval:

$$\bar{I} \pm t_{(n-1),\alpha/2} * \sqrt{\frac{S_I^2}{n}}$$

Is contained within the limits $[\frac{1}{m}, m]$.

Mixed scaled criterion:

For higher values of σ_{WR}, The hypotheses to be tested are:

$$H_0: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} > \theta$$

$$H_a: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

Where $\theta = \frac{(\ln(m))^2}{(0.25)^2}$

Mixed scaled criterion

- The strategy is to construct a (1-α) *100% confidence interval for the quantity $(\mu_T - \mu_R)^2 - \theta\ \sigma_{WR}^2$ and to observe its upper bound.
- Rejection of the null hypothesis, H_0, supports BE.
- This criterion is accompanied by a point estimate constraint according to which the geometric mean ratio (point estimate of the log-transformed response has to fall within the pre-specified limits: $[\frac{1}{m}, m]$.

Data considered

Three sources of data have been studied to develop/validate the statistical test:

- Redacted data that was used for industry research. This contained a variety of topical products (creams, ointments, gels), for a variety of different drugs, including products containing 2 active ingredients. Such data sets were about:

1. Products known to be BE
2. Multiple lots of the same RLD, assumed to be BE to themselves

Data considered

- Data coming from information made available to FDA in product applications (ANDA), for which there was a clinical and an IVPT study

- Data coming from GDUFA grants

Data considered

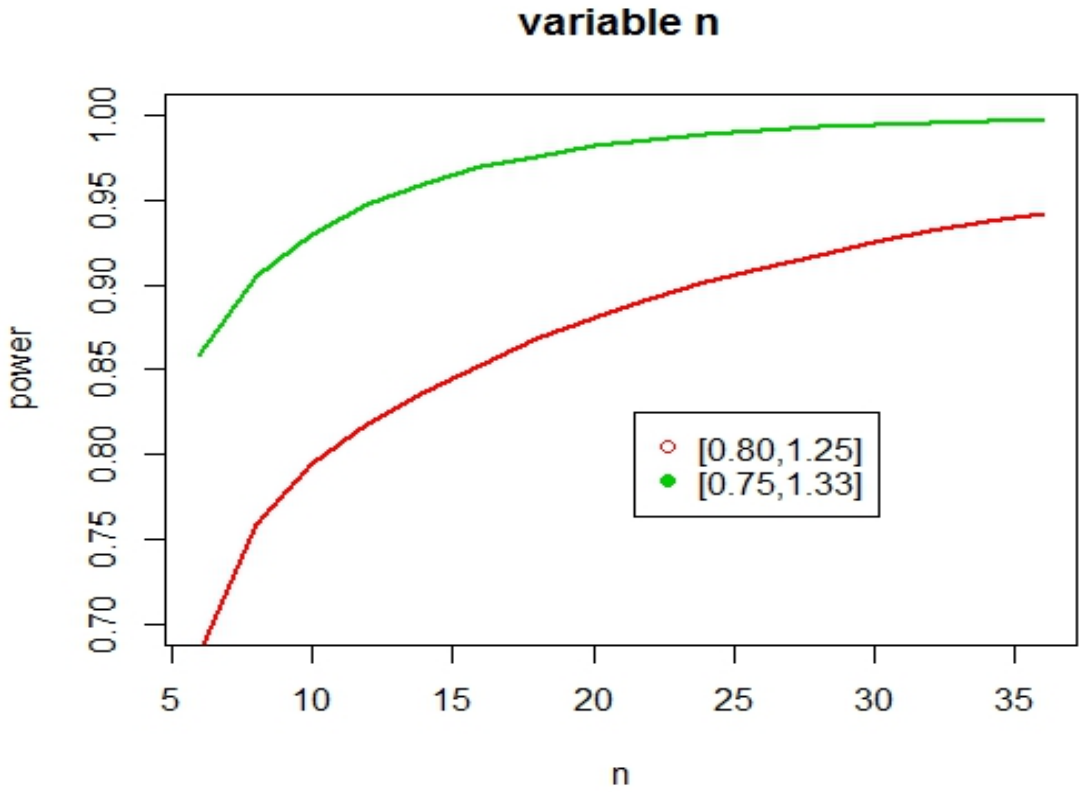
The available sources of data:

- Gave us a good range of sources of real-world variability
- Allowed us to determine the parameters which are important markers for evaluating BE

Performance and results

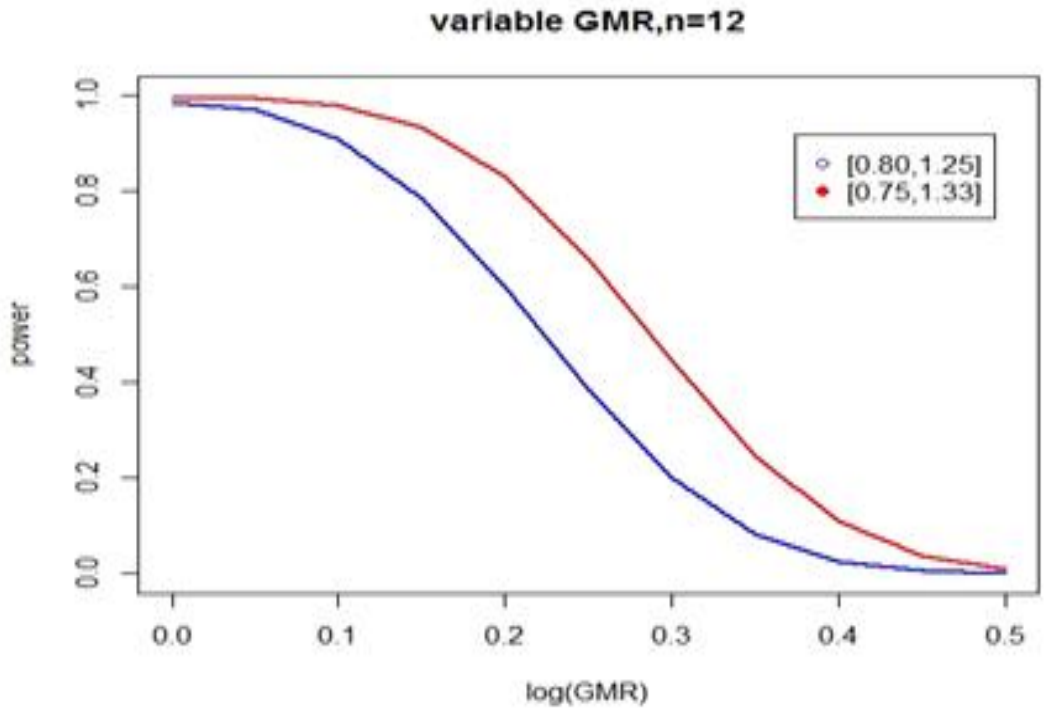
- The results obtained with IVPT and the suggested statistical analysis, were in agreement with the original results that led to regulatory approval of marketed products. This speaks in favor of the ***validity of this model for assessing BE***
- The test has been used for comparing two batches of the same reference product and successfully captured the similarity of these products in terms of BE. The outcomes advocate the ***model's sensitivity to meaningful differences and its resistance to the hazard of rejecting good products***.

Power simulations



DIA DEVELOP INNOVATE ADVANCE

Power simulations



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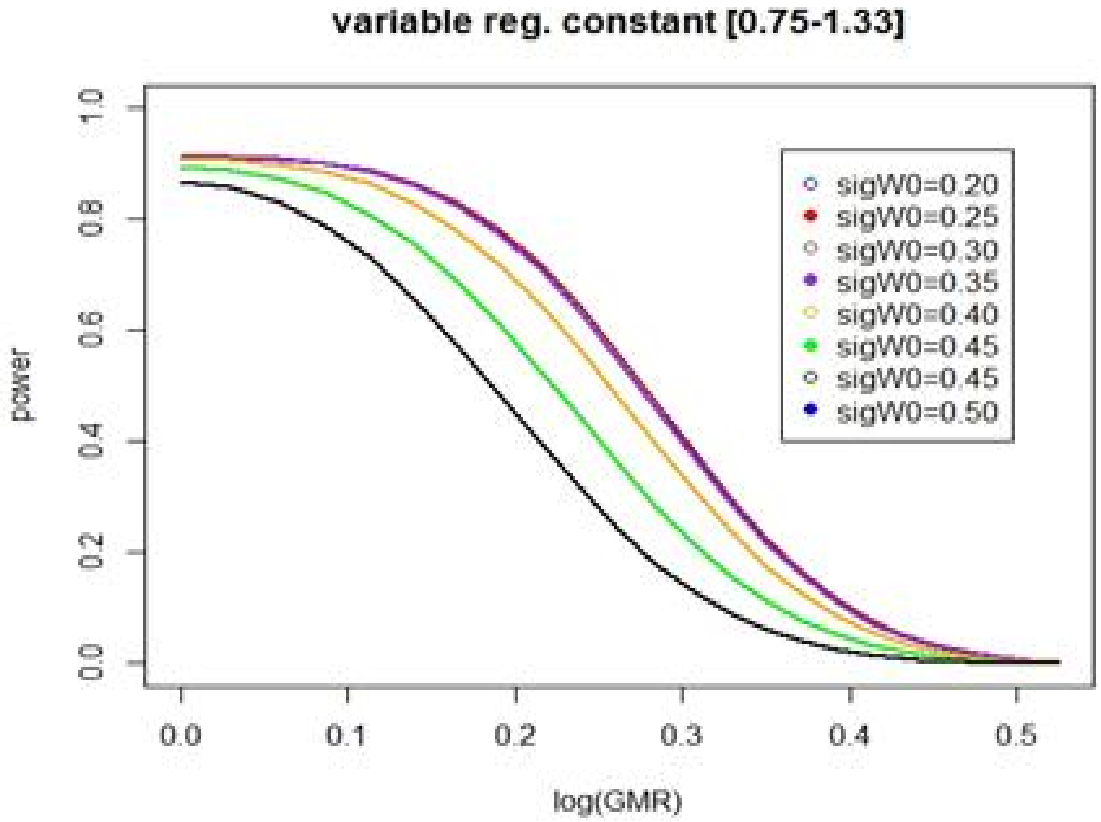

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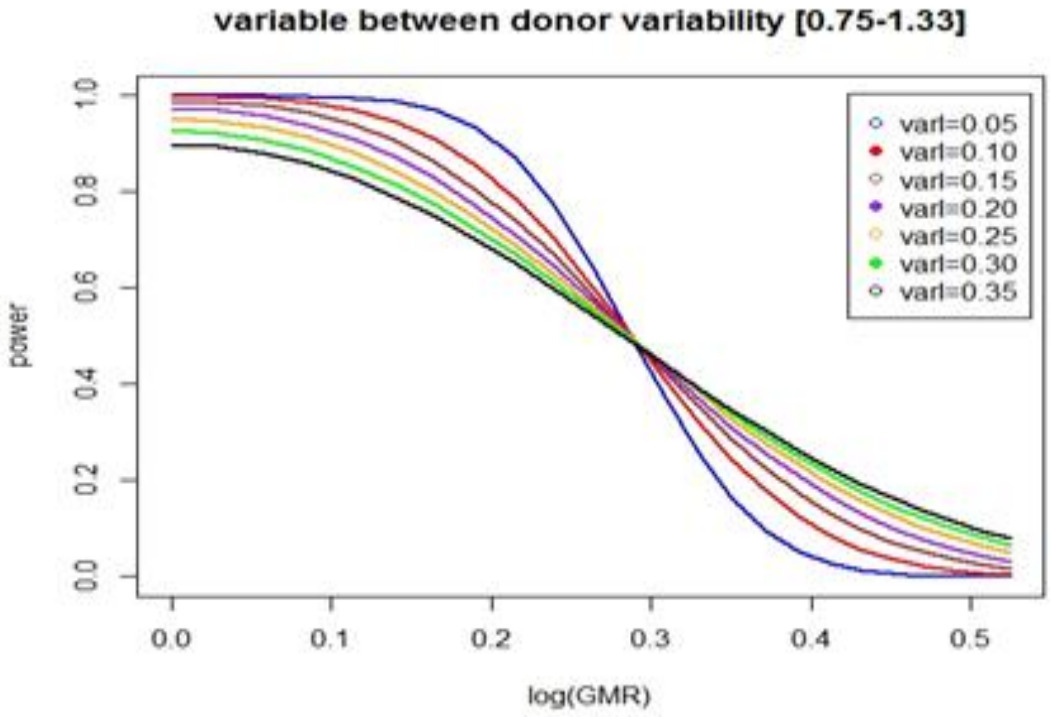

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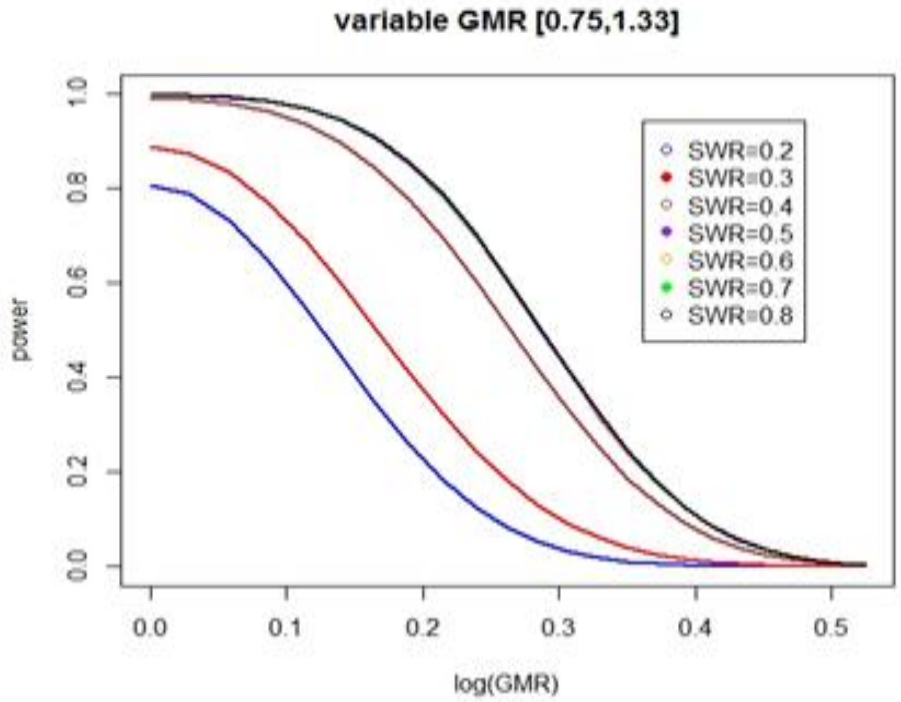

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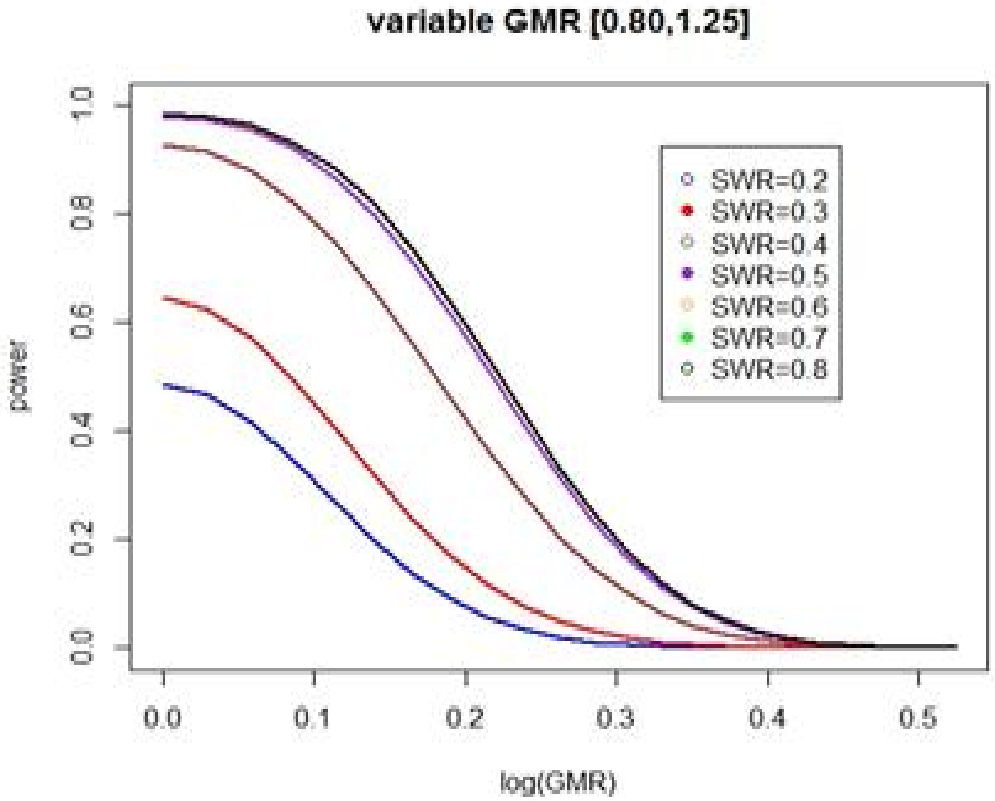

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