# Autocorrelation reduces sample time clustering in optimal design

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## ABSTRACT

**Background**: Optimal experimental design has been shown to be a useful way to improve the information content of experiments. Often these designs are optimized over sample times and result in the occurrence of samples clustered at the same time point. Such designs are both non-intuitive and likely to be less informative in reality, as they don't appropriately take into account error generation mechanisms. Further, the designs are clinically less appealing as multiple samples at the same time are often practically impossible and counter-intuitive to experimentalists. The clustering in optimal design occurs because the design is trying to minimize the signal-to-noise ratio between the measurement variable and the residual variability and is compounded by the assumption that the measurements between observations at the same time are independent from one another. Previous work (Federov et al.) has investigated the use of stochastic differential equations in models for optimal design to incorporate information about autocorrelation (AC). However this implementation was limited to a few simple PK models and would not be amenable for extension to more complex models.

**Objectives**: To develop a general method for optimal design implementation of the AR1 autocorrelation model and to compare optimal designs with varying degrees of autocorrelation between measurements within an individual.

**Methods**: The optimal designs were computed using PopED (http://poped.sf.net/), into which an AR1 model was implemented, allowing for correlation between measurements of an individual. Numerous models and were used to compute optimal designs with a range of correlation strengths. The designs were optimized for sampling times and compared to one another.

**Results**: Clusters of sample times in designs without autocorrelation are spread apart in models with AC present and the spread increases with increasing AC. The AR1 model is simple to implement and possible to use in any desired model. Optimal designs ignoring an existing AC are inferior to designs that take such patterns into account.

**Conclusions**: AC is a principled way to reduce or eliminate clustering from optimal designs. Recent work has also shown that incorporating AC can be important in hypothesis testing when model building and ignoring AC may result in biased parameter estimates (Silber et al. 2009). The present results demonstrate that incorporating AC will lead to more intuitive, practical and informative designs.

**References**:

[**1**] Silber, H.E., et al, The impact of misspecification of residual error or correlation structure on the type-I error rate for covariate inclusion, J Pharmacokinet Pharmacodyn, 2009.

[**2**] Fedorov. V.V., et al, Stochastic pharmacokinetic models: selection of sampling times, PAGE, 2008.