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A Time-Variant Parameter as a Wiener Process using the effects Modeling Framework

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Abstract: This paper describes Modeling a parameter in such a way, however, requires a priori knowledge of the time course of the parameter. In many cases, the time course of the parameter is unknown or is actually the quantity of interest. What is needed in these cases is a way to fit the parameter as an arbitrarily shaped function. Typical pharmacokinetic models consider parameters such as volume, clearance, and absorption rate to be constant over the duration of the study. More sophisticated models may attempt to parameterize changes to the constants, such as tying clearance to a circadian rhythm or modeling drug absorption with a sigmoid curve.

Introduction:

The Wiener Process is essentially a random walk W(t) with

- Zero initial value, W(0)=0
- Zero expected value, E[W(t)]=0
- Independent increments W(t)-W(s)$\sim$ N(0,t-s), for $0 < s < t$
- Variance proportional to the square root of the time between increments (steps in value).

Given that the Wiener Process, W, is either directly observed over a set $T = \{t_1, t_2, t_3, ...\}$, define

$$W(T_i) = \sum_{t \leq T_i} w_t, \quad w_i \sim N(0, (T_i - T_{i-1})\sigma_w^2)$$

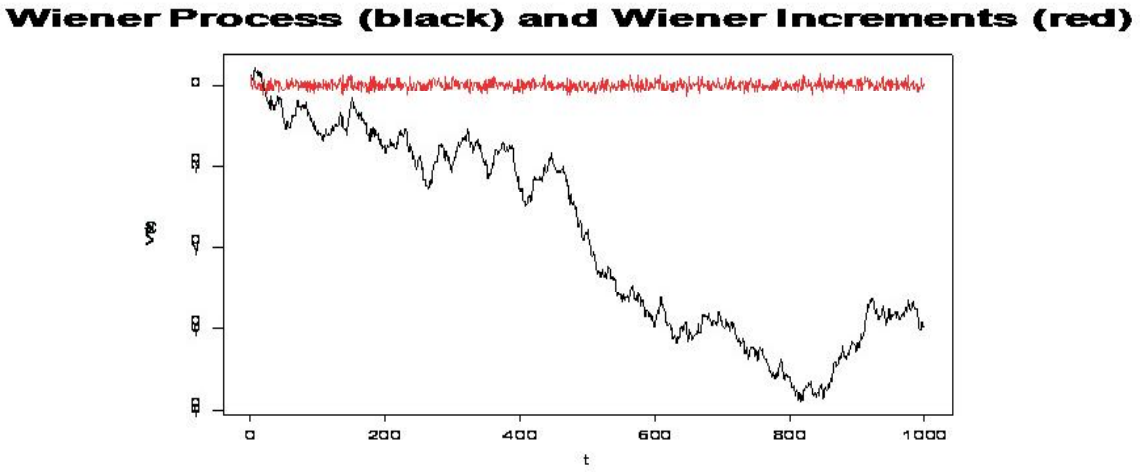
The increments of W are independent and can be transformed to identically distributed normal variables:

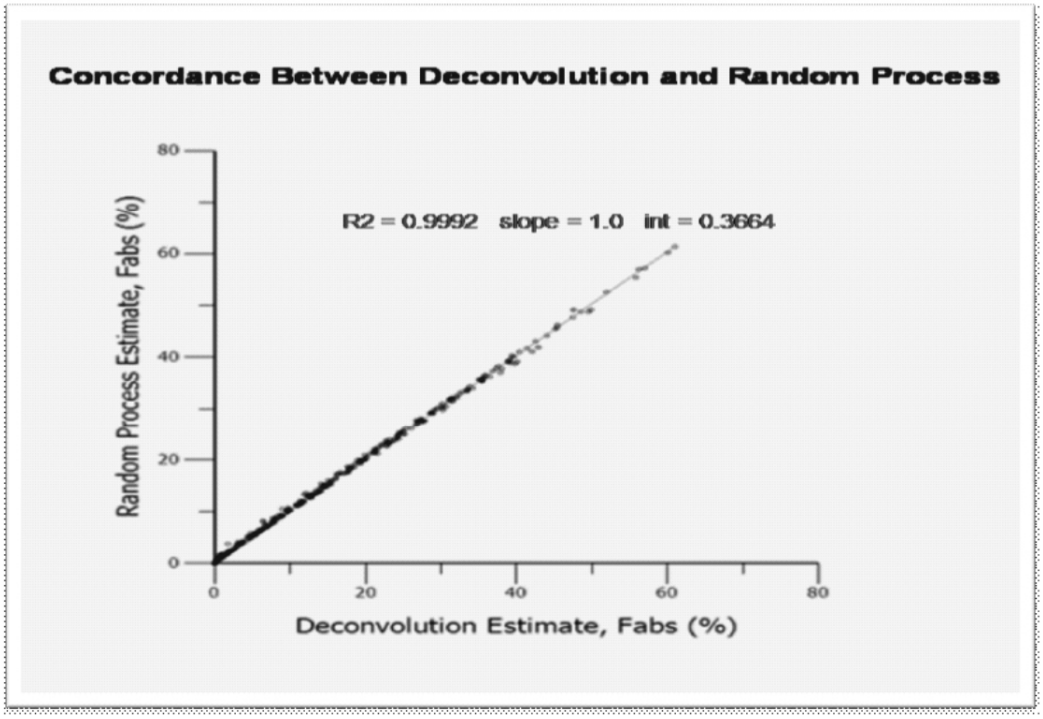
$$w_i = (T_i - T_{i-1})^{1/2}\eta_{w_i}, \qquad \eta_{w_i} \sim N(0, \sigma_w^2)$$

Then attach W to an observed or latent variable:

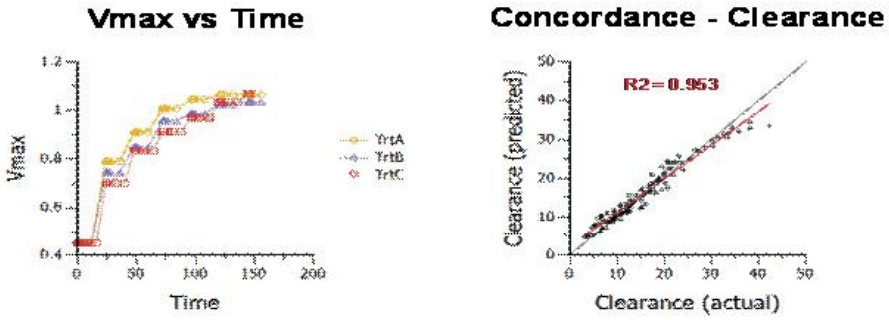
$$\theta = \overline{\theta} + W(T_i) \quad \text{or} \quad \frac{d\theta}{dt} = dW_\theta, \quad W(0) = \overline{\theta}$$

Solve the Mixed Effects model using appropriate tools.





Methods: The random process being estimated are uncoupled from the differential system and are additive, the inclusion of a random process in a model can be easily accomplished. This work demonstrates how to estimate a time-variant parameter as a Wiener process using the mixed effects modeling framework. One way to accomplish this is to include a random process in the model. Previous work has focused on modeling PKPD systems using stochastic differential equations. This approach allows for randomness in the model, but requires some specialized knowledge on the part of the modeler and some uncommon or customized tools
Results: The random process mixed effects approach, however, has fewer limitations than deconvolution. Specifically, the response model is not limited to linear, time-invariant cases. A case study is presented where estimation of fraction absorbed over time is the desired endpoint. A typical approach to this problem is to deconvolve the drug absorption rate from a known response function (PK model). The deconvolution approach is compared to the mixed effects approach with the random process model, and the results are found to be nearly identical. This approach is also useful for estimating time-varying parameters other than system inputs that is, parameters in the PK model itself. This is demonstrated in a second case study where a time varying clearance is estimated for a simulated dataset, with the clearance varying due to induction of metabolizing enzymes and competitive inhibition by a metabolite. The resulting estimate of the time course of the clearance parameter compares favorably with the simulated profile and could be used to identify an empirical model for clearance. Furthermore, modeling the clearance as a random effect allows for the selection of a simpler PK model, reducing bias in the estimated parameters. The figure shows the time course of the vmax parameter and the corresponding prediction of clearance. A case study is presented where estimation of fraction absorbed over time is the desired endpoint. A typical approach to this problem is to deconvolve the drug absorption rate from a known response function (PK model). The deconvolution approach is compared to the mixed effects approach with the random process model, and the results are found to be nearly identical.



Conclusions:

It can be used to extend the applicability of a deconvolution-like analysis or as an intermediary modeling step to identify simple models for complex hidden processes. Moreover, the analysis is accomplished using commercially available software that is available to any PKPD (pharmacokinetic pharmacodynamic) modeler. Modeling a parameter as a random process is a useful tool for PKPD modeling. It enables the scientist to quantify fluctuations in the parameter value and form hypotheses about the causes of such fluctuations

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