

The influence of parameterisation on local identifiability



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Background

- PKPD models are becoming increasingly complicated.
- Assessment of identifiability of both fixed and random effects parameters is important to ensure model validity.
- A numerical method was recently introduced for mixed effects models [1] that is based on computation of the Fisher Information matrix (M_F).
- The link between fixed effect parameterisation and random effect identifiability is not well understood.

Aim

To explore the influence of parameterization on the identifiability of a (simple) nonlinear mixed effects model.

Theory

- Numerical, local structural identifiability for fixed effects models has been established previously [2], where $|J'| = 0$ for unidentifiable models (J = Jacobian).
- This can be extended to mixed effects models, where the following relationship has been applied,

$$\forall \xi: |M_F| \xrightarrow{\sigma^2 \rightarrow 0} \Psi,$$

where $\Psi > 0$ and ξ is an $n \times 1$ vector of design points (Fig. 1).

- In cases where $unique(n) > p + 1$ (p is the number of fixed effects parameters), the model is said to be deterministically identifiable.

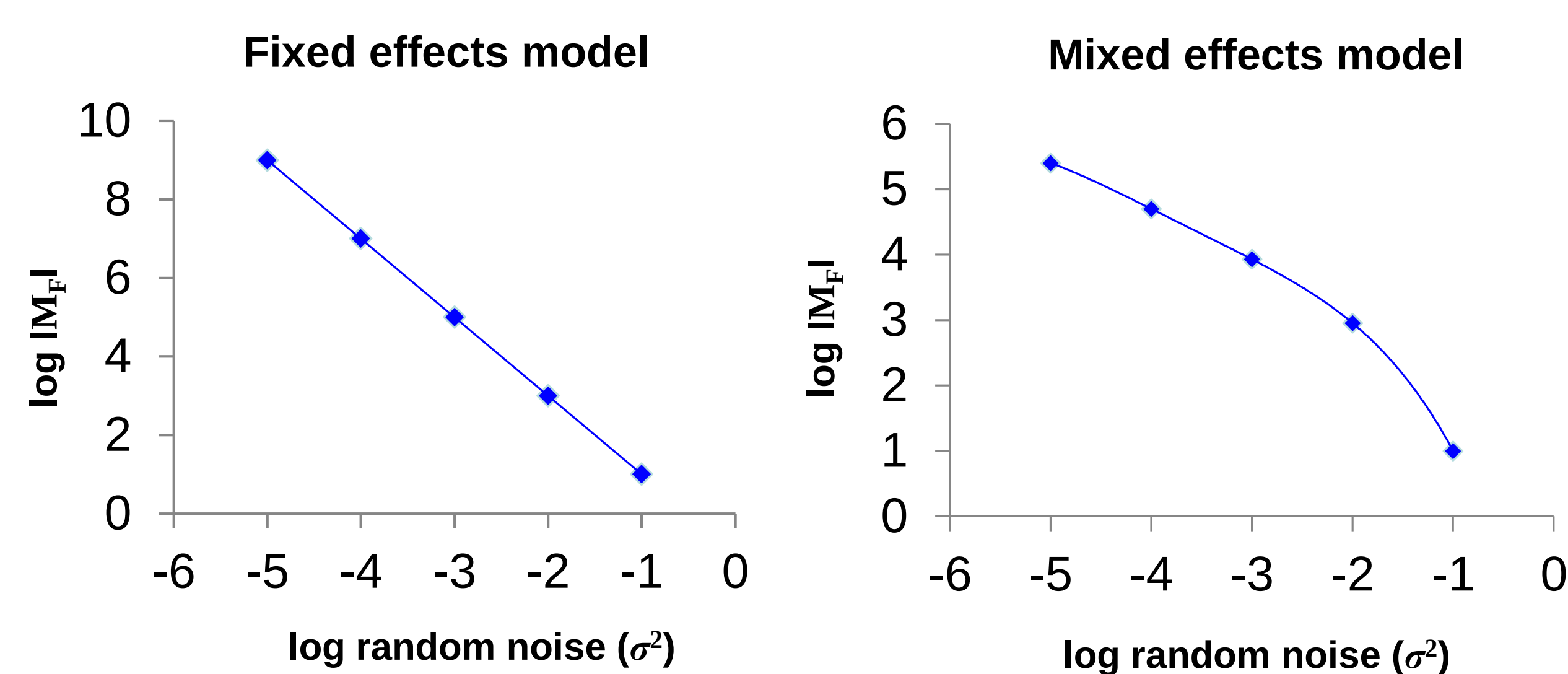


Figure 1. Illustration of locally identifiable model

Two conditions are needed for identifiability (Fig. 1 & Fig. 2)

- $\log |M_F|$ should have a continuous relationship with $\log$ random noise
- $\log |M_F|$ should approach Ψ as the noise approaches zero.

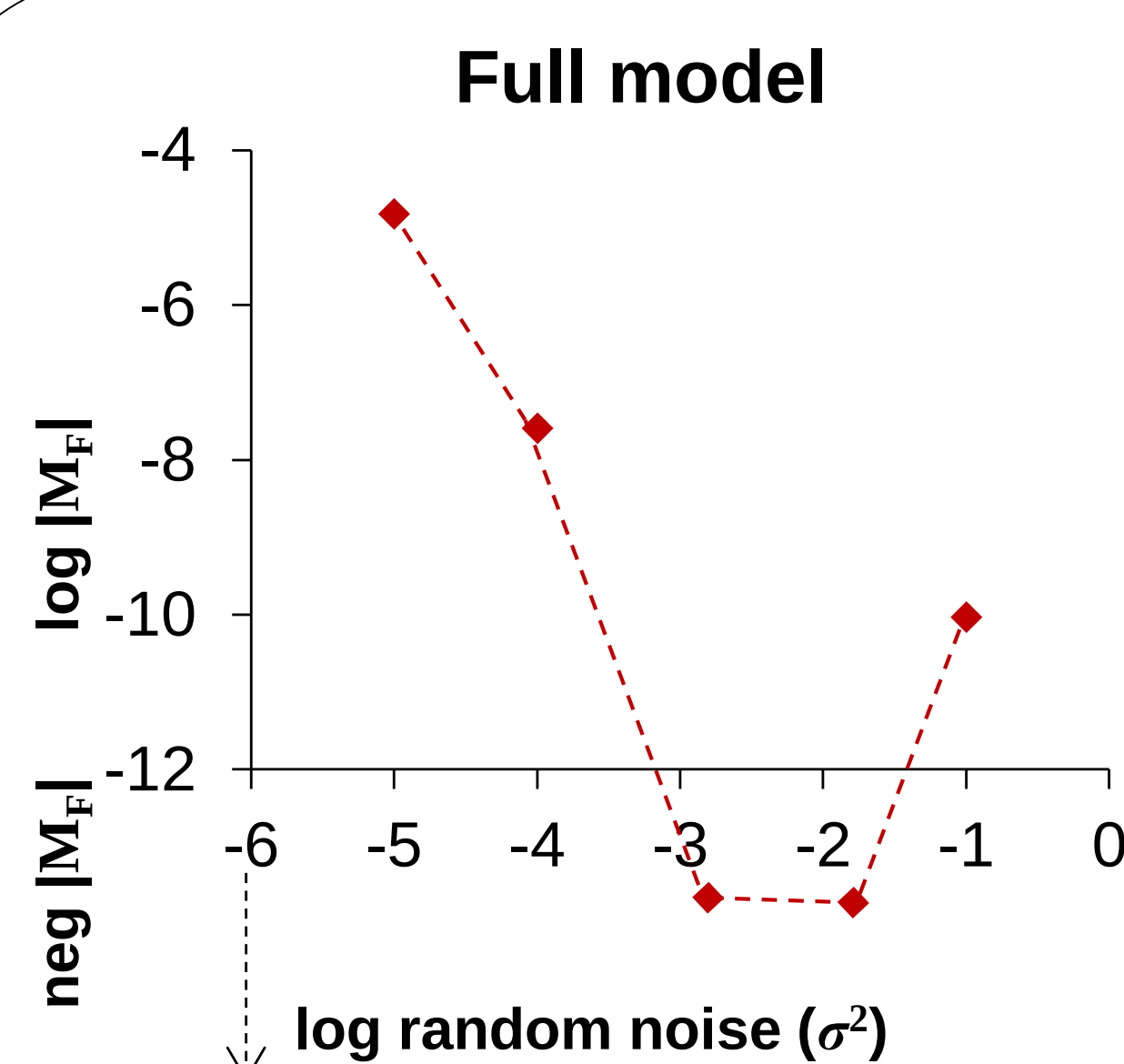


Figure 2. Illustration of a locally unidentifiable model. Here the relationship is discontinuous and contains negative values of the determinant

Methods – Parameterisation

- We choose a simple one-compartment first-order input first-order elimination model.

$$C(t) = \text{dose} \cdot F \cdot \frac{1}{V} \cdot \frac{k_a}{(k_a - k)} \cdot (e^{-k_a \cdot t} - e^{-k \cdot t})$$

- We consider two (of the three) possible fixed effects parameterisations of this model,

(i) $\{CL, V, k_a, F, \omega_{CL}^2, \omega_V^2, \omega_{k_a}^2, \omega_F^2, \sigma^2\}$, where $k = \frac{CL}{V}$

(ii) $\{k, V, k_a, F, \omega_k^2, \omega_V^2, \omega_{k_a}^2, \omega_F^2, \sigma^2\}$

Results – Local Identifiability

In this simple model we see that:-

Parameterisation 1 (CL, V):

- The fixed effect F is not identifiable, ω_F^2 is identifiable
- Note if any one of F, CL, V is fixed the model is identifiable
- When $Cov(CL, V)$ is estimated then ω_F^2 is not identifiable
- The model is identifiable when F and either $Cov(CL, V)$ or ω_F^2 are fixed

Parameterisation 2 (k, V):

- Either the fixed effect F or V is identifiable but not both
- Either ω_F^2 or ω_V^2 is identifiable but not both (Fig. 3)
- Either F or V and either ω_F^2 or ω_V^2 are required to be fixed
- When $Cov(k, V)$ is estimated both F and ω_F^2 are required to be fixed
- When F and $Cov(k, V)$ are fixed ω_F^2 is still not identifiable

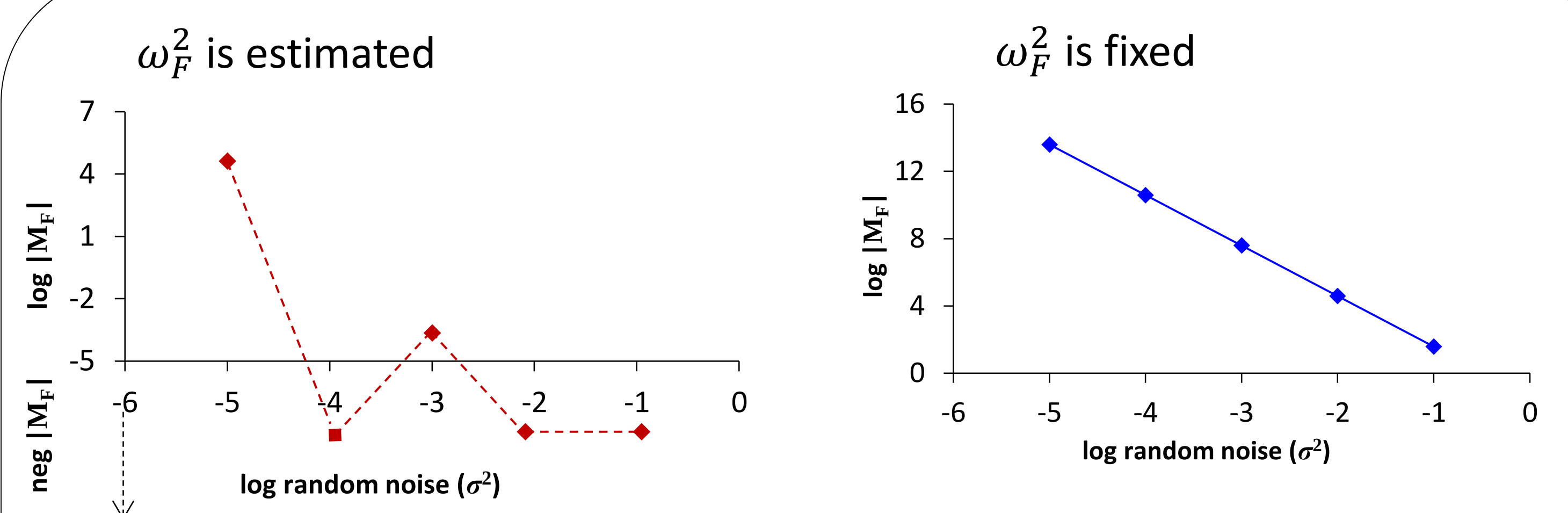


Figure 3. ω_F^2 cannot be estimated when the model is parameterised as V, k, k_a, F

Discussion

- Identifiability is important but not always obvious (even for simple models).
- Identifiability of random effects models sometimes follows that of their fixed effects component ... but not always.
- Parameterisation may appear to be a personal choice – but will affect the validity of your model.
- Download software (popt-i) to do mixed effects identifiability www.pharmacometrics.co.nz/

References

1. Shivva et al CPT:PSP 2013,2(6):1-9; e49, doi:10.1038/psp.2013.25

2. Jacquez et al Math Biosci 1985;77:201-227;