Identifiability in mixed effect models: the example of the *in vitro* erythroid differentiation

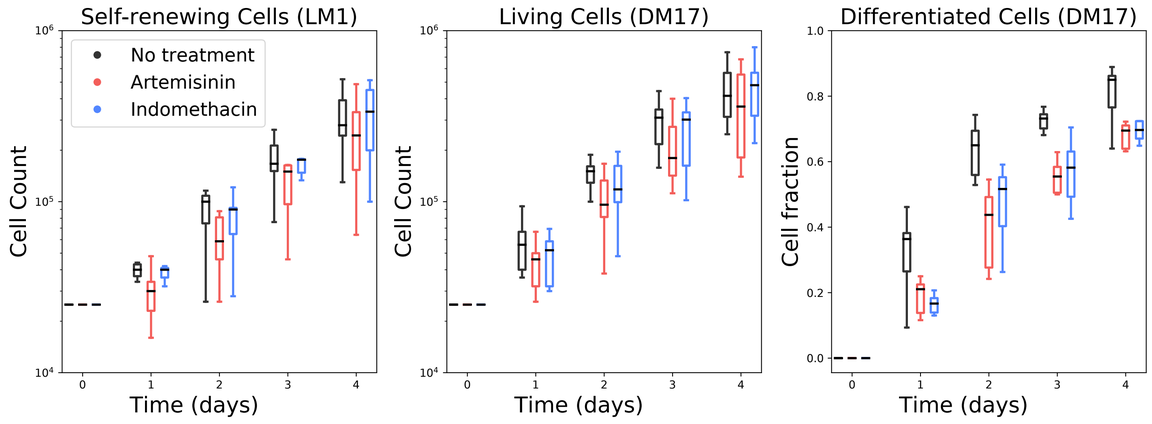
Ronan Duchesne[1,2], Anissa Guillemin[1,3], Fabien Crauste[4], Olivier Gandrillon[1,2]
ronan.duchesne@ens-lyon.fr

1: LBMC (ENS Lyon)
2: Inria team Dracula
3: MIG (Melbourne)
4: IMB (Bordeaux)

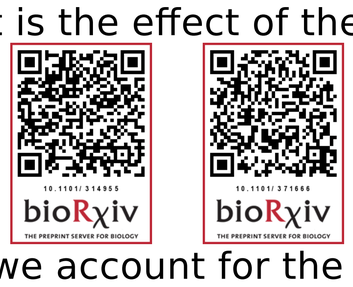
Take-home messages:

Our problem: How to define or improve identifiability in mixed effect models?
Our approach: We used a sampling of the initial guess of parameter estimates to detect unidentifiabilities in the fixed effects, and shrinkage to detect unidentifiabilities in the random effects.
Our results: We found correlations between the fixed effects which allowed us to simplify their structure. Then, we removed the random effects by decreasing shrinkage. We obtained a model with improved parameters estimates, while keeping the quality of the fit of the original, unidentifiable model.
What's next? Is this approach model-specific?

Introduction



What is the effect of the drugs?

↳ 

Can we account for the heterogeneity of cell kinetics?

Model definition

Dynamical model

$$\frac{dS}{dt} = \rho_S S(t) - \delta_{SC} S(t),$$
$$\frac{dC}{dt} = \rho_C C(t) + \delta_{SC} S(t) - \delta_{CB} C(t),$$
$$\frac{dB}{dt} = \rho_B B(t) + \delta_{CB} C(t).$$

Parameters:
ρ_S, δ_{SC}, ρ_C, δ_{CB}, ρ_B

Observables:
S (self-renewing cells)
S+C+B (living cells),
B (differentiated cells)

Parameter model

$$\rho_{i,k} = \rho_i^{pop} + \eta_k,$$
$$\eta_k \hookrightarrow \mathcal{N}(0, \omega_{\rho_i})$$

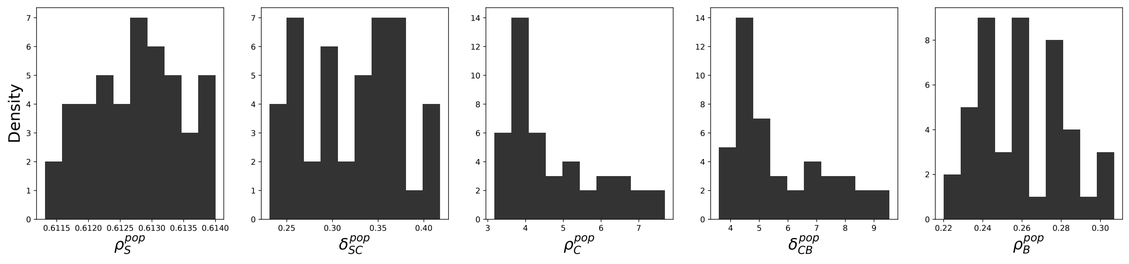
$$\Rightarrow \rho_i \hookrightarrow \mathcal{N}(\rho_i^{pop}, \omega_{\rho_i})$$
$$\delta_{ij} \hookrightarrow log\mathcal{N}(\delta_{ij}^{pop}, \omega_{\delta_{ij}})$$

Error model

For a prediction $\hat{y} = f(t, y_0, \theta)$ of data y with initial condition y_0,
$$y \hookrightarrow \mathcal{N}(\hat{y}, b.\hat{y})$$

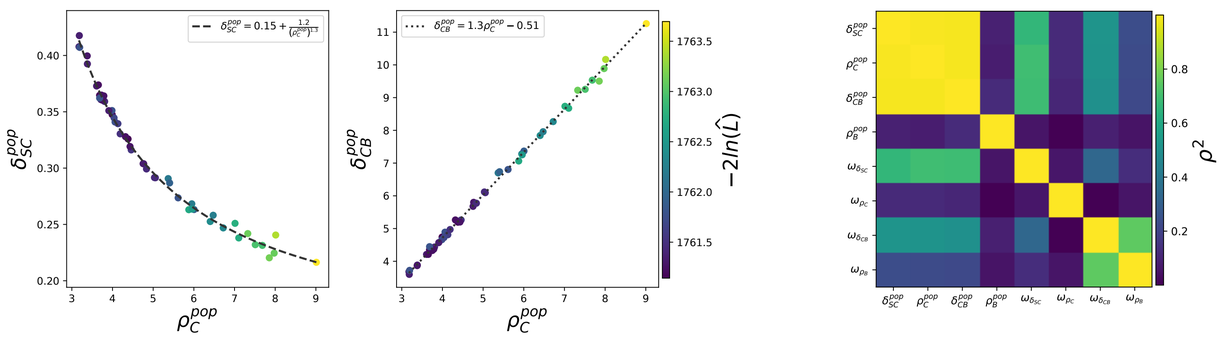
Fixed effects reduction

Population parameters identifiability



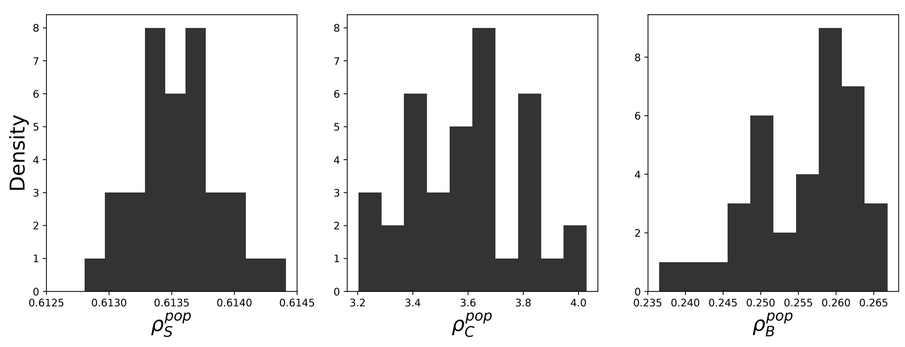
Different population parameters render the same likelihood.
↳ Some population parameters are unidentifiable.
$(\delta_{SC}^{pop}, \rho_C^{pop}, \delta_{CB}^{pop}, \rho_B^{pop}, \omega_{\delta_{SC}}, \omega_{\rho_C}, \omega_{\delta_{CB}}, \omega_{\rho_B})$

Population parameters correlations



There are correlations between optimal population parameters.
↳ We can use them to reduce the model.

Reduced model



The variance of the fixed effects estimates is reduced.

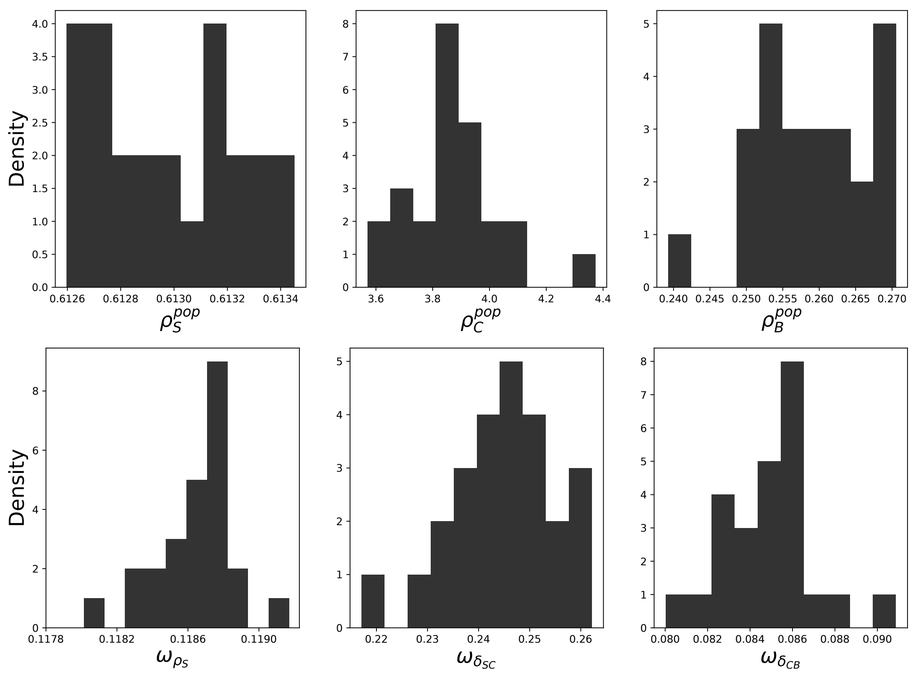
Random effects reduction

Shrinkage in the reduced models

Random Effects	s_{ρ_S}	$s_{\delta_{SC}}$	s_{ρ_C}	$s_{\delta_{CB}}$	s_{ρ_B}	$-2ln(\mathcal{L})$
5	2%	28%	65%	43%	57%	1761
4	3%	27%	-	43%	48%	1761
3	2%	28%	-	21%	-	1761

We have to remove two random effects to push all shrinkages below 20%.

Population parameters in the final model



All population parameters now have a reduced variance.

Quality of the fit