**Supplementary material S1**

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**Supplementary Material S2.**

*Comparison of models elaborated using the GLM and Mixed procedures of SAS.*

To evaluate the use of our models for predictive purposes beyond their strict range of validity, we also analyzed the data with the MIXED procedure of SAS software. The comparison of models is presented in Supplementary table S7.Model parameters were not significantly modified by the choice of fixed vs. mixed procedures, except for the BHBA models for which the variance-covariance matrix (obtained by the COVTEST option of the SAS system) differed. For the BHBA models from RfOMI and EB, coefficients for EB2 were statistically different. Differences were mostly due to the effect of the animal physiological status on the slope associated to EB², which are highly different between the models. For example, the effect of the ‘growing’ status associated to the slope was equal to -0.000721 ± 0.00013 (*P* < 0.0001) with the GLM model whereas it was equal to -0.00166 ± 0.000264 (*P* = 0.0002) with the MIXED model. Furthermore, when removing the interaction term (EB × PHY), the Mixed and GLM models were not statistically different:

Mixed model: NHF-BHBA = 0.0574ns ± 0.0656 + 0.0146\* ± 0.0058 × RfOMi + 0.000366\*\*\* ± 0.000083 × EB²

GLM model: NHF-BHBA = 0.0763ns ± 0.0541 + 0.0147\*\* ± 0.0049 × RfOMi + 0.000344\*\*\* ± 0.000051 × EB²

This clearly demonstrates that the difference between the Mixed and GLM models is due to the influence of physiological status on the slope of EB2. This is probably due to an unbalanced number of observations in each physiological status. In particular the number of available data in lactation (when the cow mobilized energy) is low. Supplementary Figure S2 shows the effect of physiological status on the slope EB of the model and illustrates the greatest difference obtained for the dairy cows. In these animals, observed values (Supplementary Figure S3) ranged from 0.143 to 0.70 mmol/h/kg BW.

Evidence was obtained that the Mixed model does not correctly predict the influence of physiological status on the EB2 slope. We predicted the net hepatic release of beta-hydroxybutyrate with the GLM and Mixed models using the same data as those used to establish the models as shown in Supplementary Figure S4 (it is a way to check if models are biased). Results indicate that the Mixed model largely overestimates the net hepatic release of beta-hydroxybutyrate in the dairy cows. Therefore, at this stage of the study, we consider it is not really appropriate to generalize the model with the Mixed procedure, and suggest to keep the GLM model waiting for additional data on dairy cows.

Supplementary Table S1: Comparison of GLM and Mixed models of responses of net hepatic and net splanchnic fluxes of acetate (NSR-C2), butyrate (NHF-C4) and ß-hydroxybutyrate (NHF-BHBA) to variations in net portal appearance (NPA), rumen-fermentable OM intake (RfOMI) or energy balance (EB).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Nutrient | Model | Equations | RMSE | Effect | |
|  |  |  |  | PHY | X \* PHY |
| NSR-C2 | GLM | 0.098 ± 0.175ns + 1.033\*\*\*± 0.077 × NPA-C2 | 0.208 | < 0.0011 | NS |
|  |  | 0.65 ± 0.303 ns + 0.0106\*\*\*± 0.0022 × RfOMI² | 0.399 | < 0.0012 | NS |
|  | MIXED | -0.083 ± 0.261 ns + 1.073\*\*\* ± 0.066 × NPA-C2 | 0.200 | 0.0243 | NS |
|  |  | 0.69 ± 0.42 ns + 0.0107\*\*\* ± 0.0018 × RfOMI² | 0.397 | < 0.0014 | NS |
|  |  |  |  |  |  |
| NHF-C4 | GLM | -0.0056 ± 0.010ns - 0.752\*\*\*± 0.067 × NPA-C4 | 0.010 | 0.045 | 0.026 |
|  | MIXED | 0.0065 ± 0.077ns - 0.864\*\*\*± 0.115 × NPA-C4 | 0.010 | NS | 0.0917 |
|  |  |  |  |  |  |
| NHF-BHBA | GLM | 0.0828 ± 0.0607 ns + 0.6098\*\* ± 0.3096 × NPA-C4 + 0.000779\*\*\* ± 0.000186 × EB² | 0.050 | NS | 0.018 |
|  |  | -0.0212 ± 0.053 ns + 0.0203\*\*± 0.0052 × RfOMI + 0.00083\*\* ± 0.000092 × EB² | 0.035 | NS | <0.0019 |
|  | MIXED | 0.0485 ± 0.0877 ns + 0.593\* ± 0.263× NPA-C4 + 0.00175 ± 0.00031 × EB² | 0.049 | NS | <0.00110 |
|  |  | -0.0732 ±0.0788 ns + 0.0216\*\*\* ± 0.00471 × RfOMI + 0.00180\*\* ± 0.00023 × EB² | 0.034 | NS | <0.00111 |

RMSE = Residual means square error for the GLM models and Residuals for the MIXED models; PHY = physiological status effect

1 physiological status effect on the intercept: Δ=0.294 for growing animals and -0.144 for gestation

2 physiological status effect on the intercept: Δ=-0.699 for non-productive adults, 0.555 for growing animals, -0.492 for gestation and 0.636 for lactation.

3 physiological status effect on the intercept: Δ=0.394 for growing animals

4 physiological status effect on the intercept: Δ=0.411 for gestation, and 0.390 for growing animals

5 physiological status effect on the intercept: Δ=-0.035 for growing animals

6 physiological status effect on the slope: Δ=0.264 for growing animals

7 physiological status effect on the slope: Δ=0.266 for growing animals

8 physiological status effect on the EB² slope: Δ=-0.00071 for non-productive adults, and 0.00098 for lactation

9 physiological status effect on the EB² slope: Δ=-0.00041 for non-productive adults, -0.00065 for growing animals, and 0.00106 for lactation. Gestation was not determined.

10 physiological status effect on the EB² slope: Δ=-0.00141 for non-productive adults, -0.00166 for growing animals, and 0.00307 for lactation.

11 physiological status effect on the EB² slope: Δ=-0.0017 for non-productive adults, -0.00149 for growing animals

Supplementary Figure S1. Adjusted models of the prediction of the net hepatic release of β-hydroxybutyrate from rumen-fermentable OM intake and energy balance, according to the physiological status of the animal. The solid lines represent the predicted values by GLM model, the dotted lines represent predicted values by MIXED model

Supplementary Figure S2. Observed range of variation of net hepatic release of β-hydroxybutyrate

Supplementary Figure S3. Relationship between predicted (from rumen-fermentable OM intake and energy balance) and observed values of net hepatic release of β-hydroxybutyrate depending on the model used for the prediction (GLM or MIXED)

Supplementary Figure S1

Supplementary Figure S2



Supplementary Figure S3