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Dear Editor,

We would like to submit our manuscript entitled «Exploring metabolism flexibility in complex organisms thanks to a quantitative study of precursor sets of a system outputs» by Oumarou Abdou-Arbi, Sophie Lemosquet, Jaap Van Milgen, Anne Siegel and Jérémie Bourdon for publication in BMC Systems Biology.

When studying a metabolism at the organ scale, a major issue is to elucidate matter exchanges between components of the system. This possesses major applications when studying milk component synthesis. Based on a biochemical description of the mammary gland metabolism, the challenge is here to predict how nutrient inputs spreads over the output components. This problem, commonly referred as «yield computation», is addressed by fixing some flux distribution (under the basis of observations) and following recursively the precursors of the outputs in the metabolic network. Such a developed approach is questionable because of the «arbitrary» choice of the flux distribution and due to some numerical issues in the recursive process implied by the presence of cycles in the metabolic network.

In the paper, we revisit the problem of yield computations by providing a formal definition to the quantitative allocation of input nutrients over the branches of the metabolic networks and more specifically over the output products (AIO). The algebraic form of this definition allows its precise computation by efficient algorithms. We finally explore several ways of dealing with such an allocation without making any hypothesis on the objective function to describe the system functioning in the context of milk production for dairy cows. As a major issue, we developed a non linear optimization framework allowing to report the intervals of extremal values taken by the AIO. This allowed discriminating the effect of nutritional treatments.

Altogether, the complete study suggests a strong flexibility which can be studied although its internal optimization functioning still cannot be elucidated because of limitations of experimentations over big animals. This method is the core of our NutritionAnalyzer web application. This application is freely available at <http://nutritionanalyzer.genouest.org>.

Some useful supplementary material is available at

<http://nutritionanalyzer.genouest.org/SupplementaryMaterial>

The access to this resource is currently protected but we aim at diffuse the data and models in a near future. Here is a temporary login and password pair : login= SuppMat passwd= tamppuss.

Thank you for your time and effort in considering our manuscript.

On behalf of the authors, your sincerely,

Anne Siegel
(Research Director, CNRS,
Leader of the system biology Team Dyliss,
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