

Tick-tock – Circadian regulation of liver metabolism represented in a kinetic model

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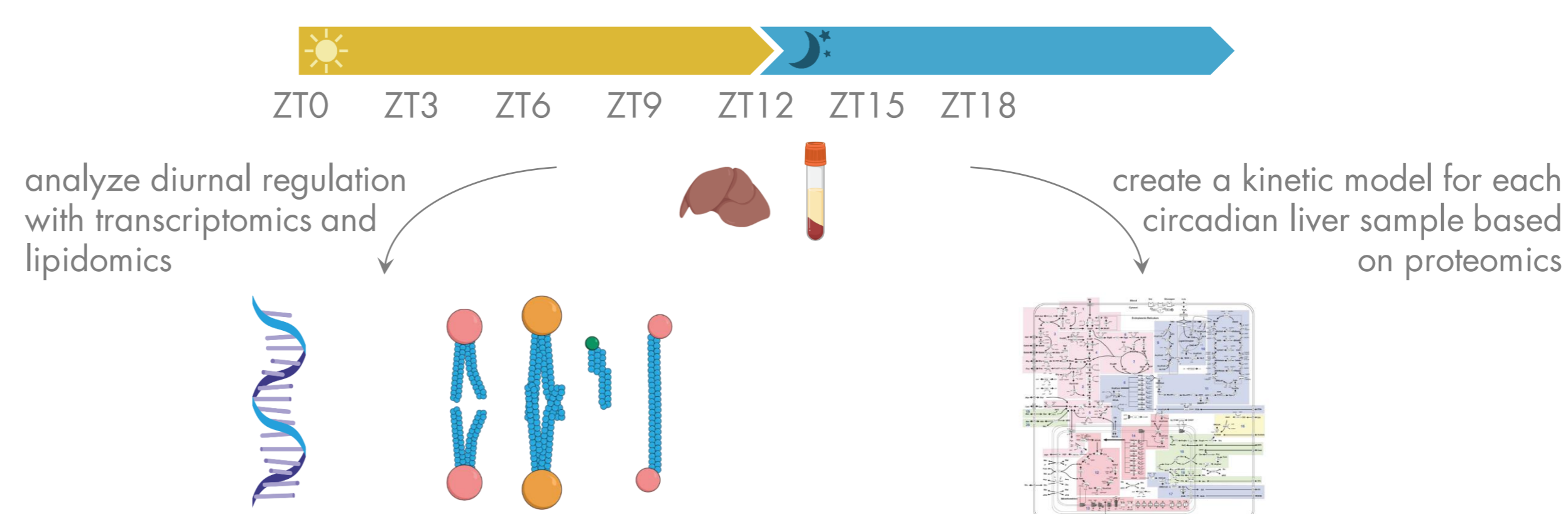
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BACKGROUND

The circadian rhythm is a decisive regulator for metabolic homeostasis especially in the liver. The importance of diurnal control is highlighted by the increased risk of liver diseases, obesity and metabolic syndrome due to disturbance of circadian rhythms. However, time resolved *in vivo* studies of liver metabolism are rare and molecularly resolved, kinetic models can be used for metabolic phenotyping based on proteomic data, enabling linking circadian rhythmicity of protein abundances to metabolic regulation.

METHODS

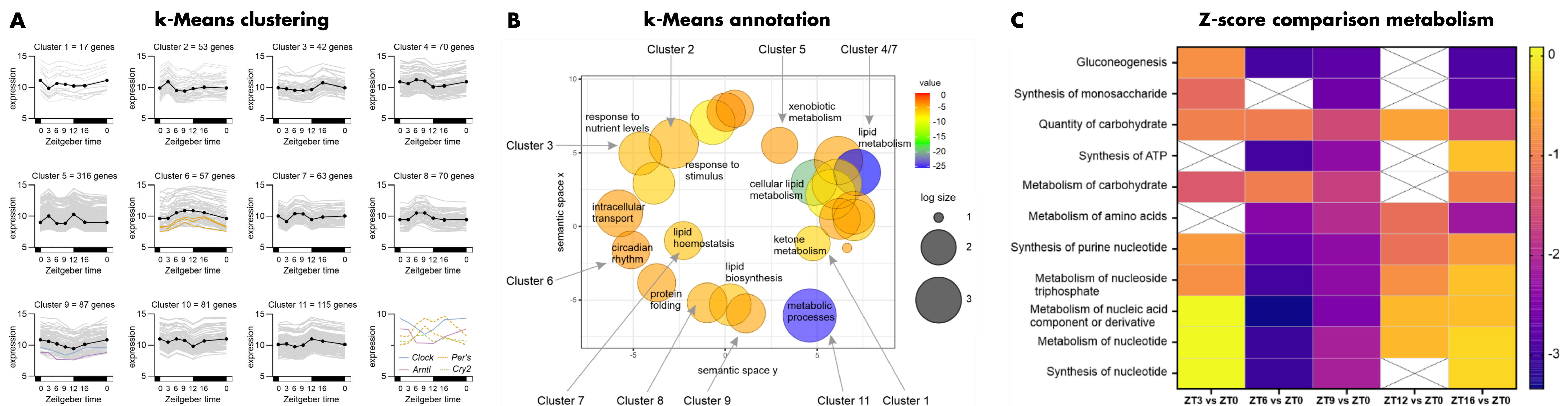


We investigated the rhythmicity of liver metabolism in male C57BL/6N mice using kinetic models (based on HEPTOKIN1, Berndt et al. 2018) for liver samples isolated throughout a day. Additionally, we performed transcriptomics and lipidomics analysis.

RESULTS

Transcriptomics Microarray from liver tissue isolated at indicated time points (n = 3-4 each). Expression changes ≥ 2 -fold between at least two time points were considered for further analysis.

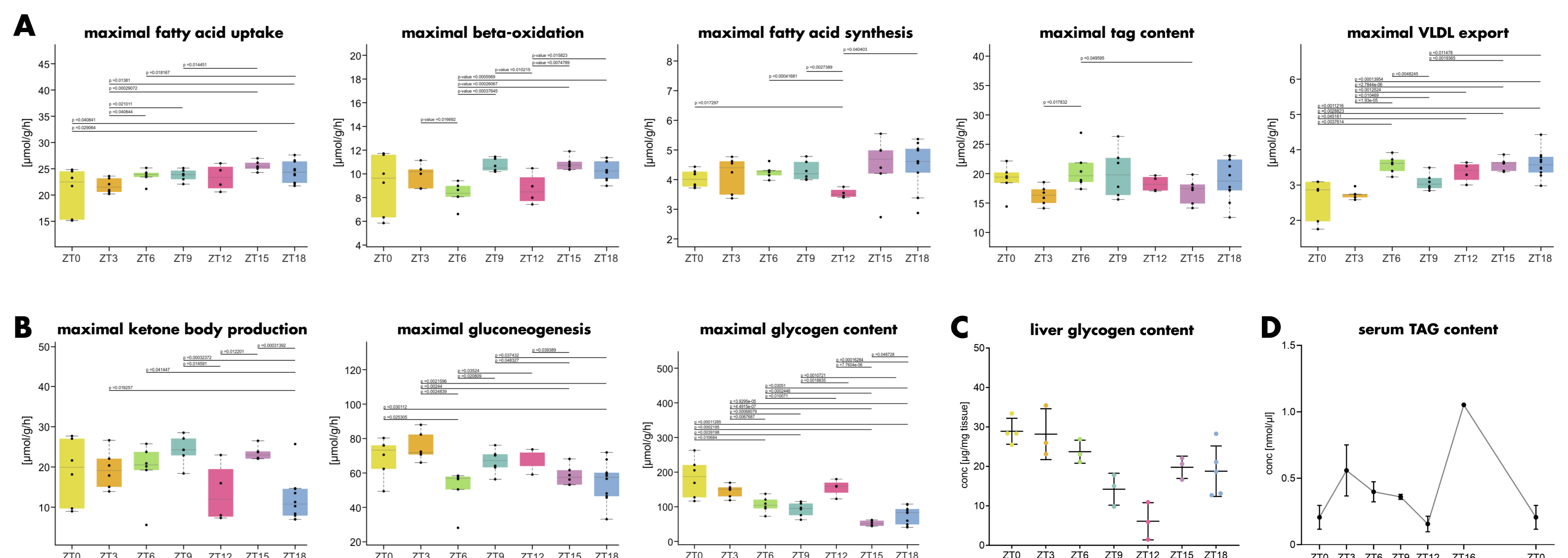
A – k-Means clustering revealed eleven clusters with specific diurnal expression profiles (based on silhouette index the optimal number of clusters was defined). The expression of the genes of the primary negative feedback loop, the molecular master circadian regulators, is highlighted in color and presents the typically alternating curves. **B** – The annotation of the genes summarized in the eleven clusters illustrates the diurnal regulated metabolic liver functions. **C** – Z-score analysis reveals the circadian regulation of liver metabolism in more detail. Z-Score analysis relative to ZT0.



Metabolic Modelling Individual kinetic models for each tissue sample were generated. The maximal metabolic capacities were calculated based on the protein concentrations (gained by proteomics) applied on the diurnal setting of the model HEPATOKIN1.

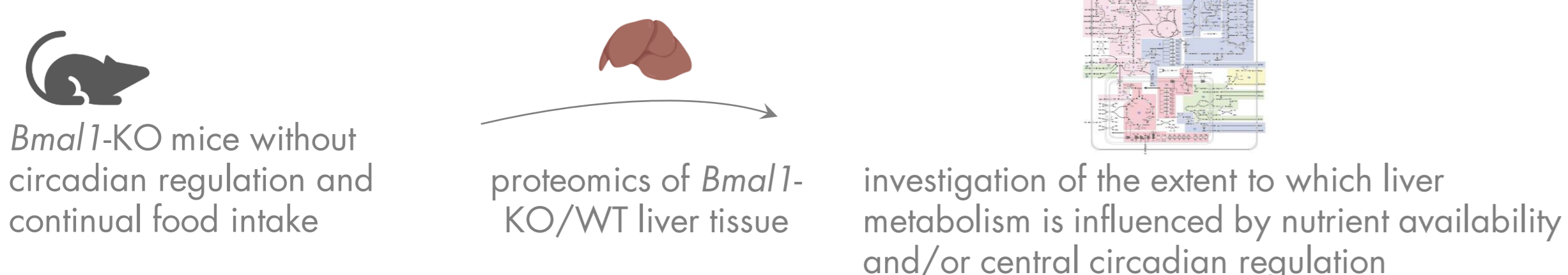
A – Maximal metabolic capacities for fatty acid related metabolism. **B** – Maximal metabolic capacities for carbohydrate related metabolism.

C – Quantification of glycogen content in liver tissue shows a maximum in the starved stage and decreasing content during the day, similar to the modelled maximal glycogen content. **D** – Analysis of circulating lipids in serum. Serum TAG content represents the lipids secreted by adipose tissue and liver and partly reflects the modelled maximal VLDL export.



PROSPECTIVE AND CONCLUSION

Prospective



Conclusion

The model helps to better understand whether circadian rhythms are intrinsic and independent of nutrient availability or follow diurnal dietary patterns. By accounting for the circadian regulatory properties of all enzymes, our model integrates the accumulated knowledge from decades of biochemical research and allows quantitative predictions of system behavior as a function of circadian rhythmicity.