Meal-induced (post-prandial) **Blood Glucose** responses

In this example, we observe three clearly-defined fluctuations in **Blood Glucose** that correspond to breakfast, lunch, and dinner (marked as t_m on the x-axis).

Circadian fluctuations in Blood Glucose

Blood Glucose is also affected by the time of day— relative to the circadian rhythm. Evidence in the literature shows that significant changes in blood glucose occur in healthy individuals throughout the circadian cycle.

There are several disorders— commonly comorbid with diabetes— that are broadly referred to as metabolic syndrome that primarily manifest as some form of disruption of healthy circadian metabolic dynamics.

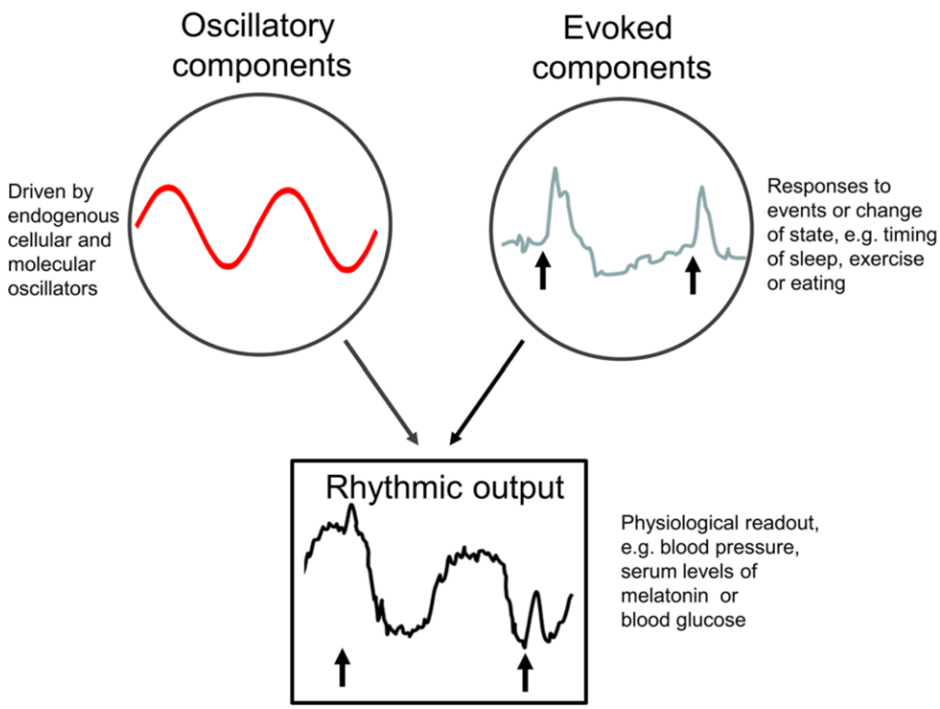

FIGURE 1 Oscillatory and evoked components contribute to rhythmic outputs. Daily rhythms in physiology (such as blood pressure, glucose, hormone levels, and the rates of distribution, metabolism and excretion of substances) are a composite of both internal oscillatory components driven by cellular and molecular clocks and evoked components in response to external stimuli or behavioural change. Understanding these relative contributions allows for them to be targeted by circadian medicine. Adapted from Klerman and Czeisler *Recent Progress in Hormone Research* 1999.

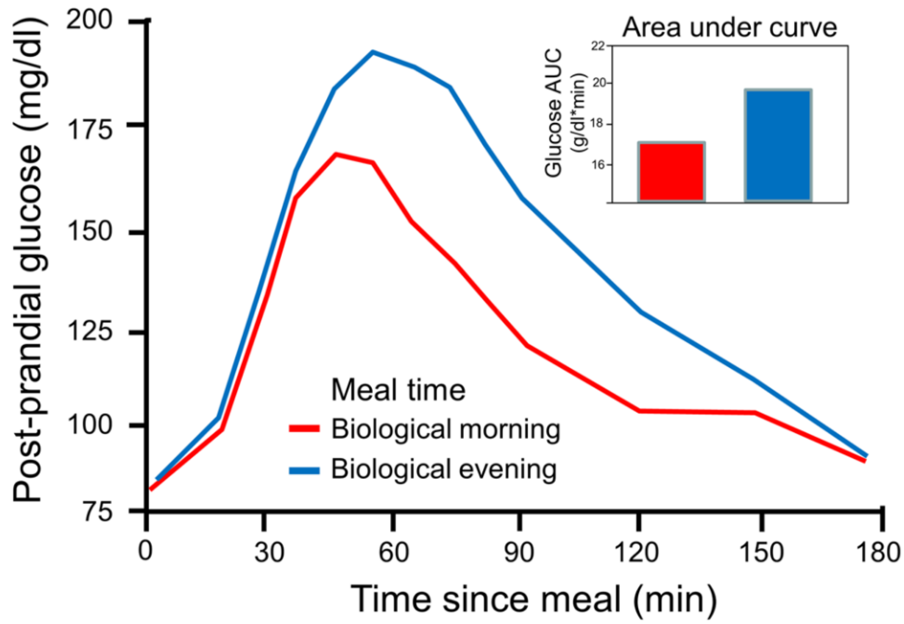

FIGURE 2 Meal timing relative to the circadian clock influences blood glucose levels. Postprandial glucose profiles differ depending on whether a nutritionally identical meal is consumed in the biological morning (red) or biological evening (blue), with impacts not only on the temporal profile of blood glucose levels but also on the cumulative total blood glucose (area under curve shown in inset). This highlights the importance of circadian timing on human health and disease management (such as diabetes). Adapted from Morris, C. J., et al., *Proceedings of the National Academy of Sciences* 2015.

(Klerman et al., 2022)

Health relevance of **Cortisol**, **Melatonin** signals

Cortisol & **Melatonin** can be thought of as opposing forces.

Melatonin is released by the pineal gland as part of the onset of sleep to peak around midnight. **Melatonin** deficiency can cause a decrease in sleep quality/duration.

Cortisol in contrast is an endogenous "wake-up call" that peaks around 7AM (sunrise). Without sufficient **Cortisol**, patients can feel lethargic even if they've had decent sleep.

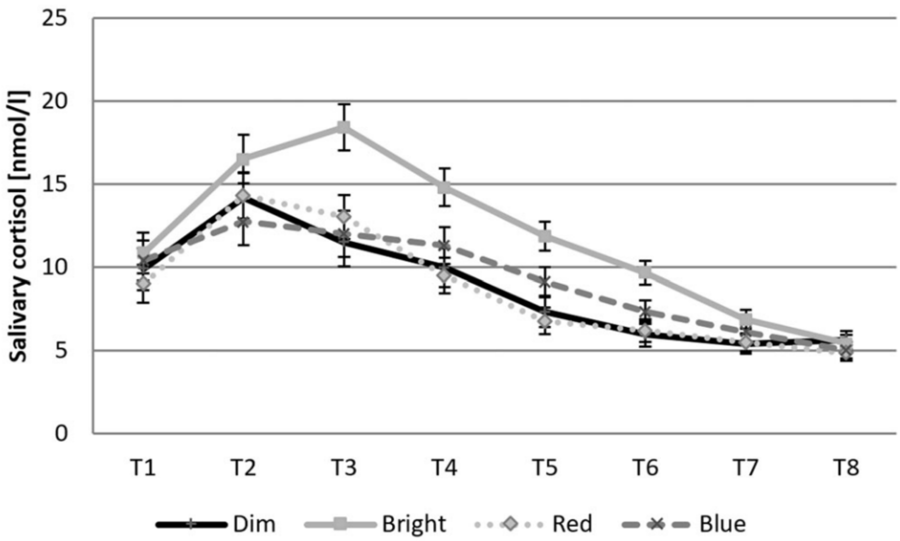

Figure 2. Mean (± SE) salivary cortisol levels across measurement points for dim white, bright white, blue and red light conditions.

(Petrowski et al., 2021)

Computational modeling of chronometabolic pathways

This example chronometabolic model of circadian-ultradian glucose dynamics is a representative implementation of the physiofunctional framework. By definition, the model therefore incorporates the health-relevant physiology. This is accomplished by careful quantification of a few key biophysical relationships— namely the interdependence of glucose and the endogenous hormones Cortisol, Melatonin, and Adiponectin.

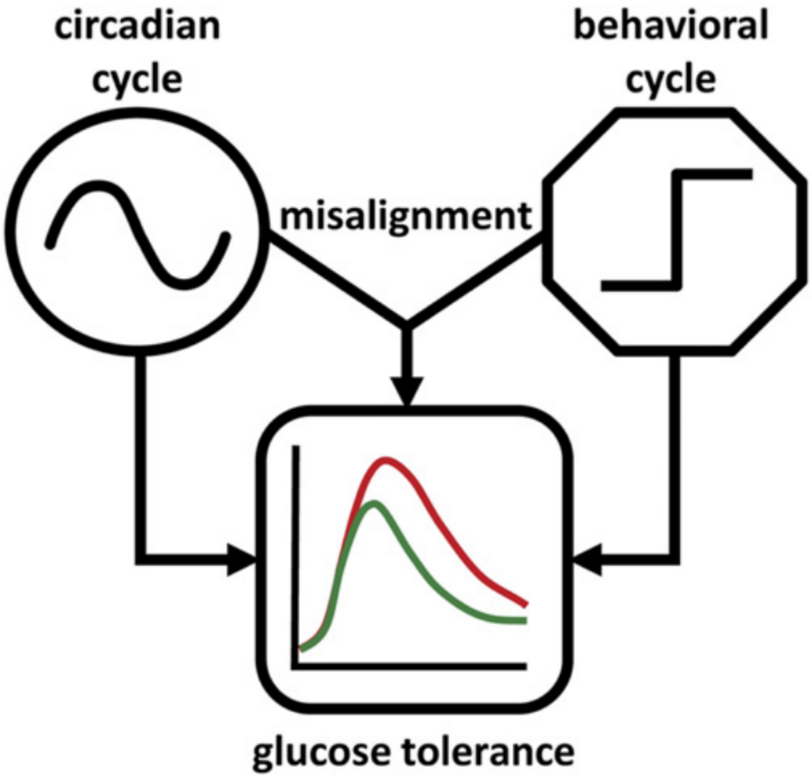

Fig. 1. Schematic diagram of the separate effects of the endogenous circadian system, the behavioral cycle, and circadian misalignment (interaction between the circadian cycle and behavioral cycle) on glucose tolerance. In addition, our analysis tested whether the effects of the endogenous circadian system, behavioral cycle, and circadian misalignment on glucose tolerance were dependent on circadian misalignment exposure duration (acute vs. repeated).

(Morris et al., 2015)

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