# Supplementary Table

Table 1: List of parameters tested for Morris Method

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Value** | **Units** | **Description** |
| kg2 | 2 | nM.h-1 | Rate of PGC-1α mRNA degradation |
| kg10 | 5 | h-1 | Rate of FOXO1 deactivation |
| kg9 | 3 | h-1 | Rate of FOXO1 activation |
| kg1 | 2 | nM.h-1 | Rate of PGC-1α transcription |
| kg3b | 3 | h-1 | Rate of PGC-1α translation |
| kg3d | 3 | h-1 | Rate of PGC-1α degradation |
| kg3t | 2 | h-1 | Rate of PGC-1α nuclear import |
| kg4t | 2 | h-1 | Rate of PGC-1α nuclear export |
| kg5 | 0.1 | h-1 | Rate of PGC-1α activation |
| kg12 | 3 | h-1 | Degradation rate of gluconeogenic genes mRNA |
| kg11 | 70 | h-1 | Transcription rate of gluconeogenic genes |
| kg8 | 0.8 | h-1 | Rate of active PGC-1α degradation |
| sirtT | 5 | μM | Sum of active and inactive SIRT1 |
| GRT | 1.81 | nM | Total GR concentration(33) |
| kon,GR | 1 | L.nmol-1.h-1 | Second order rate constant of mineralocorticoid and receptor binding(47) |
| kre,GR | 1 | h-1 | Rate of mineralocorticoid receptor recycling from nucleus to cytoplasm(47) |
| kg7 | 1 | nM | Inhibition constant for binding of cortisol-receptor complex to GRE |
| k1i | 0.56 | nM | Inhibition constant of Per-Cry transcription(10) |
| km1 | 5 | 1 | Maximum extent of NADH converting to NAD+ |
| k4b | 2.16 | nM | Michaelis constant of Bmal1 transcription(10) |

# Supplementary Figures

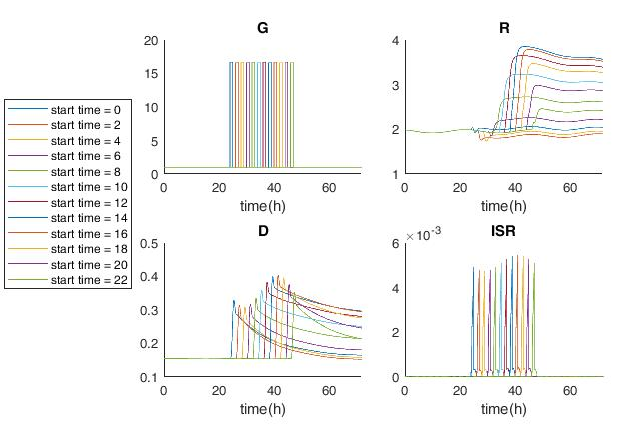


Figure 1: Simulation results for glucose pulse stimulation. G is glucose in mmol/L, R is reserve pool in arbitrary units, D is docked pool in arbitrary units, and ISR is insulin secretion rate in pmol/min

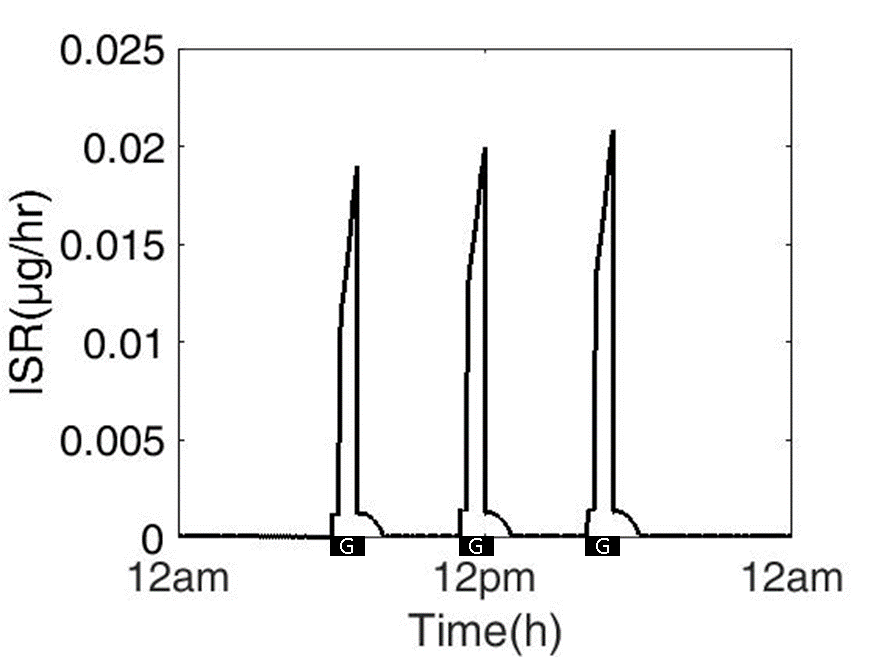


Figure 2: Sample simulation results for 3 meals/day glucose stimulation. Glucose concentration G is in mmol/L (A) and ISR is in μg/hr (B).

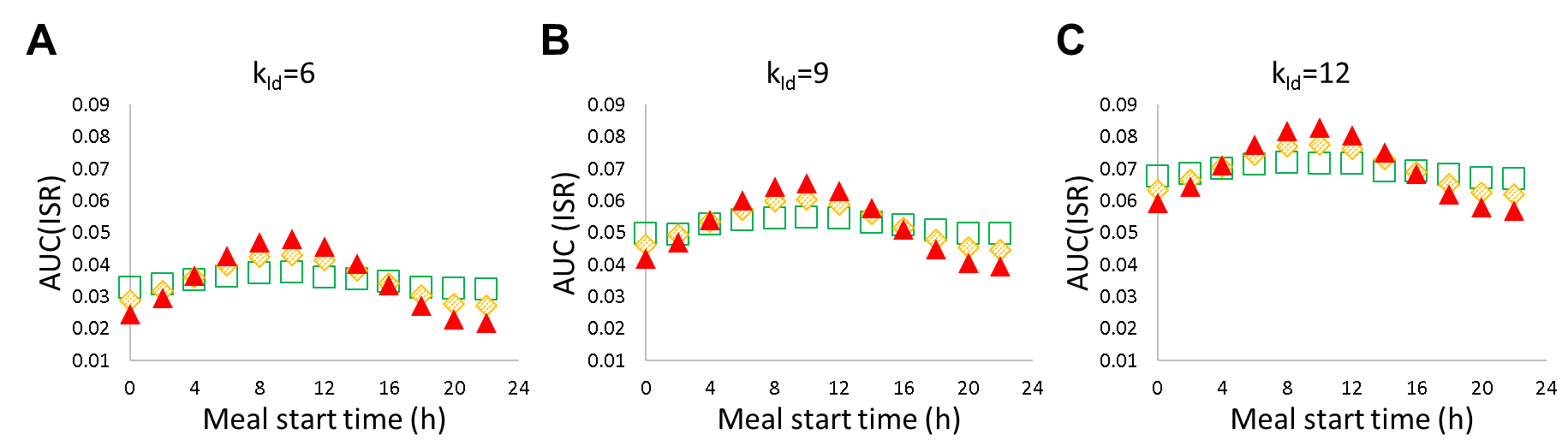


Figure 3: Effect of breakfast start time on AUC of ISR (μg) with differing rhythms of bV. In this figure, k­id is the vertical shift. Low amplitude (kia=1) rhythm is shown in green squares, medium amplitude (kia=3) in yellow diamonds, and high amplitude (kia=5) in red triangles.

# Description of the light/feeding entrained Clock Model

We propose a mathematical model to study the interaction between circadian rhythms and metabolism, represented by the dynamics of the peripheral clocks and the transcription of gluconeogenic genes. This model was built upon our previous works (7, 33, 34), introducing novel elements describing the network of peripheral clocks, cortisol-receptor complex, SIRT1 deacetylation of PGC-1α and FOXO1. The model consists of two compartments: 1) a central compartment receiving the light/dark cycle and feeding/fasting cycle as inputs and processing them via the HPA axis; and 2) a peripheral compartment representing a human hepatocyte expressing the convoluted effects of signaling molecules secreted from the central compartment..

## Central Compartment

The central compartment receives and processes the photic and metabolic cues. The light/dark cycle governs cortisol release from the HPA-axis, consisting of the negative feedback by cortisol on CRH and ACTH (33, 34). The feeding rhythm is processed via a series of transit compartments and eventually regulates the NAD+ oscillations in the periphery. Cortisol and NAD+ together modulate the intertwined network of core clocks and hepatic metabolism.

In our model, the light/dark cycle and feeding/fasting cycle are represented as step functions, similarly to earlier studies (7, 34, 44, 49). Although in nature, light and food do not appear and disappear sharply, laboratory experiments involving time-restricted feeding provide illumination and chow in an on/off manner (15, 25, 54); therefore, step functions are sufficiently representative for recreating laboratory conditions *in silico*, while also contributing to the simplicity of the model. The feeding/fasting rhythm is represented by Equation ( 5 ) of the main text, while light/dark cycle is represented by Equation ( 1 ) of the main text. Under a nominal case where light and feeding are aligned, both light and feed are set to 1 between the hours of 6 am and 6pm. Equations ( 6 ) and ( 7 ) of the main text represent the transit compartment each with a delay (τf) of 3 hours, reflecting the observation that NAD+ level peaks 5-6 hours after the beginning of the active period in rat liver (48). The feed signal through these transit compartments will eventually modify the redox relations between NAD+ and NADH and modify the cellular NAD+/NADH ratio (17).

The light signal regulates the self-sustained oscillations of CRH and ACTH in the HPA axis and the secretion of cortisol from the central compartment to the peripheral compartment (27, 34). Equations ( 2 )-( 4 ) of the main text represent a Goodwin oscillator, which has been modified to include Michaelis-Menten kinetics in the synthesis and degradation of each component to avoid the use of unrealistically high Hill coefficients (22). The photic signal is communicated via the retinal ganglion cells (RGCs) in the eye (38), then the hypothalamic suprachiasmatic nucleus (SCN) integrates the signals and regulates the circadian rhythms of the cortisol and the periphery (18, 55).The SCN mediates secretion of light-induced arginine vasopressin (AVP) (30). Decrease in AVP secretion leads to increased level of cortisol (28), CRH, and ACTH (35). Therefore, we ultimately regulate the production of cortisol by light-induced degradation of CRH in Equation ( 2 ) of the main text. Equation ( 3 ) of the main text describes the secretion of ACTH in the anterior lobe of the pituitary gland stimulated by the production of CRH in the hypothalamus, and Equation ( 4 ) of the main text describes the production of cortisol due to ACTH acting on the adrenal cortex. Then, cortisol negatively regulates CRH and ACTH through receptor mediated activities, completing the negative feedback loop and maintaining sustained oscillations for all three components of the HPA axis. Equations ( 1 )-( 4 ) were derived from a corticosteroid pharmacodynamics model (47), describing the signal transduction pathway involving cortisol-receptor dynamics. In Equation ( 1 ), receptor mRNA dynamics are represented. The indirect response term complies with downregulation of receptor mRNA upon methylprednisolone (MPL) treatment. The receptor protein dynamics is modeled in Equation ( 2 ), while the binding of receptor to cortisol is modeled in Equation ( 3 ). Equation ( 4 ) represents the cortisol-receptor complex translocating to the nucleus where it will inhibit CRH and ACTH secretion. Finally Equation ( 5 ) models the pro-inflammatory cytokines in the HPA axis, which has an HPA-activating effect represented as induction of ACTH and cortisol using indirect response (44).

The feeding signal modifies the HPA axis through a transit compartment variable, EntF, in Equation ( 4 ) of the main text. The transit compartment represents the electric signal from the periphery transmitted to the SCN via ventromedial arcuate nucleus (vmARC). The vmARC is often associated with satiety because metabolic hormones such as ghrelin, leptin, insulin, and their receptors are highly expressed in it and is modulated by them (3, 23, 53, 58) (45, 56, 59). The vmARC forms a complex with the subepidermal layer of the median eminence (seME), and have been shown to have reciprocal connections with the SCN (62). We lumped the above observations into a single transit compartment for simplicity, modifying the cortisol production in the HPA axis in Equation ( 4 ) of the main text. Parameter kn of this equation is the coupling strength of the feeding signal to the HPA axis.

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## Peripheral Compartment

### *Incorporation of Environmental Signals*

The peripheral compartment represents a human hepatocyte, encompassing a network of reactions involving the clock genes, cytokines, and metabolic enzymes in the liver. The dynamics of the peripheral compartment is entrained to the signaling molecules secreted from the central compartment, while also sending information back to the central compartment that modify the HPA-axis activity. Cortisol secreted from the HPA axis is entrained by both the light/dark cycle and the feeding/fasting cycle, while NAD+ is tied to the feeding/fasting cycle. Through transcription, translation, and receptor-mediated activities, these molecules activate a set of downstream reactions that will eventually influence the circadian dynamics of hepatic gluconeogenesis.

The cortisol dynamics in the periphery is primarily governed by the secretion from the central compartment. In Equation ( 6 ), the diffusion of cortisol to the cytoplasm in hepatocyte from the HPA axis is modeled as a transit compartment. Cortisol performs a broad spectrum of physiological functions in all parts of the body, regulating metabolism and immune functions. Therefore, it is ubiquitously present in all tissues of human body, although the cellular response to cortisol may differ in magnitude and specificity depending on the context (40). In the liver, cortisol regulates metabolism such as gluconeogenesis and lipogenesis, working with the large amount of glucocorticoid receptors present in the tissue (9). There is evidence that cortisol controls the circadian clock machinery in the periphery. Dexamethasone, a glucocorticoid hormone analog, can alter the phase of circadian gene expression in different tissues including liver, kidney, and heart (8). The cortisol in the periphery binds to either the mineralocorticoid (MR) or and glucocorticoid (GR) receptors, activating them. The cortisol-receptor interactions were previously modeled by our group (33). We assume that cortisol activates these two receptors by phosphorylation, and we model the dynamics of the receptors using Michaelis-Menten kinetics in Equations ( 7 ) and ( 10 ). Here, MRT and GRT represent the total receptor concentrations, whle MR and GR are the phosphorylated active receptors. The dynamics of the cortisol-receptor complex are modeled in Equations ( 8 ) and ( 11 ). In these equations, the binding rate and nuclear import rate govern the dynamics of the receptor-ligand complex. Once the cortisol-receptor complex is in the nucleus, its dynamics is controlled by the nuclear import and export rates, described by Equations ( 9 ) and ( 12 ).

Inside the nucleus, cortisol-MR and cortisol-GR complex influence the dynamics of the PCGs and pro-inflammatory cytokines. Equations describing the circadian behavior of pro-inflammatory cytokines were adapted from previous works by our group (33, 44). These equations were originally developed for an immune subsystem, but they were adapted to model circadian rhythms in a hepatocyte based on the justification that liver serves as an immunological organ (46). Upon bacterial infection, human hepatocytes express pro-inflammatory cytokines including interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), and growth related GRO-α, GRO-β, and GRO-γ (51). This shows that hepatocytes both initiate and amplify inflammatory responses. Additionally, lipopolysaccharide (LPS) induced endotoxic shock to animals subjected to chronic jet lag causes exaggeration of abolition or alteration of circadian rhythmicity in the liver (14). This experiment suggests that influence of pro-inflammatory cytokines on circadian expression of clock genes should be included in the model for a liver subsystem as well. Cortisol is a key driver for secretion of cytokines with circadian dynamics, such as interferon γ (IFN-γ), interleukin 1 (IL-1), and TNF-α (32). The cortisol-GR complex mediates cytokine inhibition, suggested by experimental evidence that treatment with GR antagonist reduces expression of cytokines (2, 29, 31, 41). The PCGs are also involved in the mediation of pro-inflammatory cytokines, evidenced by BMAL1 deficient mice myeloid cells showing exacerbated immune responses and increased levels of cytokines under endotoxin or bacterial challenges (16, 21, 39). The cortisol-GR complex mediated inhibition and BMAL1 mediated indirect inhibition of cytokines are described by Equation ( 13 ). The translated cytokines bind to the cytokine receptor and form a complex (abbreviated PR), and feeds back to the cytokine mRNA due to autocrine effects (1). Equation ( 14 ) models the translation of cytokine mRNA, and Equation ( 15 ) models the cytokine receptor mRNA, incorporating the cortisol-mediated upregulation of cytokine receptors as an indirect stimulation. The translation of cytokine receptor is described by Equation ( 16 ), and the cytokine-receptor complex is described by Equation ( 17 ).

While the entrainment information from the photic input is delivered to the PCGs via the cortisol-receptor complex, the feeding entrainment information is transmitted to the periphery via NAD+ and SIRT1 in our model. The NAD+ level in the periphery is influenced by the combination of two main reactions, the NAD+ salvage pathway and reduction to NADH. During feeding, accumulation of NADH occurs due to continuous glycolytic throughput, resulting in limited NAD+ concentration (26). While fasting, glycolytic NAD+ demand is decreased, resulting in higher NAD+ concentration (26). This relationship is described by the third term in Equation ( 8 ) of the main text, where the feeding signal is the driving force for the inhibition term. The feeding signal reaches NAD+ after a series of transit compartments based on the observation that NAD+ level reaches the peak 5-6 hours after animals are placed in the active period in rat liver (48). The regeneration of NAD+ from NADH is represented as the first term in the same equation using Michaelis-Menten kinetics. Here, nad represents the combined concentration of NAD+ and NADH; therefore the quantity (nad-NAD) is the concentration of NADH ready to be oxidized. The effects of the NAD+ salvage cycle is incorporated in the second and fourth terms of Equation ( 8 ) of the main text. Nicotinamide (NAM) is released from NAD+ in ADP-ribose transfer reactions, then NAM is converted to nicotinamide mononucleotide (NMN), assisted by the rate limiting enzyme nicotinamide phosphoribosyltransferase (NAMPT) (64). Finally, NMN is converted back to NAD+ via catalyzation by nicotinamide mononucleotide adenylyltransferase (NMNAT), completing the NAD+ salvage pathway cycle (64). Equations ( 18 )-( 19 ) and Equation ( 8 ) of the main text represent the reactions involved in the NAD+ salvage pathway, using Michaelis-Menten kinetics.

The NAD+ plays two important roles in our model. First, it communicates the energy state of the hepatocyte to the SCN. As aforementioned, the electric signaling activity of vmARC is modulated by metabolic hormones and their receptors (3, 23, 45, 53, 56, 58, 59). Tracer experiments show that the SCN reciprocally communicates with the vmARC (62). From these observations, we hypothesize that the energy state of the periphery is delivered to the SCN via electric signaling in the vmARC, and we lumped the hormonal and electric signaling activity into a transit compartment, EntF, described in Equation ( 20 ). Second, NAD+ is the activating agent of SIRT1, using direct binding as a means to alter the conformation of the catalytic site, allowing binding of substrates (13, 65). The activity of NAD+ and SIRT1 was adapted for modeling circadian clocks in the liver by other groups (57, 60) previously, because they play a major role in entraining the PCGs to the feeding rhythms. The activation of SIRT1 is modeled using Michaelis-Menten kinetics in Equation( 9 ) of the main text. In this equation, sirtT is a constant representing the total (active and inactive) concentration of SIRT1. The dynamics of active SIRT1 depends on the concentration of inactive SIRT1 protein availability and the concentration of the activator NAD+. The rationale for modeling active SIRT1 level in this manner is that experimental evidence shows that SIRT1 protein concentration stays relatively constant throughout the day whereas its enzymatic activity oscillates with a circadian rhythm (11).

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### *Entrainment of PCGs*

The equations for entrainment of PCGs by cortisol was developed in our previous work (34). Equations ( 21 )-( 27 ) incorporate a series of transcriptional and translational feedback loops, resulting in an autonomous oscillations of the PCGs. Since the basic structure behind the core clock machinery involving PER/CRY and CLOCK/BMAL1 protein complexes are similar across the different tissues (12, 36, 50, 52), the equations originally developed for an immune subsystem can successfully describe the clock gene rhythms in a hepatic subsystem as well. Modeling work by another group (57) utilized the negative and positive feedback loops involving these two protein complexes to model circadian rhythms of a hepatocyte, further justifying the adaptation of these equations. The experimental observation that cortisol-GR complex binds to the promoter region of *Per1* and *Per2* genes (61) is accounted for in Equation ( 21 ). The transcription of *Per* and *Cry* is stimulated when CLOCK/BMAL1 protein complex binds to an Ebox enhancer. The translated PER/CRY protein is under negative feedback control as it translocates to the nucleus and inhibits its own translational activity. The exponent p in Equation ( 21 ) is a Hill-function coefficient, describing the switch-like behavior of the translational activities. The pro-inflammatory cytokines indirectly stimulates the transcription of *Per/Cry*, because studies show that *Per1*, *Cry1*, and *Cry2* expression are induced upon treatment with IL-6 or TNF-α (37, 42, 63). Equation ( 22 ) describes the formation of PER/CRY complex formation, and Equation ( 23 ) shows the dynamics of nuclear PER/CRY. Inside the nucleus, PER/CRY suppresses the activation of REV-ERBα, which is promoted by CLOCK/BMAL1 complex (19). Since REV-ERBα negatively regulates the transcription of Bmal1, PER/CRY effectively induces BMAL1 transcription, shown in Equation ( 24 ). Equation ( 25 ) describes the dynamics of BMAL1 protein, while Equations ( 26 ) and ( 27 ) show the levels of nuclear BMAL1 and CLOCK/BMAL1 protein complex.

The feeding rhythms govern the activation of SIRT1 by NAD+. SIRT1 then exerts influence on some of the clock components in a bidirectional mode. The NAD+ activated SIRT1 binds to CLOCK/BMAL1 and forms CLOCK/BMAL1/SIRT1 complex. This complex promotes the expression of NAMPT (20), which is the rate limiting enzyme of the NAD+ salvage cycle. Therefore, SIRT1 auto-regulates its activation through interacting with core peripheral clock components. The binding of SIRT1 to CLOCK/BMAL1 complex is modeled in Equation ( 28 ). The regeneration of CLOCK/BMAL1 from CLOCK/BMAL1/SIRT1 complex is represented in the last term of Equation ( 27 ). The NAMPT dynamics is described by Equation ( 29 ), using linear production and degradation terms. SIRT1 binding to the CLOCK/BMAL1 complex alters the rhythms of the clock genes by taking away the CLOCK/BMAL1 availability, which promotes the expression of *Per/Cry* gene. SIRT 1 also facilitates the degradation of PER2 protein via deacetylation (5, 11), incorporated into Equation ( 23 ) describing the nuclear PER/CRY dynamics. Experiment showing abnormally high PER2 accumulation in SIRT1-deficient mouse embryonic fibroblasts (MEFs) also supports this modification (4).

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### *Expression of Gluconeogenic Genes*

The transcription of gluconeogenic genes, represented by *Pck1/G6pc* in our model, and the sequence of transcriptional and enzymatic regulations leading up to this event is represented in Equations ( 10 )-( 15 ) in the Methods section of the main text along with detailed explanations and supporting information.

In summary, our model is a collection of numerous ODEs describing transcription, translation, and molecular interactions that are interconnected to form a larger network describing the circadian rhythms and gluconeogenic gene expression in a human hepatocyte. However, quantified level or activity for the model components are not always available in an hourly manner. Therefore, extrapolations are made from diverse animal studies across species to capture the key characteristics in order to constrain the parameters. Such practice is common in systems biology and the field has accepted that accurate and relevant predictions are more valuable than constraining every single parameter of the model (24). To that end, parameters were estimated to capture the qualitative characteristics (such as phase relations and amplitude changes due to environmental changes) where necessary. The circadian amplitude and phase relation of G6P and PEPCK were the most important observations when estimating the parameters for Equations ( 10 )-( 15 ). Under *ad libitum* feeding, both the protein level and activity level of thsese two enzymes peak during the transition time from light to dark period, when animals transition from inactive to active period (6, 43). When animals are placed under a restricted feeding schedule where food is available for only 2 hours during their inactive period, the change in the circadian rhythms of these two enzymes is apparent. The protein levels peak just before or during the two-hour window when food is available to the animals. This is the highest peak during a 24-hour period although a smaller peak appears during the active period. Additionally, the amplitude of the rhythms for PEPCK protein level is increased under restricted feeding, although similar change is less obvious for G6P. The parameters were constrained such that the phase shift and amplitude change occurs for the transcription of *Pck1/G6pc* based on the location of the major peak. The method of parameter estimation for the rest of the model is described in our previous work (7).

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