# Appendix 1

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, 37, 38), 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 (37, 38). 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, 38, 49, 55). 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 (17, 27, 60); 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 (54). The feed signal through these transit compartments will eventually modify the redox relations between NAD+ and NADH and modify the cellular NAD+/NADH ratio (19).

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 (29, 38). 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 (24). The photic signal is communicated via the retinal ganglion cells (RGCs) in the eye (43), then the hypothalamic suprachiasmatic nucleus (SCN) integrates the signals and regulates the circadian rhythms of the cortisol and the periphery (20, 61).The SCN mediates secretion of light-induced arginine vasopressin (AVP) (32). Decrease in AVP secretion leads to increased level of cortisol (30), CRH, and ACTH (39). 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 (53), 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 (49).

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, 25, 59, 66) (50, 64, 67). 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 (70). 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.

( 1 )

( 2 )

( 3 )

( 4 )

( 5 )

## 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 (45). 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 (37). 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 (37, 49). 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 (52). 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 (57). 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 (16). 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 (34). The cortisol-GR complex mediates cytokine inhibition, suggested by experimental evidence that treatment with GR antagonist reduces expression of cytokines (2, 31, 33, 46). 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 (18, 23, 44). 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 (28). While fasting, glycolytic NAD+ demand is decreased, resulting in higher NAD+ concentration (28). 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 (54). 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) (72). Finally, NMN is converted back to NAD+ via catalyzation by nicotinamide mononucleotide adenylyltransferase (NMNAT), completing the NAD+ salvage pathway cycle (72). 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, 25, 50, 59, 64, 66, 67). Tracer experiments show that the SCN reciprocally communicates with the vmARC (70). 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 (15, 73). The activity of NAD+ and SIRT1 was adapted for modeling circadian clocks in the liver by other groups (65, 68) 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).

( 6 )

( 7 )

( 8 )

( 9 )

( 10 )

( 11 )

( 12 )

( 13 )

( 14 )

( 15 )

( 16 )

( 17 )

( 18 )

( 19 )

( 20 )

### *Entrainment of PCGs*

The equations for entrainment of PCGs by cortisol was developed in our previous work (38). 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, 40, 56, 58), 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 (65) 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 (69) 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 (42, 47, 71). 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 (21). 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 (22), 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).

( 21 )

( 22 )

( 23 )

( 24 )

( 25 )

( 26 )

( 27 )

( 28 )

( 29 )

### *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 (26). 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, 48). 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).

# Appendix 2

## Local Sensitivity Analysis

The local sensitivity analysis was performed on all 130 parameters of the model. The relative sensitivity coefficient for every parameter was calculated using the following equation (55):

( 1 )

In Equation ( 1 ),

pk = tested parameter

y = measured response

Each parameter was varied by 1% in the positive direction, and the relative local sensitivity coefficients for each parameter based on the amplitude of *Pck1/G6pc*

mRNA were computed.

## Morris Method

The Morris method is a computationally effective screening method that identifies a few important parameters in models involving many parameters. The method first computes elementary effects, or the changes in an output due solely to changes in a particular input (41). In the input space, r trajectories are constructed by first generating a random starting point, then moving one factor at a time in a random order (13). Once the elementary effects are calculated, they are averaged to assess the overall importance of the input (13). The elementary effects were calculated for k=112 peripheral parameters using the Morris method. This method is a one-at-a-time (OAT) method first introduced by Morris (41) and later refined by Campolongo (13). The Morris method calculates the elementary effects for each factor using the following equation (14):

( 2 )

In the above equation, Y is a deterministic function of k input factors (parameters). Because each input parameter xi is scaled in the interval [0, 1], the right side of the equation is divided by Δi, which is a value in {1/(p - 1),…,1 - 1/(p – 1)}. Here, p is the number of levels. The mean (Equation ( 3 )) and variance (Equation ( 4 )) of the elementary effects are considered together to determine the ranking of factors in the order of importance.

( 3 )

( 4 )

Since radial sampling strategy has proved effective for efficiently covering the input space, Sobol’s quasi-random numbers (62, 63) were used to generate radial sampling points between ±20% of the nominal values (Table 1), adopting from the implementation methods presented in (14). The repetition r = 100 was used for analyzing our model. To create the samples, Sobol’s quasi-random sequence was generated to populate a matrix of size (r+1, 2k). Then, the first row of this matrix was removed. The resulting matrix was divided into matrix **A** (left half), and matrix **B** (right half), each with a dimension of r x k. Each row in matrix **A** is used as a “base point” for the method, defining the set of inputs for the second term of the numerator in Equation ( 2 ). Each row in matrix **B** is used as an “auxiliary point” to constitute the radial design. From matrix **A** and **B**, matrix **AB(i)** is created to achieve the radial design such that for each factor i, ith element of ith row of matrix **A** is replaced with the counterpart of matrix **B** as shown in Figure 1. Then each row in matrix **AB(i)** is the set of input for the first term in the numerator of equation ( 2 ). This design yields a computational cost of r(k+1).

Figure 1: Radial design of input factors for Morris method. For each parameter, the ith element of ith row of matrix **A** is replaced with the counterpart of matrix **B** to constitute the matrix **AB(i**).

Using this method, the mean and variance of the elementary effects for the peripheral parameters were considered together to sort the factors in the order of importance. This resulted in 20 factors exhibiting the mean of elementary effects greater than 1.5. These factors were further analyzed using RS-HDMR for both primary and interaction effects of input variables in output variance.

## RS-HDMR Uncertainty Analysis

HDMR is a variance-based method developed by Rabitz and coworkers (51) aimed to reduce the computational cost for representing input-output relationships in high-dimensional systems. We followed the RSHDMR uncertainty analysis method presented in (36) to analyze the 20 selected parameters from sensitivity analysis using the Morris Method. The basis for uncertainty analysis using RS-HDMR method is that output f(**x**) can be expressed as a combination of the input x using statistical ANOVA decomposition, as Equation ( 5 ) shows.

( 5 )

In Equation ( 5 ), f0 is a constant representing the mean response to f(**x**). First order component function fi(xi) gives the independent contributions to f(x) by the ith input variable acting alone. Second order component function fij(xi,xj) gives the pair correlated contribution to f(x) by the input variables xi and xj. The last term contains any residual nth order correlated contribution of all input variables. For most real-world applications, HDMR expansion to the second order is sufficient, and Equation ( 5 ) reduces to Equation ( 6 ).

( 6 )

The variables xi were sampled between ±20% of the nominal values (presented in Table 1), using Sobol’s quasi-random sequence, and then were rescaled such that 0 ≤ xi ≤ 1 for all I by performing transformation of the input variables. Then, the output function f(**x**) is defined in the unit hypercube Kn = {(x1,x2,…,xn)|0 ≤ xi ≤1, i=1,2,…,n}, and the component functions of RS-HDMR possess the following forms:

( 7 )

( 8 )

( 9 )

Here, d**x**i and d**x**ij are the product of dx1dx2…dxn without dxi and dxidxj, respectively. The first order component f0 is simply the mean value of f(**x**) over the whole domain. The individual component functions presented in Equations ( 7 )-( 9 ) have a direct statistical correlation interpretation which leads to the decomposition of model output variance into its individual input variable contributions. Because of the orthogonality of the component functions, the variance can be expressed as Equation ( 10 ).

( 10 )

To reduce the sampling effort, the component functions are usually approximated by basis functions of three types: orthonormal polynomials, cubic spline, and polynomials. Among these basis functions, orthonormal polynomials provide the most saving in computational cost (35). Therefore we employed a set of orthonormal polynomials in Equations ( 11 )-( 13 ) as a basis to approximate the component functions in Equations ( 14 ) and ( 15 ) (36).

( 11 )

( 12 )

( 13 )

( 14 )

( 15 )

The coefficients for the component functions in Equations ( 14 ) and ( 15 ) were estimated using Equations ( 16 ) and ( 17 ). Finally, these coefficients were used to calculate the first order (primary effect) and second order variance (interaction effect) using the Equations ( 18 ) and ( 19 ).

( 16 )

( 17 )

( 18 )

( 19 )

# Appendix 3

Table : Parameter values and descriptions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Parameter** | **Value** | **Units** | **Description/Reference** |
| 1 | kp1 | 0.7965 | µM.h-1 | Rate constant of CRH production(38) |
| 2 | Kp1 | 1.0577 | µM | Dissociation constant for CRH production(38) |
| 3 | Vd1 | 0.5084 | µM.h-1 | Rate of CRH enzymatic degradation(38) |
| 4 | Kd1 | 1.9627 | µM | Michaelis constant of CRH enzymatic degradation(38) |
| 5 | kfp | 0.1 | µM -1 | Efficiency of P on ACTH and F stimulation/ estimated |
| 6 | kp2 | 0.4 | µM.h-1 | Rate of ACTH production |
| 7 | Kp2 | 1.0577 | µM | Dissociation constant for ACTH production(38) |
| 8 | Vd2 | 0.5129 | µM.h-1 | Rate of ACTH enzymatic degradation(38) |
| 9 | Kd2 | 0.3069 | µM | Michaelis constant of ACTH enzymatic degradation(38) |
| 10 | kp3 | 0.15 | µM.h-1 | Rate of F central production/ estimated(49) |
| 11 | kn | 1.5 |  | Coupling constant of cortisol to cellular energy state |
| 12 | Vd3 | 3.4 | µM.h-1 | Rate of F central enzymatic degradation |
| 13 | Kd3 | 0.4695 | µM | Michaelis constant of F central enzymatic degradation(38) |
| 14 | ksynRm | 2.9 | fmol.g-1.h-1 | Synthesis rate or glucocorticoid receptor mRNA(53) |
| 15 | IC50Rm | 26.2 | nmol.L-1.mgprotein-1 | Concentration of FR(N) at which mRNA, Rsynthesis drops to its half(53) |
|  | R0 | 540.7 | nmol.L-1.mgprotein-1 | Baseline value of free cytosolic glucocorticoid receptor(53) |
|  | Rm0 | 25.8 | fmol.g-1 | Baseline value of glucocorticoid receptor mRNA(53) |
| 16 | kdgrRm | ksynRm/Rm0 |  | Degradation rate of glucocorticoid receptor mRNA(53) |
| 17 | ksynR | (R0/Rm0)\*kdgrR |  | Synthesis rate of free cytosolic receptor(53) |
| 18 | rf | 0.49 |  | Fraction of cortisol recycled(53) |
| 19 | kre | 0.57 | h-1 | Rate of receptor recycling from nucleus to cytoplasm(53) |
| 20 | kon | 0.00329 | L.nmol-1.h-1 | Second order rate constant of glucocorticoid receptor binding(53) |
| 21 | kdgrR | 0.0572 | h-1 | Degradation rate of cytosolic glucocorticoid receptor(53) |
| 22 | kt | 0.63 | h-1 | Rate of receptor translocation to the nucleus(53) |
| 23 | τ | 0.25 | h | Delay in Cortisol production following ACTH stimulation |
| 24 | kMR | 0.34 | nM.h-1 | Base transcription rate of MR(37) |
| 25 | kF,MR | 1.1011 | 1 | Maximum extent of Fperiphery mediated activation of MR(37) |
| 26 | KF,MR | 0.5 | nM | Michaelis constant for Fperiphery mediated activation of MR(37) |
| 27 | MRT | 1.45 | nM | Total MR concentration(37) |
| 28 | KMR | 0.21 | nM | Michaelis constant for MR production(37) |
| 29 | kMR,deg | 0.70 | nM.h-1 | Degradation rate for MR(37) |
| 30 | KMR,deg | 1.65 | nM | Michaelis constant for degradation of MR(37) |
| 31 | kb,MR | 0.00329 | nM-1.h-1 | Degradation rate for cortisol/mineralocorticoid receptor binding(53) |
| 32 | kr,MR | 0.001 |  |  |
| 33 | kon,MR | 1 | L.nmol-1.h-1 | Second order rate constant of mineralocorticoid and receptor binding(37) |
| 34 | kt,MR | 1 | h-1 | Rate of mineralocorticoid receptor translocation to the nucleus/(53) |
| 35 | kre,MR | 1 | h-1 | Rate of mineralocorticoid receptor recycling from nucleus to cytoplasm(37) |
| 36 | kGR | 1.18 | nM.h-1 | Base transcription rate of GR(37) |
| 37 | kF,GR | 15 | 1 | Maximum extent of Fperiphery mediated activation of GR(37) |
| 38 | KF,GR | 30 | nM | Michaelis constant for Fperiphery mediated activation of GR(37) |
| 39 | GRT | 1.81 | nM | Total GR concentration(37) |
| 40 | KGR | 0.74 | nM | Michaelis constant for GR production(37) |
| 41 | kGR,deg | 1.52 | nM.h-1 | Degradation rate for GR(37) |
| 42 | KGR,deg | 1.05 | nM | Michaelis constant for degradation of GR(37) |
| 43 | kb,GR | 0.00329 | nM-1.h-1 | Degradation rate for cortisol/glucocorticoid receptor binding(53) |
| 44 | kr,GR | 0.001 |  |  |
| 45 | kon,GR | 1 | L.nmol-1.h-1 | Second order rate constant of mineralocorticoid and receptor binding(53) |
| 46 | kt,GR | 1 | h-1 | Rate of mineralocorticoid receptor translocation to the nucleus(53) |
| 47 | kre,GR | 1 | h-1 | Rate of mineralocorticoid receptor recycling from nucleus to cytoplasm(53) |
| 48 | kmRNARpin | 0.61 | µM.h-1 | Base transcription rate of mRNARP(37) |
| 49 | kfr | 1.07 | 1 | Maximum extent of FMR(N) mediated transcription of mRNARP(37) |
| 50 | Kfr | 0.5 | µM | Michaelis constant for FMR(N) mediated transcription of mRNARP(37) |
| 51 | kpc | 0.3 | 1 | Maximum extent of BMAL1 mediated suppression of mRNAP and mRNATLR4 estimated |
| 52 | Kpc | 25 | µM | Michaelis constant for BMAL1 mediated suppression of mRNAP and mRNATLR4 estimated |
| 53 | kmRNARpout | 0.19 | h-1 | Degradation rate of mRNARP(37) |
| 54 | kinP | 0.29 | h-1 | Translation rate of P(37) |
| 55 | koutP | 1.06 | h-1 | Degradation rate of P(37) |
| 56 | kmRNARpin | 0.61 | µM.h-1 | Base transcription rate of mRNARP(37) |
| 57 | kfr2 | 0.8 | 1 | Maximum extent of FMR(N) mediated transcription of mRNARP(37) |
| 58 | Kfr2 | 0.5 | µM | Michaelis constant for FMR(N) mediated suppression of mRNARP(37) |
| 59 | kmRNARpout | 0.19 | h-1 | Degradation rate of mRNARP(37) |
| 60 | kinRp | 1.11 | h-1 | Translation rate of RP(37) |
| 61 | kd | 0.14 | µM-1.h-1 | P–Rp binding rate constant(37) |
| 62 | koutRp | 0.26 | h-1 | Degradation rate of RP(37) |
| 63 | koutPRp | 1.3 | h-1 | Dissociation rate of PRP(37) |
| 64 | v1b | 4 | nM.h-1 | Maximal rate of Per-Cry transcription(10) |
| 65 | k1b | 1 | nM | Michaelis constant of Per-Cry transcription(10) |
| 66 | k1i | 0.56 | nM | Inhibition constant of Per-Cry transcription(10) |
| 67 | c | 0.01 | nM | Concentration of constitutive activator(10) |
| 68 | p | 8 |  | Hill coefficient of inhibition of Per-Cry transcription(10) |
| 69 | kf | 0.1 | nM-1 | Efficiency of P on transcription of Per-Cry/estimated(49) |
| 70 | (ent)kc | 0.009 | nM.h-1 | Coupling strength/estimated |
| 71 | k1d | 0.12 | h-1 | Degradation rate of Per-Cry mRNA(10) |
| 72 | k2b | 0.3 | nM-1.h-1 | Complex formation rate of Per-Cry mRNA(10) |
| 73 | q | 2 |  | No. of PER-CRY complex forming subunits(10) |
| 74 | k2d | 0.05 | h-1 | Degradation rate of cytoplasmatic PER-CRY(10) |
| 75 | k2t | 0.24 | h-1 | Nuclear import rate of the PER-CRY complex |
| 76 | k3t | 0.02 | h-1 | Nuclear export rate of PER-CRY complex |
| 77 | k3d | 0.02 | h-1 | Degradation rate of the nuclear PER-CRY complex |
| 78 | v4b | 3.6 | nM.h-1 | Maximal rate of Bmal1 transcription(10) |
| 79 | k4b | 2.16 | nM | Michaelis constant of Bmal1 transcription(10) |
| 80 | r | 3 |  | Hill coefficient of activation of Bmal1 transcription(10) |
| 81 | k4d | 0.75 | h-1 | Degradation rate of Bmal1 mRNA(10) |
| 82 | k5b | 0.24 | h-1 | Translation rate of BMAL1(10) |
| 83 | k5d | 0.06 | h-1 | Degradation rate of cytoplasmatic BMAL1(10) |
| 84 | k5t | 0.45 | h-1 | Nuclear import rate of BMAL1(10) |
| 85 | k6t | 0.06 | h-1 | Nuclear export rate of BMAL1(10) |
| 86 | k6d | 0.12 | h-1 | Degradation rate of nuclear BMAL1(10) |
| 87 | k6a | 1 | h-1 | Activation rate of nuclear CLOCK-BMAL1 |
| 88 | k7a | 0.1 | h-1 | Deactivation rate of CLOCK-BMAL1 |
| 89 | k7d | 0.5 | h-1 | Degradation rate of CLOCK-BMAL1 |
| 90 | km8a | 10 | h-1 | Association rate of CLOCK-BMAL1-SIRT1 |
| 91 | km8d | 20 | h-1 | Dissociation rate of CLOCK-BMAL1-SIRT1 |
| 92 | τf | 3 | h | Delay between feeding and NAD+ reduction to NADH |
| 93 | km1 | 5 | 1 | Maximum extent of NADH converting to NAD+ |
| 94 | Km1 | 2 | μM | Michaelis constant for NADH converting to NAD+ |
| 95 | km2 | 40 | 1 | Maximum extent of NMN converting to NAD+ |
| 96 | Km2 | 1 | μM | Michaelis constant for NMN converting to NAD+ |
| 97 | km3 | 5 | 1 | Maximum extent of NAD+ converting to NADH upon feeding |
| 98 | Km3 | 1 | μM | Michaelis constant NAD+ converting to NADH upon feeding |
| 99 | km4 | 20 | 1 | Maximum extent of NAD+ converting to NAM |
| 100 | Km4 | 20 | μM | Michaelis constant for NAD+ converting to NAM |
| 101 | km5 | 40 | 1 | Maximum extent of NAM converting to NMN, mediated by NAMPT |
| 102 | Km5 | 5 | μM | Michaelis constant for of NAM converting to NMN, mediated by NAMPT |
| 103 | km11 | 5 | 1 | Maximum extent of entrainment of cortisol by feeding |
| 104 | Km11 | 2 | μM | Michaelis constant for entrainment of cortisol by feeding |
| 105 | km12 | 1 | μMh-1 | Rate of cortisol entraining signal degradation |
| 106 | km6 | 5 | 1 | Maximum extent of SIRT1 activation mediated by NAD |
| 107 | Km6 | 1 | μM | Michaelis constant of SIRT1 activation mediated by NAD |
| 108 | sirtT | 5 | μM | Sum of active and inactive SIRT1 |
| 109 | km7 | 2 | 1 | Maximum extent of SIRT1 degradation |
| 110 | Km7 | 1 | μM | Michaelis constant for SIRT1 degradation |
| 111 | km9d | 0.1 | μM-1h-1 | Rate of CLOCK/BMAL1/SIRT1 complex degradation |
| 112 | km10a | 2 | μMh-1 | Rate of NAMPT production mediated by CLOCK/BMAL1/SIRT1 complex |
| 113 | km10d | 2 | h-1 | Rate of NAMPT degradation |
| 114 | nad | 1 | μM | Sum of NAD+ and NADH |
| 115 | kg1 | 2 | nM.h-1 | Rate of PGC-1α transcription |
| 116 | kg2 | 2 | nM.h-1 | Rate of PGC-1α mRNA degradation |
| 117 | kg3b | 3 | h-1 | Rate of PGC-1α translation |
| 118 | kg3d | 3 | h-1 | Rate of PGC-1α degradation |
| 119 | kg3t | 2 | h-1 | Rate of PGC-1α nuclear import |
| 120 | kg4t | 2 | h-1 | Rate of PGC-1α nuclear export |
| 121 | kg5 | 0.1 | h-1 | Rate of PGC-1α activation |
| 122 | kg7 | 1 | nM | Inhibition constant for binding of cortisol-receptor complex to GRE |
| 123 | kg8 | 0.8 | h-1 | Rate of active PGC-1α degradation |
| 124 | kg8d | 0.5 | h-1 | Rate of deactivation of PGC-1α |
| 125 | kg9 | 3 | h-1 | Rate of FOXO1 activation |
| 126 | kg10 | 5 | h-1 | Rate of FOXO1 deactivation |
| 127 | kg11 | 70 | h-1 | Transcription rate of gluconeogenic genes |
| 128 | kg12 | 3 | h-1 | Degradation rate of gluconeogenic genes mRNA |
| 129 | kg13 | 0.1 | h-1 | Rate of Bmal1 transcription activation by active PGC-1α |
| 130 | s | 8 |  | Hill coefficient for inhibition of cortisol-receptor complex and GRE binding |

Table : Local sensitivity analysis results for all parameters. Parameters are ranked in the order of the greatest absolute value of the sensitivity coefficient.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Rank | Parameter | Sensitivity Coefficient | Rank | Parameter | Sensitivity Coefficient |
| 1 | kg7 | -2.7553 | 66 | k7a | -0.2847 |
| 2 | Kp1 | 2.7151 | 67 | km1 | -0.2768 |
| 3 | Kp2 | 2.7151 | 68 | k6d | -0.2677 |
| 4 | kp1 | -2.5703 | 69 | Km1 | 0.2668 |
| 5 | k1i | 2.5432 | 70 | k3t | -0.2568 |
| 6 | Vd1 | 2.3136 | 71 | kg8d | 0.2536 |
| 7 | kg9 | -1.5493 | 72 | kF,GR | -0.2271 |
| 8 | kre | -1.4941 | 73 | Kd2 | -0.2206 |
| 9 | kg3b | -1.3020 | 74 | Kd3 | 0.2165 |
| 10 | kg1 | -1.3020 | 75 | τf | -0.2137 |
| 11 | sirtT | -1.2862 | 76 | s | -0.2126 |
| 12 | kg10 | 1.2188 | 77 | MRT | -0.2054 |
| 13 | kp3 | -1.2139 | 78 | k2b | 0.1853 |
| 14 | k1d | -1.1960 | 79 | kf | 0.1641 |
| 15 | kg2 | 1.1922 | 80 | KMR,deg | 0.1601 |
| 16 | kdgrRm | -1.1883 | 81 | koutRp | 0.1533 |
| 17 | kg3t | -1.0969 | 82 | kMR,deg | 0.1229 |
| 18 | km7 | 1.0740 | 83 | k6t | 0.1180 |
| 19 | kg5 | -1.0721 | 84 | km5 | -0.1070 |
| 20 | p | -1.0668 | 85 | Km4 | -0.1069 |
| 21 | kp2 | -1.0282 | 86 | Km11 | 0.0994 |
| 22 | kg12 | 0.9811 | 87 | KF,GR | -0.0986 |
| 23 | ksynR | 0.9737 | 88 | kpc | -0.0982 |
| 24 | kon | 0.9679 | 89 | km8a | -0.0973 |
| 25 | kg11 | -0.9570 | 90 | kMR | -0.0914 |
| 26 | kg4t | 0.9537 | 91 | k2d | -0.0907 |
| 27 | GRT | -0.9535 | 92 | kt,MR | -0.0877 |
| 28 | Vd3 | 0.9477 | 93 | kt,GR | -0.0877 |
| 29 | km6 | -0.9290 | 94 | k7d | 0.0864 |
| 30 | kg3d | 0.9030 | 95 | IC50Rm | -0.0862 |
| 31 | ksynRm | 0.9026 | 96 | km4 | 0.0822 |
| 32 | kg8 | 0.8428 | 97 | kfr | -0.0770 |
| 33 | Kd1 | -0.8290 | 98 | kfr2 | -0.0734 |
| 34 | kdgrR | -0.7678 | 99 | k6a | 0.0719 |
| 35 | q | -0.7186 | 100 | k5b | 0.0622 |
| 36 | kon,MR | -0.7174 | 101 | Vd2 | 0.0588 |
| 37 | kon,GR | -0.7174 | 102 | km2 | -0.0576 |
| 38 | kinRp | -0.6258 | 103 | kg13 | -0.0559 |
| 39 | nad | -0.6243 | 104 | kr,MR | 0.0541 |
| 40 | koutP | 0.6083 | 105 | kr,GR | 0.0541 |
| 41 | k2t | -0.5700 | 106 | Kfr | 0.0524 |
| 42 | kmRNARpin | -0.5614 | 107 | k4d | -0.0517 |
| 43 | kinP | -0.5614 | 108 | km11 | 0.0491 |
| 44 | Km7 | -0.5600 | 109 | τ | -0.0443 |
| 45 | kre,MR | 0.5514 | 110 | k5d | -0.0416 |
| 46 | kre,GR | 0.5514 | 111 | rf | 0.0339 |
| 47 | kmRNARpout | 0.5435 | 112 | Km5 | -0.0301 |
| 48 | kGR | -0.5086 | 113 | km10a | -0.0300 |
| 49 | Km3 | -0.4975 | 114 | Kpc | 0.0255 |
| 50 | kGR,deg | 0.4967 | 115 | Kfr2 | 0.0243 |
| 51 | koutPRp | 0.4783 | 116 | v4b | -0.0232 |
| 52 | k1b | -0.4490 | 117 | kF,MR | 0.0232 |
| 53 | kn | -0.4480 | 118 | k5t | 0.0228 |
| 54 | kd | -0.4473 | 119 | k4b | -0.0219 |
| 55 | kmRNARpout | 0.4316 | 120 | Km2 | -0.0176 |
| 56 | k3d | -0.4302 | 121 | km8d | 0.0148 |
| 57 | v1b | 0.4122 | 122 | r | 0.0146 |
| 58 | kmRNARpin | -0.4034 | 123 | km10d | -0.0141 |
| 59 | kfp | -0.3635 | 124 | KMR | -0.0140 |
| 60 | (ent)kc | 0.3542 | 125 | c | 0.0093 |
| 61 | KGR | 0.3512 | 126 | km12 | 0.0079 |
| 62 | Km6 | 0.3330 | 127 | km9d | 0.0028 |
| 63 | km3 | 0.3137 | 128 | KF,MR | 0.0025 |
| 64 | kt | -0.3042 | 129 | kb,MR | 0.0021 |
| 65 | KGR,deg | -0.2918 | 130 | kb,GR | 0.0021 |

# References

1. **Akira S, Hirano T, Taga T, and Kishimoto T**. Biology of multifunctional cytokines: IL 6 and related molecules (IL 1 and TNF). *FASEB J* 4: 2860-2867, 1990.

2. **Amano Y, Lee SW, and Allison AC**. Inhibition by glucocorticoids of the formation of interleukin-1 alpha, interleukin-1 beta, and interleukin-6: mediation by decreased mRNA stability. *Mol Pharmacol* 43: 176-182, 1993.

3. **Aronsson M, Fuxe K, Dong Y, Agnati LF, Okret S, and Gustafsson JA**. Localization of glucocorticoid receptor mRNA in the male rat brain by in situ hybridization. *Proc Natl Acad Sci U S A* 85: 9331-9335, 1988.

4. **Asher G, Gatfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, Mostoslavsky R, Alt FW, and Schibler U**. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* 134: 317-328, 2008.

5. **Asher G, and Schibler U**. Crosstalk between components of circadian and metabolic cycles in mammals. *Cell Metab* 13: 125-137, 2011.

6. **Ashman PU, and Seed JR**. Biochemical studies in the vole, Microtus montanus. II. The effects of a Trypanosoma brucei gambiense infection on the diurnal variation of hepatic glucose-6-phosphatase and liver glycogen. *Comp Biochem Physiol B* 45: 379-392, 1973.

7. **Bae S-A, and Androulakis IP**. The Synergistic Role of Light-Feeding Phase Relations on Entraining Robust Circadian Rhythms in the Periphery. *Gene Regulation and Systems Biology* 2017: 0-0, 2017.

8. **Balsalobre A, Brown SA, Marcacci L, Tronche F, Kellendonk C, Reichardt HM, Schutz G, and Schibler U**. Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science* 289: 2344-2347, 2000.

9. **Bamberger CM, Schulte HM, and Chrousos GP**. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. *Endocr Rev* 17: 245-261, 1996.

10. **Becker-Weimann S, Wolf J, Herzel H, and Kramer A**. Modeling feedback loops of the Mammalian circadian oscillator. *Biophys J* 87: 3023-3034, 2004.

11. **Bellet MM, Orozco-Solis R, Sahar S, Eckel-Mahan K, and Sassone-Corsi P**. The time of metabolism: NAD+, SIRT1, and the circadian clock. *Cold Spring Harb Symp Quant Biol* 76: 31-38, 2011.

12. **Bellet MM, and Sassone-Corsi P**. Mammalian circadian clock and metabolism - the epigenetic link. *J Cell Sci* 123: 3837-3848, 2010.

13. **Campolongo F, Cariboni J, and Saltelli A**. An effective screening design for sensitivity analysis of large models. *Environ Modell Softw* 22: 1509-1518, 2007.

14. **Campolongo F, Saltelli A, and Cariboni J**. From screening to quantitative sensitivity analysis. A unified approach. *Comput Phys Commun* 182: 978-988, 2011.

15. **Cao D, Wang M, Qiu X, Liu D, Jiang H, Yang N, and Xu RM**. Structural basis for allosteric, substrate-dependent stimulation of SIRT1 activity by resveratrol. *Genes Dev* 29: 1316-1325, 2015.

16. **Cermakian N, Lange T, Golombek D, Sarkar D, Nakao A, Shibata S, and Mazzoccoli G**. Crosstalk between the circadian clock circuitry and the immune system. *Chronobiology International* 30: 870-888, 2013.

17. **Chung H, Chou W, Sears DD, Patterson RE, Webster N, and Ellies LG**. Time-restricted feeding improves insulin resistance and hepatic steatosis in a mouse model of postmenopausal obesity. *Metabolism* 2016.

18. **Curtis AM, Fagundes CT, Yang G, Palsson-McDermott EM, Wochal P, McGettrick AF, Foley NH, Early JO, Chen L, Zhang H, Xue C, Geiger SS, Hokamp K, Reilly MP, Coogan AN, Vigorito E, FitzGerald GA, and O'Neill LA**. Circadian control of innate immunity in macrophages by miR-155 targeting Bmal1. *Proc Natl Acad Sci U S A* 112: 7231-7236, 2015.

19. **Diaz-Munoz M, Vazquez-Martinez O, Aguilar-Roblero R, and Escobar C**. Anticipatory changes in liver metabolism and entrainment of insulin, glucagon, and corticosterone in food-restricted rats. *Am J Physiol Regul Integr Comp Physiol* 279: R2048-2056, 2000.

20. **Dibner C, Schibler U, and Albrecht U**. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol* 72: 517-549, 2010.

21. **Duez H, and Staels B**. Rev-erb-alpha: an integrator of circadian rhythms and metabolism. *J Appl Physiol (1985)* 107: 1972-1980, 2009.

22. **Eckel-Mahan K, and Sassone-Corsi P**. Metabolism and the circadian clock converge. *Physiol Rev* 93: 107-135, 2013.

23. **Gibbs JE, Blaikley J, Beesley S, Matthews L, Simpson KD, Boyce SH, Farrow SN, Else KJ, Singh D, Ray DW, and Loudon AS**. The nuclear receptor REV-ERBalpha mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc Natl Acad Sci U S A* 109: 582-587, 2012.

24. **Gonze D, Bernard S, Waltermann C, Kramer A, and Herzel H**. Spontaneous synchronization of coupled circadian oscillators. *Biophys J* 89: 120-129, 2005.

25. **Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, Sirinathsinghji DJ, Smith RG, Van der Ploeg LH, and Howard AD**. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. *Brain Res Mol Brain Res* 48: 23-29, 1997.

26. **Gutenkunst RN, Waterfall JJ, Casey FP, Brown KS, Myers CR, and Sethna JP**. Universally sloppy parameter sensitivities in systems biology models. *PLoS Comput Biol* 3: 1871-1878, 2007.

27. **Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong EA, Gill S, Leblanc M, Chaix A, Joens M, Fitzpatrick JAJ, Ellisman MH, and Panda S**. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab* 15: 848-860, 2012.

28. **Hipkiss AR**. Energy metabolism, altered proteins, sirtuins and ageing: converging mechanisms? *Biogerontology* 9: 49-55, 2008.

29. **Jung CM, Khalsa SB, Scheer FA, Cajochen C, Lockley SW, Czeisler CA, and Wright KP, Jr.** Acute effects of bright light exposure on cortisol levels. *J Biol Rhythms* 25: 208-216, 2010.

30. **Kalsbeek A, vanderVliet J, and Buijs RM**. Decrease of endogenous vasopressin release necessary for expression of the circadian rise in plasma corticosterone: A reverse microdialysis study. *Journal of Neuroendocrinology* 8: 299-307, 1996.

31. **Knudsen PJ, Dinarello CA, and Strom TB**. Glucocorticoids inhibit transcriptional and post-transcriptional expression of interleukin 1 in U937 cells. *J Immunol* 139: 4129-4134, 1987.

32. **Kow LM, and Pfaff DW**. Vasopressin Excites Ventromedial Hypothalamic Glucose-Responsive Neurons Invitro. *Physiology & Behavior* 37: 153-158, 1986.

33. **Kutteh WH, Rainey WE, and Carr BR**. Glucocorticoids inhibit lipopolysaccharide-induced production of tumor necrosis factor-alpha by human fetal Kupffer cells. *J Clin Endocrinol Metab* 73: 296-301, 1991.

34. **Leonard BE**. HPA and immune axes in stress: involvement of the serotonergic system. *Neuroimmunomodulation* 13: 268-276, 2006.

35. **Li GY, Wang SW, and Rabitz H**. Practical approaches to construct RS-HDMR component functions. *Journal of Physical Chemistry A* 106: 8721-8733, 2002.

36. **Li GY, Wang SW, Rabitz H, Wang SY, and Jaffe P**. Global uncertainty assessments by high dimensional model representations (HDMR). *Chem Eng Sci* 57: 4445-4460, 2002.

37. **Mavroudis PD, Corbett SA, Calvano SE, and Androulakis IP**. Circadian characteristics of permissive and suppressive effects of cortisol and their role in homeostasis and the acute inflammatory response. *Math Biosci* 260: 54-64, 2015.

38. **Mavroudis PD, Corbett SA, Calvano SE, and Androulakis IP**. Mathematical modeling of light-mediated HPA axis activity and downstream implications on the entrainment of peripheral clock genes. *Physiol Genomics* 46: 766-778, 2014.

39. **Mazzocchi G, Malendowicz LK, Rebuffat P, Tortorella C, and Nussdorfer GG**. Arginine-vasopressin stimulates CRH and ACTH release by rat adrenal medulla, acting via the V1 receptor subtype and a protein kinase C-dependent pathway. *Peptides* 18: 191-195, 1997.

40. **Mohawk JA, Green CB, and Takahashi JS**. Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci* 35: 445-462, 2012.

41. **Morris MD**. Factorial Sampling Plans for Preliminary Computational Experiments. *Technometrics* 33: 161-174, 1991.

42. **Motzkus D, Albrecht U, and Maronde E**. The human PER1 gene is inducible by interleukin-6. *J Mol Neurosci* 18: 105-109, 2002.

43. **Newman LA, Walker MT, Brown RL, Cronin TW, and Robinson PR**. Melanopsin forms a functional short-wavelength photopigment. *Biochemistry* 42: 12734-12738, 2003.

44. **Nguyen KD, Fentress SJ, Qiu Y, Yun K, Cox JS, and Chawla A**. Circadian gene Bmal1 regulates diurnal oscillations of Ly6C(hi) inflammatory monocytes. *Science* 341: 1483-1488, 2013.

45. **Nicolaides NC, Charmandari E, Chrousos GP, and Kino T**. Recent advances in the molecular mechanisms determining tissue sensitivity to glucocorticoids: novel mutations, circadian rhythm and ligand-induced repression of the human glucocorticoid receptor. *BMC Endocr Disord* 14: 71, 2014.

46. **Paliogianni F, and Boumpas DT**. Glucocorticoids regulate calcineurin-dependent trans-activating pathways for interleukin-2 gene transcription in human T lymphocytes. *Transplantation* 59: 1333-1339, 1995.

47. **Perez-Aso M, Feig JL, Mediero A, and Cronstein BN**. Adenosine A2A receptor and TNF-alpha regulate the circadian machinery of the human monocytic THP-1 cells. *Inflammation* 36: 152-162, 2013.

48. **Perez-Mendoza M, Rivera-Zavala JB, and Diaz-Munoz M**. Daytime restricted feeding modifies the daily variations of liver gluconeogenesis: adaptations in biochemical and endocrine regulators. *Chronobiol Int* 31: 815-828, 2014.

49. **Pierre K, Schlesinger N, and Androulakis IP**. The role of the hypothalamic-pituitary-adrenal axis in modulating seasonal changes in immunity. *Physiol Genomics* physiolgenomics 00006 02016, 2016.

50. **Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, and Horvath TL**. Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* 304: 110-115, 2004.

51. **Rabitz H, Alis OF, Shorter J, and Shim K**. Efficient input-output model representations. *Comput Phys Commun* 117: 11-20, 1999.

52. **Racanelli V, and Rehermann B**. The liver as an immunological organ. *Hepatology* 43: S54-S62, 2006.

53. **Ramakrishnan R, DuBois DC, Almon RR, Pyszczynski NA, and Jusko WJ**. Fifth-generation model for corticosteroid pharmacodynamics: application to steady-state receptor down-regulation and enzyme induction patterns during seven-day continuous infusion of methylprednisolone in rats. *J Pharmacokinet Pharmacodyn* 29: 1-24, 2002.

54. **Ramsey KM, Yoshino J, Brace CS, Abrassart D, Kobayashi Y, Marcheva B, Hong HK, Chong JL, Buhr ED, Lee C, Takahashi JS, Imai S, and Bass J**. Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. *Science* 324: 651-654, 2009.

55. **Rao R, DuBois D, Almon R, Jusko WJ, and Androulakis IP**. Mathematical modeling of the circadian dynamics of the neuroendocrine-immune network in experimentally induced arthritis. *Am J Physiol Endocrinol Metab* 311: E310-324, 2016.

56. **Reppert SM, and Weaver DR**. Coordination of circadian timing in mammals. *Nature* 418: 935-941, 2002.

57. **Rowell DL, Eckmann L, Dwinell MB, Carpenter SP, Raucy JL, Yang SK, and Kagnoff MF**. Human hepatocytes express an array of proinflammatory cytokines after agonist stimulation or bacterial invasion. *Am J Physiol-Gastr L* 273: G322-G332, 1997.

58. **Rutter J, Reick M, Wu LC, and McKnight SL**. Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. *Science* 293: 510-514, 2001.

59. **Schwartz MW, Seeley RJ, Campfield LA, Burn P, and Baskin DG**. Identification of targets of leptin action in rat hypothalamus. *J Clin Invest* 98: 1101-1106, 1996.

60. **Segall LA, Verwey M, and Amir S**. Timed restricted feeding restores the rhythms of expression of the clock protein, Period2, in the oval nucleus of the bed nucleus of the stria terminalis and central nucleus of the amygdala in adrenalectomized rats. *Neuroscience* 157: 52-56, 2008.

61. **Skene DJ, Lockley SW, James K, and Arendt J**. Correlation between urinary cortisol and 6-sulphatoxymelatonin rhythms in field studies of blind subjects. *Clin Endocrinol* 50: 715-719, 1999.

62. **Sobol' IyM**. On the distribution of points in a cube and the approximate evaluation of integrals. *Zhurnal Vychislitel'noi Matematiki i Matematicheskoi Fiziki* 7: 784-802, 1967.

63. **Sobol IM**. Uniformly distributed sequences with an additional uniform property. *USSR Computational Mathematics and Mathematical Physics* 16: 236-242, 1976.

64. **Spanswick D, Smith MA, Mirshamsi S, Routh VH, and Ashford ML**. Insulin activates ATP-sensitive K+ channels in hypothalamic neurons of lean, but not obese rats. *Nat Neurosci* 3: 757-758, 2000.

65. **Tareen SH, and Ahmad J**. Modelling and analysis of the feeding regimen induced entrainment of hepatocyte circadian oscillators using petri nets. *PLoS One* 10: e0117519, 2015.

66. **Unger J, McNeill TH, Moxley RT, 3rd, White M, Moss A, and Livingston JN**. Distribution of insulin receptor-like immunoreactivity in the rat forebrain. *Neuroscience* 31: 143-157, 1989.

67. **van den Top M, Lee K, Whyment AD, Blanks AM, and Spanswick D**. Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. *Nat Neurosci* 7: 493-494, 2004.

68. **Woller A, Duez H, Staels B, and Lefranc M**. A Mathematical Model of the Liver Circadian Clock Linking Feeding and Fasting Cycles to Clock Function. *Cell Rep* 17: 1087-1097, 2016.

69. **Yamamoto T, Nakahata Y, Tanaka M, Yoshida M, Soma H, Shinohara K, Yasuda A, Mamine T, and Takumi T**. Acute physical stress elevates mouse period1 mRNA expression in mouse peripheral tissues via a glucocorticoid-responsive element. *J Biol Chem* 280: 42036-42043, 2005.

70. **Yi CX, van der Vliet J, Dai J, Yin G, Ru L, and Buijs RM**. Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. *Endocrinology* 147: 283-294, 2006.

71. **Yoshida K, Hashiramoto A, Okano T, Yamane T, Shibanuma N, and Shiozawa S**. TNF-alpha modulates expression of the circadian clock gene Per2 in rheumatoid synovial cells. *Scand J Rheumatol* 42: 276-280, 2013.

72. **Zhang T, Berrocal JG, Frizzell KM, Gamble MJ, DuMond ME, Krishnakumar R, Yang T, Sauve AA, and Kraus WL**. Enzymes in the NAD+ salvage pathway regulate SIRT1 activity at target gene promoters. *J Biol Chem* 284: 20408-20417, 2009.

73. **Zhao X, Allison D, Condon B, Zhang F, Gheyi T, Zhang A, Ashok S, Russell M, MacEwan I, Qian Y, Jamison JA, and Luz JG**. The 2.5 A crystal structure of the SIRT1 catalytic domain bound to nicotinamide adenine dinucleotide (NAD+) and an indole (EX527 analogue) reveals a novel mechanism of histone deacetylase inhibition. *J Med Chem* 56: 963-969, 2013.