The supplementary Figure S1 represents a new model of the mammalian circadian clock. This model allows to investigate the coupling of the cell cycle to the circadian clock via the additional elements MYC, WEE1, INK4a and ARF. The circadian cell cycle regulation model (CCRM) is based on the published core-clock model (CCM) [1] from which 20 equations, 20 variables and 71 parameters were adapted. For the CCM, we used existent values for degradation rates, transcription rates etc. that were either retrieved from the literature or estimated based on known phases and amplitudes using LTI (linear-time-invariant) systems theory. First, we created a linear ODE version of both feedback loops in the network and applied LTI to the linearised system allowing for a partial determination of the parameters by an analytical calculation of amplitudes and phases as functions of the parameters. Each feedback loop was then closed, re-establishing the feedback. The parameters were optimised in order to achieve the optimal amplitude and phase-relations as retrieved from the literature. In a subsequent step, values for the corresponding parameters of the nonlinear system were determined using a Taylor expansion.

In the model, different members of one gene family are represented by a single composite variable: Per (Per1,2,3), Cry (Cry1,2), Ror (Rora,β,γ), Rev-Erb (Rev-Erba,β) and Bmal (Bmal1,2). The mRNA and the cytoplasmic/nuclear protein abundances are distinguished for each gene entity and the nuclear shuttling and accumulation were modelled using nuclear import and export rates. Despite the merging of clock elements that belong to the same gene family, their peak phases of expression are within the observed experimental intervals considered for the construction of the mathematical model. This allows for the appropriate assembly of phase differences between the different gene families and as such, for the generation of the necessary delays, needed for the production of a circadian output in gene and protein expression.

The new model adds 26 new ODEs and adjusts 2 ODEs for Bmal and Per from the CCM (Table 3). The number of variables is increased to 46 (Table 1) and the number of parameters to 170
The missing parameters for the new variables were estimated based on the average values of the previous parameters. We further based our calculations on key biological assumptions relevant for the mammalian circadian oscillator, such as a period of about 23.65 hours and measured phase/amplitude relations between the components of the model, for the wild type scenario.

The model comprises two major compartments, the nucleus (grey) and the cytoplasm (Figure S1). There are 20 species included, represented by genes (highlighted in blue boxes), their corresponding cytoplasmic proteins (highlighted in yellow boxes) and cytoplasmic protein complexes (indexed “C”) and nuclear proteins and nuclear protein complexes (indexed “N”). The transcriptional activation and phosphorylation/dephosphorylation processes are represented by green lines, transcriptional repressions are represented by red lines. Translation and nuclear importation/exportation processes are represented by black lines while complex formation/dissociation processes are indicated by brown lines. Time units are given in hours and concentration units are given as arbitrary units (a.u.).

In the following section, the model design is explained in detail.
A new circadian model including the cell cycle check point elements Wee1, Myc, Ink4a/Arf

The CLOCK/BMAL complex regulates the expression of several cell cycle checkpoint genes, such as Wee1 and Myc by directly binding to the E-box cis-elements in their promoter region [2, 3]. The binding of CLOCK/BMAL activates the transcription of Wee1 while it represses Myc transcription. Following the design principle of the previously published core-clock model [1], the PER/CRY\textsubscript{pool} (which includes all possible PER/CRY heterodimers) has an inhibitory effect on the CLOCK/BMAL-mediated transcriptional regulation of target genes (Figure 1).

**Figure 1:** Wee1 and Myc are regulated by the CLOCK/BMAL heterodimer complex. The transcription of Wee1 and Myc is activated and inhibited by the CLOCK/BMAL complex, respectively. These regulations are indirectly repressed by PER/CRY heterodimers. Green arrows represent transcriptional activation; red lines represent transcriptional repression processes; translation and nuclear import processes are represented by black arrows.

The PER proteins, together with the nuclear protein NONO, have been found to activate the transcription of Ink4a by binding to its promoter in a circadian manner [4]. As the PER/CRY\textsubscript{pool} is positively correlated with PER, the activator of Ink4a, this series of interactions can be modelled as a positive correlation between the PER/CRY\textsubscript{pool} and Ink4a transcription without losing essential dynamic features of the system. The INK4a protein, which is known as a potent inhibitor of D-type cyclin-dependent kinases, competes for binding to CDK4/6 with CycD and
inhibits the subsequent phosphorylation of RB1 (*Figure 2A*) [5]. In this model, we use CDK to represent all CDKs inhibited by INK4a, namely CDK4 and CDK6.

It has been shown that the expression of ARF, another protein encoded by the CDKN2A locus, can be activated by MYC (*Figure 2B*) [6]. Even though it is not clear if this activation is achieved through a direct binding to the promoter of the *Arf* gene, it is common to model the interaction using Hill-type kinetics [7]. Accumulated ARF stabilizes p53 by binding to MDM2, an E3 ubiquitin ligase targeting p53 in the nucleus (*Figure 2B*) [8].

![Figure 2](image1.png)

**Figure 2**: Schematic representation of *Ink4a* and *Arf* reactions considered in the model. Green arrows represent transcriptional activation; brown arrows represent complex formation/dissociation processes; translation and nuclear import processes are represented by black arrows.

**The INK4a/RB/E2F pathway and its regulation of Bmal**

In order to interpret the circadian phenotype of INK4a/ARF-knockout MEFs, it is necessary to extend the model with a feedback from INK4a and ARF to the core circadian clock. For this, we used the INK4a-CDK/CycD-Rb-E2F pathway (*Figure 3*). The transcription factor MYC directly induces the synthesis of *Cdk4* [9]. CDK4 and another cyclin D-dependent kinase, CDK6, form an active complex with CycD and play an important role in the phosphorylation of RB1, the key regulator of the E2F family of transcription factors. Once RB1 is phosphorylated, active
E2F will be released from the RB1/E2F complex [10-12]. MotifMap, a database of candidate regulatory motif sites in humans, reports that several E2F activators such as E2F1, E2F2, and E2F3a can potentially bind to the promoter of Bmal1 to activate its transcription [13]. On the other hand, the formation of the CDKs/CycD complex is inhibited by INK4a, which has a negative effect on RB1 phosphorylation and reinforces the inhibition of E2F [5]. MYC also promotes the transcription of the three E2Fs [14, 15]. In this model, we used E2F to represent the three activators belonging to E2F family, i.e. E2F1, E2F2, and E2F3a. The heterodimer MYC:MAX has also been reported to bind to E-boxes and thereby to influence the circadian clock either by inducing REV-ERBα to dampen the expression and oscillation of BMAL1 [16] or by direct repression of BMAL1 and CLOCK via MIZ1 [17]. Moreover, MYC has been reported to repress Per1 transcriptional activation by CLOCK/BMAL1 via competitive targeting of E-box sequences of the Per1 promoter [18]. In the model, this connection is included implicitly via the Bmal inhibition rate.

In addition, the tumor suppressor protein p53 inhibits the phosphorylation of RB1 via the p21/p27-CDK/CycE-RB1 pathway. Both p21 and p27 are inhibitors of the cyclin E-dependent kinase CDK2, which regulates RB1 phosphorylation and E2F activity synergistically with CDK4/CycD and CDK6/CycD, thus influencing Bmal transcription [19, 20]. The transcription of p21 is induced by p53 [21]. To reduce the complexity, the effect of the p53- p21/p27-CDK/CycE arm was modelled as a negative correlation between p53 and the enzymatic activity of CDK/CycE (Figure 3).
Figure 3: Schematic representation of the INK4a/RB/E2F pathway and its effect on Bmal transcription. Green arrows represent transcriptional activation and phosphorylation/dephosphorylation processes; red lines represent transcriptional repression processes; brown arrows represent complex formation/dissociation processes; translation and nuclear import processes are represented by black arrows.

The ARF/MDM2/p53 pathway and its regulation of Per

The ARF/MDM2/p53/Per pathway is a feedback from ARF to the core circadian clock (Figure 4). The expression of ARF can be activated by MYC [6]. Accumulated ARF associates with MDM2 and leads to rapid degradation of MDM2, thereby inhibiting the MDM2-mediated degradation of p53 and promoting p53 stabilisation and accumulation [22]. Recent data showed that there is a p53 response element located in the promoter region of the Per2 gene which overlaps with E-box cis-elements crucial for CLOCK/BMAL-mediated Per2 transcription [23]. The binding of p53 strongly represses the transcription of Per2 by competing with CLOCK/BMAL for binding to the Per2 promoter [23], as a result p53 and Per2 are out-of-phase (Figure 5).
Figure 4: Schematic representation of the ARF/MDM2/p53 pathway and its effect on CLOCK/BMAL-mediated transcription of Per. Green arrows represent transcriptional activation; red lines represent transcriptional repression processes; brown arrows represent complex formation/dissociation processes; translation and nuclear import processes are represented by black arrows.

Figure 5: Simulated expression of Per and p53. Per and p53 show out-of-phase oscillations. The amplitude of p53 is much lower than that of Per.
Additional model analysis

To further explore the effect of RAS on the circadian clock in silico, we compared the Bmal phenotypes and the corresponding changes in period length after the perturbation by different levels of RAS overexpression represented by the parameter $k_{tt}<1$ (Figure 6). When measuring the period for the first six peaks (five periods) after introducing the perturbation of RAS (represented by $k_{tt}<1$), the same trend could be observed as for measuring the first three periods (Figure 7). Furthermore, we simulated the Bmal phenotype of the Ink4a/Arf−/− system following an inhibition of RAS (represented by $k_{tt}=1.2$) which resulted in a longer period (Figure 8) as was also observed in our experimental data (Figure S1C,E).

We additionally investigated the importance of the INK4a/RB1/E2F1 pathway (module 1) and the ARF/MDM2/p53 pathway (module 2) in reproducing the effect of RAS overexpression on the Bmal period by either uncoupling them from the core-clock system or by setting their expression to their constitutive average value (Figure 9).

In the model, we measured the period in the transient region of the simulations. This is in agreement with our RT-qPCR data in IMR-90 cells on day 5 and 11 after overexpression of RAS. The data show that despite the assumed stability of retrovirus-mediated Hras overexpression, the expression level of Hras display some biological noise: it first strongly increases (day 5) and then decreases again (Figure 10).
Figure 6: *In silico Bmal* phenotypes after perturbation by different levels of RAS. The period was measured for a transient region, defined as the mean of the time between the first four peaks (three periods) after introducing the perturbation of RAS (represented by $ktt<1$) for (A) the Ink4a/Arf$^{+/+}$ system and (B) the Ink4a$^{-/-}$ system. When measuring the first five periods instead, we still see the same tendency of period changes in dependency of $ktt$ for (C) the Ink4a/Arf$^{+/+}$ system and (D) the Ink4a$^{-/-}$ system.
Figure 7: The model qualitatively reproduces experimental period changes upon RAS overexpression. *In silico* expression data show that upon simulation of RAS overexpression, the Ink4a/Arf^{+/+} system acquires a longer and Ink4a/Arf^{-/-} system a shorter period compared to the corresponding simulated wild type system. The period was measured for a transient region, defined as the mean of the time between the first six peaks (five periods) after introducing the perturbation of RAS (represented by ktt<1).

Figure 8: The model predicts an increase in period length upon RAS inhibition. *In silico* expression data show that upon simulation of RAS inhibition (-RAS), the Ink4a/Arf^{-/-} system acquires a longer period compared to the corresponding system with WT RAS (ktt=1). The period was measured for a transient region, defined as the mean of the time between the first four peaks (three periods) after introducing the perturbation of RAS (overexpression represented by ktt<1 and inhibition represented by ktt>1).
Figure 9: Modular analysis of Bmal expression level after perturbation by different levels of RAS.

The importance of the INK4a/RB1/E2F1 pathway (module 1) and the ARF/MDM2/p53 pathway (module 2) in influencing the circadian period is analysed by simulating different scenarios in silico. The simulated Bmal expression profiles show phase-shifted oscillations that cause differing effects following the perturbation by RAS (represented by $k_{tt}<1$). A) Module 1 is decoupled from the core-clock or B) the oscillatory expression of its connective component E2F$_N$ is clamped to its constitutive average value. C) Module 2 is decoupled from the core-clock or D) the oscillatory expression of its connective component p53$_N$ is clamped to its constitutive average value.
Figure 10: Time-dependent change of gene levels after Hras overexpression in IMR-90 cells. RT-qPCR data show that while Bmal1 and Ink4/Arf are upregulated after retrovirus-mediated Hras overexpression in IMR-90 cells, their expression levels change over the course of the next 11 days, as does the expression of Hras itself. Numerical values are provided in S1 Data.
Table 1: List of variables. *- Phosphorylated proteins, "c"- indexed - cytoplasmic proteins, "N"- indexed - nuclear proteins.

| Variable [a.u.] | Name               | Note   |
|-----------------|--------------------|--------|
| x1              | CLOCK/BMAL         | CCM    |
| x2              | PER*<sub>N</sub>/CRY<sub>N</sub> | CCM    |
| x3              | PER<sub>N</sub>/CRY<sub>N</sub> | CCM    |
| PC              | PER/CRY<sub>pool</sub> | CCM    |
| x5              | REV-ERBN<sub>N</sub> | CCM    |
| x6              | ROR<sub>N</sub>      | CCM    |
| x7              | BMAL<sub>N</sub>   | CCM    |
| x8              | ARF<sub>N</sub>     | CCRM   |
| x9              | MDM2<sub>N</sub>   | CCRM   |
| x10             | p53<sub>N</sub>     | CCRM   |
| x11             | p53/MDM2<sub>N</sub> | CCRM   |
| x12             | ARF/MDM2<sub>N</sub> | CCRM   |
| x13             | INK4a<sub>N</sub>  | CCRM   |
| x14             | CDK/CycD<sub>N</sub> | CCRM   |
| x15             | CDK/CycD/INK4a<sub>N</sub> | CCRM   |
| x16             | E2F<sub>N</sub>     | CCRM   |
| x17             | RB<sub>N</sub>     | CCRM   |
| x18             | RB-E2F<sub>N</sub> | CCRM   |
| x19             | RB*<sub>N</sub>     | CCRM   |
| x20             | MYC<sub>N</sub>    | CCRM   |
| y1              | Per                | CCM    |
| y2              | Cry                | CCM    |
| y3              | Rev-Erb            | CCM    |
| y4              | Ror                | CCM    |
| Variable [a.u.] | Name          | Note   |
|-----------------|---------------|--------|
| y5              | Bmal          | CCM    |
| y6              | Ink4a         | CCRM   |
| y7              | Arf           | CCRM   |
| y8              | Myc           | CCRM   |
| y9              | Wee1          | CCRM   |
| y10             | Mdm2          | CCRM   |
| y11             | CDK/CycD      | CCRM   |
| y12             | E2f           | CCRM   |
| z1              | CRY\(_c\)     | CCM    |
| z2              | PER\(_c\)     | CCM    |
| z3              | PER\(*\)\(_c\) | CCM    |
| z4              | PER\(*\)\(_c\)/CRY\(_c\) | CCM |
| z5              | PER\(_c\)/CRY\(_c\) | CCM |
| z6              | REV-ERB\(_c\) | CCM |
| z7              | ROR\(_c\)     | CCM    |
| z8              | BMAL\(_c\)    | CCM    |
| z9              | ARF\(_c\)     | CCRM   |
| z10             | MDM2\(_c\)    | CCRM   |
| z11             | INK4a\(_c\)   | CCRM   |
| z12             | CDK/CycD\(_c\) | CCRM |
| z13             | E2F\(_c\)     | CCRM   |
| z14             | MYC\(_c\)     | CCRM   |
Table 2: List of parameters. aAverage value of all parameters in the same category used in [1]. bThe hill coefficients of new components was pre-set to 1 at this stage. cParameters which were fine-tuned to maintain the oscillations of the system and to fit experimental observations.

| Parameters | Name | Value | Reference |
|------------|------|-------|-----------|
| dx1        | CLOCK/BMAL | 0.08  | [1]       |
| dx2        | PER* \_N/CRY \_N | 0.06  | [1]       |
| dx3        | PER \_N/CRY \_N | 0.09  | [1]       |
| dx5        | REV-ERB \_N | 0.17  | [1]       |
| dx6        | ROR \_N | 0.12  | [1]       |
| dx7        | BMAL \_N | 0.15  | [1]       |
| dx8        | ARF \_N | 0.11  | [24]      |
| dx9        | MDM2 \_N | 0.46  | [22]      |
| dx10       | p53 \_N | 0.231 | [22]      |
| dx11       | p53/MDM2 \_N | 2.07  | [25]      |
| dx12       | ARF/MDM2 \_N | 1.39  | [22]      |
| dx13       | INK4a \_N | 0.11  | [26]      |
| dx14       | CDK/CycD \_N | 1.5   | [27, 28]  |
| dx16       | E2F \_N | 0.35  | [29]      |
| dx17       | RB \_N | 0.069 | [30]      |
| dx18       | RB-E2F \_N | 0.03  | [31, 32]  |
| dx19       | RB* \_N | 0.069 | [32, 33]  |
| dx20       | MYC \_N | 1.39  | [34, 35]  |
| dy1        | Per | 0.3   | [36]      |
| dy2        | Cry | 0.2   | [1]       |
| dy3        | Rev-Erb | 2     | [1]       |
| dy4   | Ror    | 0.2  | [1] |
| dy5   | Bmal   | 1.6  | [1] |
| dy6   | Ink4a  | 0.86a|     |
| dy7   | Arf    | 0.69 |     |
| dy8   | Myc    | 0.86 a|   |
| dy9   | Wee1   | 0.86 a|   |
| dy10  | Mdm2   | 0.36 | [37]|
| dy11  | CDK/CycD | 0.86 a|   |
| dy12  | E2f    | 0.25 |     |

**Degradation rates for cytoplasmic proteins [hour⁻¹]**

| dz1   | CRYc  | 0.23 | [1] |
| dz2   | PERc  | 0.25 | [1] |
| dz3   | PER* c| 0.6  | [1] |
| dz4   | PER*/CRYc | 0.2 | [1] |
| dz5   | PERc/CRYc | 0.2 | [1] |
| dz6   | REV-ERBc | 0.31 | [1] |
| dz7   | RORc  | 0.3  | [1] |
| dz8   | BMALc | 0.73 | [1] |
| dz9   | ARFc  | 0.3525 a|   |
| dz10  | MDM2c | 0.3525 a|   |
| dz11  | INK4ac | 0.3525 a|   |
| dz12  | CDK/CycDc | 0.7 |     |
| dz13  | E2Fc  | 0.7  |     |
| dz14  | MYCc  | 0.7  | [14]|

**Reaction rates for complex formation/dissociation**

| kfx1  | CLOCK/BMAL-complex formation | 2.3  | [1] |
| Parameter | Description | Rate Constant |
|-----------|-------------|---------------|
| kdx1      | CLOCK/BMAL-complex dissociation | 0.01 [1] |
| kfz4      | PER*/CRY$_C$-complex formation  | 1 [1] |
| kdz4      | PER$_C$/CRY$_C$-complex dissociation | 1 [1] |
| kfz5      | PER$_C$/CRY$_C$-complex formation | 1 [1] |
| kdz5      | PER$_C$/CRY$_C$-complex dissociation | 1 [1] |
| kfx11     | P53/MDM2$_N$-complex formation | 3.96 |
| kdx11     | P53/MDM2$_N$-complex dissociation | 0.0396 |
| kfx12     | ARF/MDM2$_N$-complex formation | 8 |
| kdx12     | ARF/MDM2$_N$-complex dissociation | 0.0396 |
| kfx15     | INK4a/CDK/CYCD$_N$-complex formation | 8 |
| kfx18     | RB/E2F-complex formation | 18 |

### Phosphorylation/dephosphorylation reaction rates [hour$^{-1}$]

| Parameter | Description | Rate Constant |
|-----------|-------------|---------------|
| kphz2     | PER$_C$ phosphorylation rate | 2 [1] |
| kdphz3    | PER$_C^*$ dephosphorylation rate | 0.05 [1] |
| kphx17    | RB phosphorylation rate | 18 [32] |
| kdphx19   | RB$_C^*$ dephosphorylation rate | 3.6 [32] |
| Kph       | activation constant for RB phosphorylation by CDK/CycD | 0.92 [38] |
| Kdph      | activation constant for RB$_C^*$ dephosphorylation | 0.01 [39] |
| Kbp       | inhibition constant for RB phosphorylation by p53 | 0.2 $^c$ |

### Transcription rates [a.u. hour$^{-1}$]

| Parameter | Description | Rate |
|-----------|-------------|------|
| V$_{1\max}$ | Per | 1 [1] |
| V$_{2\max}$ | Cry | 2.92 [1] |
| V$_{3\max}$ | Rev-Erb | 1.9 [1] |
| V$_{4\max}$ | Ror | 10.9 [1] |
| V$_{5\max}$ | Bmal | 1 [1] |
| V$_{6\max}$ | Ink4a | 3.544 $^a$ |
| \( V_{\text{max}} \) | Protein       | Value  |
|-----------------|--------------|--------|
| \( V_{7\text{max}} \) | Arf          | 3.544^a |
| \( V_{8\text{max}} \) | Myc          | 3.544^a |
| \( V_{9\text{max}} \) | Wee1         | 3.544^a |
| \( V_{10\text{max}} \) | Mdm2         | 5.4    |
| \( V_{11\text{max}} \) | Cdk/CycD     | 3.544^a |
| \( V_{12\text{max}} \) | E2f          | 3.544^a |

**Activation/inhibition rates**

| \( k_t \) | Functionality                        | Value   |
|-----------|--------------------------------------|---------|
| \( k_1 \) | Per activation rate                  | 3       |
| \( k_i \) | Per inhibition rate                  | 0.9     |
| \( k_t_2 \) | Cry activation rate                  | 2.4     |
| \( k_i_2 \) | Cry inhibition rate (by PER/CRY\text{pool}) | 0.7     |
| \( k_i_{21} \) | Cry inhibition rate (by REV-ERB\text{N}) | 5.2     |
| \( k_t_3 \) | Rev-Erb activation rate              | 2.07    |
| \( k_i_3 \) | Rev-Erb inhibition rate              | 3.3     |
| \( k_t_4 \) | Ror activation rate                  | 0.9     |
| \( k_i_4 \) | Ror inhibition rate                  | 0.4     |
| \( k_t_5 \) | Bmal activation rate                 | 8.35    |
| \( k_i_5 \) | Bmal inhibition rate                 | 1.94    |
| \( k_i_{i1} \) | Per inhibition rate 2 (by p53)       | 2.488^a |
| \( k_t_{5\_e} \) | Bmal activation rate (by E2F)        | 5^c     |
| \( k_t_6 \) | Ink4a activation rate                | 3.344^a |
| \( k_t_7 \) | Arf activation rate                  | 3.344^a |
| \( k_i_8 \) | Myc inhibition rate 1                | 2.488^a |
| \( k_i_{i8} \) | Myc inhibition rate 2 (PC to CB)     | 2.488^a |
| \( k_t_9 \) | Wee1 activation rate                 | 3.344^a |
| \( k_i_9 \) | Wee1 inhibition rate                 | 2.488^a |
### Supporting Information S1 Text – Model description, design and analysis

| $kt_{10}$ | Mdm2 activation rate | 1.85 | [40] |
| $kt_{11}$ | Cdk activation rate | 0.15 | ^c |
| $kt_{12}$ | E2f activation rate | 3.344 | ^a |

| Transcription fold activation (dimensionless) |
|---|---|---|---|
| $a$ | Per | 12 | [1] |
| $d$ | Cry | 12 | [1] |
| $g$ | Rev-Erb | 5 | [1] |
| $h$ | Ror | 5 | [1] |
| $i$ | Bmal | 12 | [1] |
| $a_{-1}$ | Bmal (by E2F) | 3 | ^c |
| $o$ | Ink4a | 9.2 | ^a |
| $l$ | Arf | 9.2 | ^a |
| $l_{1}$ | Wee1 | 9.2 | ^a |
| $r_{1}$ | Mdm2 | 11 | [40] |
| $r_{2}$ | Cdk4 | 9.2 | ^a |
| $r_{3}$ | E2f | 9.2 | ^a |

| Production rates [hour$^{-1}$] |
|---|---|---|---|
| $kp_{1}$ | PER$_c$ | 0.4 | [1] |
| $kp_{2}$ | CRY$_c$ | 0.26 | [1] |
| $kp_{3}$ | REV-ERB$_c$ | 0.37 | [1] |
| $kp_{4}$ | ROR$_c$ | 0.76 | [1] |
| $kp_{5}$ | BMAL$_c$ | 1.21 | [1] |
| $kp_{6}$ | INK4a$_c$ | 0.6 | ^a |
| $kp_{7}$ | ARF$_c$ | 0.6 | ^a |
| $kp_{8}$ | MYC$_c$ | 0.6 | ^a |
| $kp_{10}$ | MDM2$_c$ | 0.6 | ^a |
### kp11
CDK<sub>c</sub> 0.6<sup>a</sup>

### kp12
E2F<sub>c</sub> 0.4

### Import/Export rates [hour<sup>-1</sup>]

| kiz4   | PER*/CRY<sub>c</sub> | 0.2 | [1] |
|--------|---------------------|-----|-----|
| kiz5   | PER/CRY<sub>c</sub>  | 0.1 | [1] |
| kiz6   | REV-ERB<sub>c</sub> | 0.5 | [1] |
| kiz7   | ROR<sub>c</sub>     | 0.1 | [1] |
| kiz8   | BMAL<sub>c</sub>    | 0.1 | [1] |
| kex2   | PER*/CRY<sub>N</sub> | 0.02| [1] |
| kex3   | PER/CRY<sub>N</sub> | 0.02| [1] |
| kiz10  | MDM2<sub>c</sub>    | 0.2<sup>a</sup> |
| kiz11  | INK4a<sub>c</sub>   | 0.2<sup>a</sup> |
| kiz9   | ARF<sub>c</sub>     | 0.2<sup>a</sup> |
| kiz12  | CDK<sub>c</sub>     | 0.2<sup>a</sup> |
| kiz13  | E2F<sub>c</sub>     | 0.2<sup>a</sup> |
| kiz14  | MYC<sub>c</sub>     | 0.2<sup>a</sup> |

### Hill coefficients of transcription (dimensionless)

| b | Per activation | 5 | [1] |
| c | Per inhibition | 7 | [1] |
| e | Cry activation | 6 | [1] |
| f | Cry inhibition | 4 | [1] |
| f1| Cry inhibition | 1 | [1] |
| v | Rev-Erb activation | 6 | [1] |
| w | Rev-Erb inhibition | 2 | [1] |
| p | Ror activation | 6 | [1] |
| q | Ror inhibition | 3 | [1] |
| \( n \) | Bmal activation | 2 | [1] |
| \( m \) | Bmal inhibition | 5 | [1] |
| \( r \) | Ink4a activation | 1 \( ^b \) |
| \( s \) | Arf activation | 1 \( ^b \) |
| \( h4 \) | Myc inhibition 1 | 1 \( ^b \) |
| \( h5 \) | Myc inhibition 2 | 1 \( ^b \) |
| \( h6 \) | Wee1 activation | 1 \( ^b \) |
| \( h7 \) | Wee1 inhibition | 1 \( ^b \) |
| \( h1 \) | Mdm2 activation | 1.8 | [41] |
| \( h8 \) | Per inhibition (by p53) | 1 \( ^b \) |
| \( a_2 \) | Bmal (by E2F) | 1 \( ^b \) |
| \( h2 \) | Cdk activation | 1 \( ^b \) |
| \( h3 \) | E2F activation | 1 \( ^b \) |

**Exogenous RNA [a.u.]**

| \( y1_0 \) | Per | 0 | [1] |
| \( y2_0 \) | Cry | 0 | [1] |
| \( y3_0 \) | Rev-Erb | 0 | [1] |
| \( y4_0 \) | Ror | 0 | [1] |
| \( y5_0 \) | Bmal | 0 | [1] |
| Ink4a0 | Ink4a | 0 \( ^a \) |
| Mdm0 | Mdm2 | 0 \( ^a \) |
| Arf0 | Arf | 0 \( ^a \) |
| CDK0 | Cdk | 0 \( ^a \) |
| Myc0 | Myc | 0 \( ^a \) |
| E2F0 | E2f | 0 \( ^a \) |
| **source_p53** | p53 | 4.5 c |
|----------------|-----|-------|
| **source_RB**  | RB  | 1 c   |

**Nuclear protein [a.u.]**

| **Weight factors [a.u.]** |
|---------------------------|
| a2                        |
| PER*/CRY_{N}              |
| 1 c                       |
| a3                        |
| PER/CRY_{N}               |
| 1 c                       |
Table 3: Equations of the circadian cell cycle model.

| Equation | Description |
|----------|-------------|
| \( \frac{dy_6}{dt} = (1 + \ln \frac{1}{ktt})V_{6\text{max}} \frac{1 + o\left(\frac{PC}{k_{10}}\right)^y}{1 + \left(\frac{PC}{k_{16}}\right)} - d_{y6}y_6 \) | **Ink4a** |
| \( \frac{dy_7}{dt} = V_{7\text{max}} \frac{1 + l\left(\frac{x_{20}}{k_{7}}\right)^s}{1 + \left(\frac{x_{20}}{k_{17}}\right)^s} - d_{y7}y_7 \) | **Arf** |
| \( \frac{dy_8}{dt} = V_{8\text{max}} \frac{1}{1 + \left(\frac{k_{10}^{h_5} + PC\kappa^5}{ktt \cdot k_{10}}\right)^{h_4}} - d_{y8}y_8 \) | **Myc** |
| \( \frac{dy_9}{dt} = (1 + \ln \frac{1}{ktt})V_{9\text{max}} \frac{1 + l\left(\frac{x_1}{ktt \cdot k_{19}}\right)^{h_6}}{1 + \left(\frac{x_1}{ktt \cdot k_{19}}\right)^{h_6}} - d_{y9}y_9 \) | **Wee1** |
| \( \frac{dy_{10}}{dt} = V_{10\text{max}} \frac{1 + r_1\left(\frac{x_{10}}{k_{110}}\right)^{h_1}}{1 + \left(\frac{x_{10}}{k_{110}}\right)^{h_1}} - d_{y10}y_{10} \) | **Mdm2** |
| \( \frac{dy_{11}}{dt} = V_{11\text{max}} \frac{1 + r_2\left(\frac{x_{20}}{k_{11}}\right)^{h_2}}{1 + \left(\frac{x_{20}}{k_{11}}\right)^{h_2}} - d_{y11}y_{11} \) | **CDK/CycD** |
| \( \frac{dy_{12}}{dt} = V_{12\text{max}} \frac{1 + r_3\left(\frac{x_{20}}{k_{12}}\right)^{h_3}}{1 + \left(\frac{x_{20}}{k_{12}}\right)^{h_3}} - d_{y12}y_{12} \) | **E2f** |
| \( \frac{dz_9}{dt} = k_{p7}(y_7 + y_{70}) - ki_{x9}z_9 - d_{x9}z_9 \) | **ARF_c** |
| \( \frac{dz_{10}}{dt} = k_{p10}(y_{10} + y_{100}) - ki_{x10}z_{10} - d_{x10}z_{10} \) | **MDM2_c** |
| \( \frac{dz_{11}}{dt} = k_{p6}(y_6 + y_{60}) - ki_{x11}z_{11} - d_{x11}z_{11} \) | **INK4a_c** |
| \( \frac{dz_{12}}{dt} = k_{p11}(y_{11} + y_{110}) - ki_{x12}z_{12} - d_{x12}z_{12} \) | **CDK/CycD_c** |
| \( \frac{dz_{13}}{dt} = k_{p12}(y_{12} + y_{120}) - ki_{x13}z_{13} - d_{x13}z_{13} \) | **E2F_c** |
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**Supporting Information S1 Text – Model description, design and analysis**

| Equation | Description |
|----------|-------------|
| \( \frac{dX_c}{dt} = k_{pb}(y8 + y8_d) - k_{i24}x_{14} - d_{x14}x_{14} \) | (13) |
| \( \frac{dx}{dt} = k_{ix11}^29 + k_{d12}x_{12} - k_{f12}x_{12} - d_{x12}x_{12} \) | (14) |
| \( \frac{dx_9}{dt} = k_{i10}x_{10} + k_{d11}x_{11} + k_{d12}x_{12} - k_{f11}x_{11}x_{10} - k_{f12}x_{12}x_{12} \) | (15) |
| \( \frac{dX_{p33}}{dt} = source_{p53} + k_{d11}x_{11} - k_{f11}x_{11}x_{10} - d_{x10}x_{10} \) | (16) |
| \( \frac{dx_{p33}}{dt} = k_{f11}x_{11}x_{10} - k_{d11}x_{11} - d_{x11}x_{11} \) | (17) |
| \( \frac{dx_{2}}{dt} = k_{f12}x_{12}x_{9} - k_{d12}x_{12} - d_{x12}x_{12} \) | (18) |
| \( \frac{dx_{13}}{dt} = k_{i11}x_{11} - k_{f15}x_{13}x_{14} - d_{x13}x_{13} \) | (19) |
| \( \frac{dx_{14}}{dt} = k_{i12}x_{12} - k_{f15}x_{13}x_{14} - d_{x14}x_{14} \) | (20) |
| \( \frac{dx_{15}}{dt} = k_{d15}x_{15}x_{14} - d_{x15}x_{15} \) | (21) |
| \( \frac{dx_{16}}{dt} = k_{i12}x_{13} - k_{ph_{17}}(x_{14} + \frac{K_{hp}}{K_{hp} + x_{10}})x_{18} + K_{hp} - k_{f18}x_{16}x_{17} \) | (22) |
| \( \frac{dx_{17}}{dt} = source_{rb} + k_{dph_{19}}x_{19} + K_{dp} - k_{ph_{17}} \) | (23) |
| \( \frac{dx_{18}}{dt} = k_{f18}x_{16}x_{17} - k_{ph_{17}}(x_{14} + \frac{K_{hp}}{K_{hp} + x_{10}})x_{18} + K_{hp} - d_{x18}x_{18} \) | (24) |
| \( \frac{dx_{19}}{dt} = k_{ph_{17}}x_{14} + \frac{K_{hp}}{K_{hp} + x_{10}}x_{17} + \frac{K_{hp}}{x_{17} + K_{ph}}x_{18} + K_{ph} \) | (25) |
| \( \frac{dx_{20}}{dt} = k_{i24}x_{14} - d_{x20}x_{20} \) | (26) |
| \( \frac{dY_{5}}{dt} = V_{5_{max}} \frac{1 + i(x_{6}^{m})_{K_{i5}}}{1 + (x_{5}^{m})_{K_{i5}} + (x_{6}^{m})_{K_{i5}} + (x_{16}^{n_{2}})_{K_{i5,e}} - d_{y_{5}}y_{5} \) | (27) |
Per
\[
\frac{dy_1}{dt} = V_{1_{\text{max}}} \frac{1 + a \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b}{1 + \left( \frac{P_C}{k_{t\tau}} \right)^c + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b} - d_{y_1}y_1
\]

CLOCK/BMAL
\[
\frac{dx_1}{dt} = k_{f1}x_7 - k_{d1}x_1 - d_{x1}x_1
\]

Rev-Erb
\[
\frac{dy_3}{dt} = V_{3_{\text{max}}} \frac{1 + b \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b}{1 + \left( \frac{P_C}{k_{t\tau}} \right)^c + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^b} - d_{y3}y_3
\]

Ror
\[
\frac{dy_4}{dt} = V_{4_{\text{max}}} \frac{1 + c \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^c}{1 + \left( \frac{P_C}{k_{t\tau}} \right)^c + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^c + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^c} - d_{y4}y_4
\]

REV-ERBC
\[
\frac{dz_6}{dt} = k_{p3}(y3 + y3_0) - k_{i2}z_6 - d_{z6}z_6
\]

RORc
\[
\frac{dz_7}{dt} = k_{p4}(y4 + y4_0) - k_{i2}z_7 - d_{z7}z_7
\]

REV-ERBN
\[
\frac{dx_5}{dt} = k_{i2}z_6 - d_{z5}x_5
\]

RORn
\[
\frac{dx_6}{dt} = k_{i2}z_7 - d_{z6}x_6
\]

BMALc
\[
\frac{dz_8}{dt} = k_{p5}(y5 + y5_0) - k_{i2}z_8 - d_{z8}z_8
\]

BMALN
\[
\frac{dx_7}{dt} = k_{i2}z_8 + k_{d2}x_1 - k_{f2}x_7 - d_{z7}x_7
\]

Cry
\[
\frac{dy_2}{dt} = V_{2_{\text{max}}} \frac{1 + d \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^e}{1 + \left( \frac{P_C}{k_{t\tau}} \right)^f + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^e + \left( \frac{x_1}{k_{tt} \cdot k_{t\tau}} \right)^e} - d_{y2}y_2
\]

CRYc
\[
\frac{dz_1}{dt} = k_{p2}(y2 + y2_0) + k_{d2}z_4 + k_{d5}z_5 - k_{f2}z_1z_2 - k_{f2}z_1z_3 - d_{z1}z_1
\]

PERc
\[
\frac{dz_2}{dt} = k_{p1}(y1 + y1_0) + k_{d2}z_5 + k_{p2}z_3 - k_{f2}z_2z_1 - k_{p2}z_2 + d_{z2}z_2
\]

PERc*
\[
\frac{dz_3}{dt} = k_{p2}z_2z_2 + k_{d2}z_4 - k_{p2}z_2z_3 + k_{f2}z_2z_3 - d_{z2}z_3
\]

PER*c/CRYc
\[
\frac{dz_3}{dt} = k_{f2}z_1z_3 + k_{e}z_2z_2 - k_{i2}z_4 + k_{d2}z_4 - d_{z4}z_4
\]

PER/CYc
\[
\frac{dz_5}{dt} = k_{f2}z_1z_2 + k_{e}z_3z_3 - k_{i2}z_5 + k_{d2}z_5 - d_{z5}z_5
\]
| Equation | Description |
|----------|-------------|
| \( \frac{dx_2}{dt} = ki_z x_4 - ke_x x_2 - d x_2 x_2 \) | \( \text{PER}/\text{CRY}_N \) |
| \( \frac{dx_3}{dt} = ki_z x_5 - ke_x x_3 - d x_3 x_3 \) | \( \text{PER}/\text{CRY}_N \) |
| \( PC = x_2 + x_3 \) | \( \text{PER}/\text{CRY}_\text{pool} \) |

Note: \( k_i_z, k_e_x, d \) are constants.
Table 4: Robustness analysis of the model parameters. The robustness analysis was conducted to investigate how minor changes in the parameter values effect on the overall system. The parameter values were both decreased and increased by 10% and the subsequent variation of the overall system period compared to the wild type period. -10%: 10% decrease in the parameter value; +10%: 10% increase in the parameter value; $T_{\text{new}}$: new value for $T$ after the perturbation; DT%: variation of the new period value to the wild type value. The wild-type period is 23.65 h.

| Parameter | $-10\%$ | $+10\%$ |
|-----------|---------|---------|
|           | $T_{\text{new}}$ | DT% | $T_{\text{new}}$ | DT% |
| $dx1$     | 23.89   | 1.019   | 23.49 | -0.693 |
| $dx2$     | 23.85   | 0.846   | 23.52 | -0.554 |
| $dx3$     | 23.7    | 0.224   | 23.62 | -0.144 |
| $dx5$     | 24.04   | 1.653   | 23.19 | -1.953 |
| $dx6$     | 23.82   | 0.723   | 23.49 | -0.698 |
| $dx7$     | 23.66   | 0.059   | 23.64 | -0.059 |
| $dx8$     | 23.65   | 0       | 23.65 | 0       |
| $dx9$     | 23.65   | 0.004   | 23.65 | -0.004 |
| $dx10$    | 23.65   | 0       | 23.65 | 0       |
| $dx11$    | 23.65   | 0       | 23.65 | 0       |
| $dx12$    | 23.65   | 0       | 23.65 | 0       |
| $dx13$    | 23.65   | -0.008  | 23.65 | 0.008   |
| $dx14$    | 23.65   | 0       | 23.65 | 0       |
| $dx16$    | 23.67   | 0.068   | 23.63 | -0.068 |
| $dx17$    | 23.65   | 0       | 23.65 | 0       |
| $dx18$    | 23.65   | 0       | 23.65 | 0       |
| $dx19$    | 23.65   | 0       | 23.65 | 0       |
| $dx20$    | 23.67   | 0.072   | 23.64 | -0.063 |
| $dy1$     | 23.78   | 0.529   | 23.62 | -0.14  |
| $dy2$     | 23.66   | 0.03    | 23.65 | -0.021 |
| $dy3$     | 23.95   | 1.277   | 23.36 | -1.209 |
| $dy4$     | 23.82   | 0.706   | 23.49 | -0.685 |
| $dy5$     | 23.94   | 1.222   | 23.42 | -0.989 |
| $dy6$     | 23.64   | -0.051  | 23.67 | 0.08   |
| $dy7$     | 23.65   | -0.004  | 23.65 | 0.004  |
| $dy8$     | 23.67   | 0.072   | 23.64 | -0.063 |
| $dy9$     | 23.65   | 0       | 23.65 | 0       |
| $dy10$    | 23.66   | 0.021   | 23.65 | -0.021 |
| $dy11$    | 23.67   | 0.093   | 23.64 | -0.047 |
| $dy12$    | 23.67   | 0.076   | 23.63 | -0.08  |
| Parameter | $T_{\text{new}}$ | DT%  | $T_{\text{new}}$ | DT%  |
|-----------|-----------------|------|-----------------|------|
| $dz1$     | 23.66           | 0.0381 | 23.64           | -0.038 |
| $dz2$     | 23.65           | -0.0085 | 23.65           | 0.008 |
| $dz3$     | 23.67           | 0.0719 | 23.64           | -0.051 |
| $dz4$     | 23.68           | 0.1184 | 23.63           | -0.076 |
| $dz5$     | 23.65           | -0.0085 | 23.65           | 0.013 |
| $dz6$     | 23.82           | 0.7019 | 23.48           | -0.702 |
| $dz7$     | 23.75           | 0.4144 | 23.55           | -0.406 |
| $dz8$     | 24.04           | 1.649  | 23.33           | -1.336 |
| $dz9$     | 23.65           | -0.004 | 23.65           | 0.004 |
| $dz10$    | 23.65           | 0.013  | 23.65           | -0.013 |
| $dz11$    | 23.64           | -0.047 | 23.66           | 0.059 |
| $dz12$    | 23.67           | 0.076  | 23.64           | -0.047 |
| $dz13$    | 23.67           | 0.068  | 23.63           | -0.068 |
| $dz14$    | 23.66           | 0.055  | 23.64           | -0.051 |
| $kfx1$    | 23.77           | 0.5116 | 23.55           | -0.427 |
| $kdx1$    | 23.65           | 0.0085 | 23.65           | -0.008 |
| $kfx4$    | 23.65           | -0.0211 | 23.66           | 0.021 |
| $kdz4$    | 23.66           | 0.0381 | 23.64           | -0.034 |
| $kfx5$    | 23.65           | 0.0169 | 23.65           | -0.017 |
| $kdz5$    | 23.65           | -0.0169 | 23.65           | 0.017 |
| $kfx11$   | 23.65           | -0.004 | 23.65           | 0     |
| $kdx11$   | 23.65           | 0      | 23.65           | 0     |
| $kfx12$   | 23.65           | 0      | 23.65           | 0     |
| $kdx12$   | 23.65           | 0      | 23.65           | 0     |
| $kfx15$   | 23.65           | 0.013  | 23.65           | -0.013 |
| $kfx18$   | 23.65           | 0.004  | 23.65           | -0.004 |
| $kphz2$   | 23.65           | 0.0042 | 23.65           | -0.004 |
| $kdphz3$  | 23.65           | 0      | 23.65           | 0     |
| $kphx17$  | 23.63           | -0.068 | 23.66           | 0.038 |
| $kdphx19$ | 23.66           | 0.03   | 23.64           | -0.042 |
| $Kph$     | 23.65           | 0.017  | 23.65           | -0.017 |
| $Kdp$     | 23.65           | 0      | 23.65           | 0     |
| $Kbp$     | 23.64           | -0.03  | 23.66           | 0.021 |
| $V1max$   | 23.7            | 0.224  | 23.6            | -0.199 |
| $V2max$   | 23.67           | 0.093  | 23.64           | -0.063 |
| $V3max$   | 23.48           | -0.727 | 23.81           | 0.672 |
| $V4max$   | 23.6            | -0.199 | 23.68           | 0.131 |
| Parameter  | -10% T<sub>new</sub> | DT%  | +10% T<sub>new</sub> | DT%  |
|------------|---------------------|------|---------------------|------|
| V5max      | 23.57               | -0.342 | 23.72               | 0.288 |
| V6max      | 23.67               | 0.085  | 23.64               | -0.051 |
| V7max      | 23.65               | 0.004  | 23.65               | -0.004 |
| V8max      | 23.63               | -0.068 | 23.67               | 0.063  |
| V9max      | 23.65               | 0      | 23.65               | 0      |
| V10max     | 23.64               | -0.025 | 23.65               | 0.017  |
| kt1        | 23.68               | 0.118  | 23.83               | 0.77   |
| ki1        | 23.66               | 0.042  | 23.69               | 0.182  |
| kt2        | 23.6                | -0.199 | 23.69               | 0.186  |
| ki2        | 23.77               | 0.486  | 23.61               | -0.161 |
| ki21       | 23.67               | 0.063  | 23.64               | -0.051 |
| kt3        | 24.01               | 1.522  | 23.55               | -0.44  |
| ki3        | 23.64               | -0.034 | 23.66               | 0.03   |
| kt4        | 23.64               | -0.047 | 23.67               | 0.072  |
| ki4        | 23.47               | -0.753 | 23.69               | 0.165  |
| kt5        | 23.68               | 0.14   | 23.61               | -0.178 |
| ki5        | 23.81               | 0.681  | 23.51               | -0.6   |
| kii1       | 23.65               | 0.004  | 23.65               | -0.004 |
| kt5_e      | 23.67               | 0.076  | 23.63               | -0.072 |
| kt6        | 23.64               | -0.034 | 23.66               | 0.042  |
| kt7        | 23.65               | 0      | 23.65               | 0      |
| ki8        | 23.65               | -0.004 | 23.65               | 0.004  |
| kii8       | 23.65               | 0.004  | 23.65               | -0.004 |
| kt9        | 23.65               | 0      | 23.65               | 0      |
| ki9        | 23.65               | 0      | 23.65               | 0      |
| kt10       | 23.65               | 0.017  | 23.65               | -0.017 |
| kt11       | 23.66               | 0.03   | 23.65               | -0.021 |
| kt12       | 23.66               | 0.042  | 23.64               | -0.038 |
| a          | 23.67               | 0.101  | 23.63               | -0.08  |
| d          | 23.68               | 0.135  | 23.63               | -0.097 |
| g          | 23.32               | -1.404 | 23.95               | 1.285  |
| h          | 23.61               | -0.186 | 23.68               | 0.118  |
| i          | 23.59               | -0.245 | 23.7                | 0.211  |
| a_1        | 23.59               | -0.266 | 23.71               | 0.233  |
| o          | 23.67               | 0.076  | 23.64               | -0.055 |
| l          | 23.65               | 0      | 23.65               | -0.004 |
| l1         | 23.65               | 0      | 23.65               | 0      |
### Supporting Information S1 Text – Model description, design and analysis

| Parameter | $T_{\text{new}}$ | $\Delta T$% | $T_{\text{new}}$ | $\Delta T$% |
|-----------|-----------------|----------|-----------------|----------|
| $r_1$     | 23.65           | -0.013   | 23.65           | 0.008    |
| $r_2$     | 23.64           | -0.047   | 23.67           | 0.08     |
| $r_3$     | 23.64           | -0.055   | 23.66           | 0.051    |
| $kp_1$    | 23.7            | 0.224    | 23.6            | -0.199   |
| $kp_2$    | 23.67           | 0.093    | 23.64           | -0.063   |
| $kp_3$    | 23.48           | -0.727   | 23.81           | 0.672    |
| $kp_4$    | 23.6            | -0.199   | 23.68           | 0.131    |
| $kp_5$    | 23.57           | -0.342   | 23.72           | 0.288    |
| $kp_6$    | 23.67           | 0.085    | 23.64           | -0.051   |
| $kp_7$    | 23.65           | 0.004    | 23.65           | -0.004   |
| $kp_8$    | 23.63           | -0.068   | 23.67           | 0.063    |
| $kp_{10}$ | 23.64           | -0.025   | 23.65           | 0.017    |
| $kp_{11}$ | 23.64           | -0.047   | 23.67           | 0.085    |
| $kp_{12}$ | 23.63           | -0.097   | 23.67           | 0.08     |
| $kiz_4$   | 23.68           | 0.11     | 23.63           | -0.106   |
| $kiz_5$   | 23.69           | 0.182    | 23.61           | -0.161   |
| $kiz_6$   | 23.78           | 0.562    | 23.55           | -0.423   |
| $kiz_7$   | 23.64           | -0.051   | 23.65           | 0.008    |
| $kiz_8$   | 23.62           | -0.144   | 23.67           | 0.085    |
| $kex_2$   | 23.68           | 0.14     | 23.62           | -0.127   |
| $kex_3$   | 23.65           | 0.008    | 23.65           | -0.008   |
| $kiz_{10}$| 23.65           | -0.017   | 23.65           | 0.013    |
| $kiz_{11}$| 23.66           | 0.059    | 23.64           | -0.042   |
| $kiz_9$   | 23.65           | 0.004    | 23.65           | -0.004   |
| $kiz_{12}$| 23.64           | -0.047   | 23.67           | 0.068    |
| $kiz_{13}$| 23.63           | -0.076   | 23.67           | 0.063    |
| $kiz_{14}$| 23.64           | -0.051   | 23.66           | 0.047    |
| $b$       | 23.65           | -0.013   | 23.79           | 0.575    |
| $c$       | 24              | 1.476    | 23.47           | -0.753   |
| $e$       | 23.63           | -0.106   | 23.68           | 0.114    |
| $f$       | 23.65           | -0.021   | 23.67           | 0.063    |
| $f_{1}$   | 23.65           | -0.017   | 23.65           | 0.013    |
| $v$       | 23.41           | -1.006   | 23.83           | 0.748    |
| $w$       | 23.57           | -0.33    | 23.71           | 0.254    |
| $p$       | 23.66           | 0.03     | 23.64           | -0.025   |
| $q$       | 23.74           | 0.381    | 23.34           | -1.332   |
| $n$       | 23.75           | 0.44     | 23.56           | -0.389   |
| Parameter      | T_{\text{new}} -10% | DT\% | T_{\text{new}} +10% | DT\% |
|----------------|----------------------|------|----------------------|------|
| m              | 23.19                | -1.928 | 24.05                | 1.674 |
| r              | 23.65                | -0.004 | 23.65                | 0.017 |
| s              | 23.65                | -0.004 | 23.65                | 0.004 |
| h4             | 23.65                | -0.017 | 23.65                | 0.017 |
| h5             | 23.65                | -0.008 | 23.65                | 0.004 |
| h6             | 23.65                | 0      | 23.65                | 0     |
| h7             | 23.65                | 0      | 23.65                | 0     |
| h1             | 23.66                | 0.021  | 23.65                | -0.021|
| h8             | 23.65                | 0.008  | 23.65                | -0.008|
| a_2            | 23.65                | -0.017 | 23.65                | 0.017 |
| h2             | 23.65                | -0.017 | 23.65                | 0.017 |
| h3             | 23.67                | 0.08   | 23.63                | -0.085|
| source_p53    | 23.65                | 0.017  | 23.65                | -0.017|
| source_Rb     | 23.65                | 0.008  | 23.65                | -0.008|
Table 5: Effect of gene knock-outs on RNA circadian period – comparison of *in silico* with experimental data. WT, wild type; +, period increase; -, period increase; AR, arrhythmic phenotype; - then AR, decrease in the period followed by arrhythmic phenotype; + then AR, increase in the period followed by arrhythmic phenotype; nd, not defined.

| Gene       | Mutation phenotype | Animal model -- mouse | *in silico* data mutants | knock-out |
|------------|--------------------|-----------------------|--------------------------|-----------|
| *Bmal1*    | AR [42, 43]        | AR                    | AR                       |           |
| *Bmal2*    | nd                 |                       |                          |           |
| *Per1*     | - then AR [42, 43] | + then AR             | AR                       |           |
| *Per2*     | - then AR [42, 43] |                       |                          |           |
| *Per3*     | - [42, 43]         |                       |                          |           |
| *Per1+Per3*| - then AR [43]    |                       |                          |           |
| *Per2+Per3*| - then AR [43]    |                       |                          |           |
| *Per1+Per2*| AR [43]            |                       |                          |           |
| *Cry1*     | - [42, 43]         | AR                    | +                        |           |
| *Cry2*     | + [42, 43]         |                       |                          |           |
| *Cry1+Cry2*| AR [43]            |                       |                          |           |
| *Rev-erbα* | - [42, 43]         | AR                    | AR                       |           |
| *Rev-erbβ* | nd                 |                       |                          |           |
| *Rora*     | - [44]             | AR                    | AR                       |           |
| *Rorb*     | + [45]             |                       |                          |           |
| *Rory*     | nd                 |                       |                          |           |
| *Ink4a*    | WT                 | +                     | +                        |           |
| *Arf*      | nd                 | WT                    | WT                       |           |
| *Myc*      | nd                 | -                     | -                        |           |
| *Mdm2*     | nd                 | -                     | +                        |           |
| *CDK/CycD* | nd                 | WT                    | WT                       |           |
| *E2f*      | nd                 | -                     | -                        |           |
| *p53*      | nd                 | nd                    | +                        |           |
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