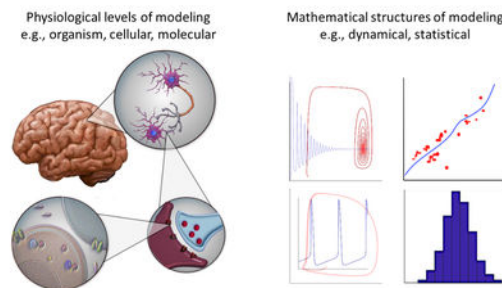# Mathematical modeling of circadian rhythms

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Abstract

Circadian rhythms are endogenous ~24-h oscillations usually entrained to daily environmental cycles of light/dark. Many biological processes and physiological functions including mammalian body temperature, the cell cycle, sleep/wake cycles, neurobehavioral performance, and a wide range of diseases including metabolic, cardiovascular, and psychiatric disorders are impacted by these rhythms. Circadian clocks are present within individual cells and at tissue and organismal levels as emergent properties from the interaction of cellular oscillators. Mathematical models of circadian rhythms have been proposed to provide a better understanding of and to predict aspects of this complex physiological system. These models can be used to: (i) manipulate the system *in silico* with specificity that cannot be easily achieved using *in vivo* and *in vitro* experimental methods and at lower cost, (ii) resolve apparently contradictory empirical results, (iii) generate hypotheses, (iv) design new experiments, and (v) design interventions for altering circadian rhythms. Mathematical models differ in structure, the underlying assumptions, the number of parameters and variables, and constraints on variables. Models representing circadian rhythms at different physiologic scales and in different species are reviewed to promote understanding of these models and facilitate their use.

GRAPHICAL/VISUAL ABSTRACT AND CAPTION

Keywords

Biological oscillators; circadian clock; mathematical modeling; statistical modeling; circadian rhythms; dynamic systems

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INTRODUCTION

"A useful model should be minimally complex to account for an existing set of data and maximally specific about what its parameters mean in physiological terms. It should not aim at completeness. The essence of a model's usefulness is in being a simplification of nature, rather than in approaching the complexity of nature itself" (Daan & Beersma, 1984).

Circadian physiology

Circadian (~24-h) rhythms are observed in almost all species including simple cyanobacteria, fungi, plants, Drosophila, and mammals, and at multiple scales from gene regulation in individual cells to emergent tissue- and organism-level behaviors that arise from synchrony among many cells and tissues (Ko & Takahashi, 2006; Siepka, Yoo, Park, Lee, & Takahashi, 2007). Circadian rhythmicity and its underlying mechanisms vary across species and different scales with three common principles: (i) they are endogenously generated and self-sustaining (i.e., they exist in constant environmental conditions (e.g., constant darkness)); (ii) they can be entrained (i.e., external stimuli affect phase and/or period to synchronize the rhythms with the stimuli); and (iii) they are temperature-compensated (i.e., moderate variation in the temperature of the external environment does not significantly affect the oscillator's period0.

The circadian system is composed of oscillators at cellular, tissue, and system levels. In mammals, almost every cell type is hypothesized to contain a functional genetic circadian oscillator. The master pacemaker for the mammals is a population of ~20,000 neuronal circadian oscillators in the suprachiasmatic nucleus (SCN) of the hypothalamus (Mohawk, Green, & Takahashi, 2012). The SCN is entrained by ocular light inputs; ocular light exposure is the most effective stimulus for phase shifting and entraining this central clock (Duffy & Czeisler, 2009), and in turn regulates these downstream oscillators in peripheral tissues (Ko & Takahashi, 2006). A range of signals from the SCN entrain peripheral oscillators to regulate many key physiological functions, including sleep/wake state, cardiovascular function, metabolism, reproduction, immune function, neurobehavioral performance, alertness, and mood (Lowrey & Takahashi, 2004). Peripheral clocks in other tissues are not directly sensitive to light - relying on the central clock to relay that information - and can be entrained by other signals, such as temperature or meal timing (Fuller, Lu, & Saper, 2008; Wahlstrom *et al.*, 2014). The type and mechanisms of these entraining, synchronizing, and/or inter-tissue communication stimuli is an active current area of investigation.

Since the endogenous circadian pacemaker cannot be monitored directly in humans, biological markers of the circadian clock have been used for statistical modeling (Klerman, Gershengorn, Duffy, & Kronauer, 2002). When collected under appropriately controlled inpatient conditions, core body temperature (CBT) (Czeisler, Allan, & Kronauer, 1986), plasma cortisol (Klerman *et al.*2002), and plasma melatonin (Klerman *et al.*, 2002), or in less controlled outpatient conditions, salivary melatonin (Benloucif *et al.*, 2008), can be used to estimate properties of the central circadian pacemaker such as changes in phase or changes in amplitude between conditions, and therefore to study the response of the circadian system

to environmental stimuli. The choice of marker and analysis method are important. For example, Klerman *et al.* (Klerman, *et al.*, 2002) compared the variability of these markers across repeated measurements of phase in the same individuals under free-running conditions; plasma melatonin rhythms were found to be more precise (i.e., lower standard deviation) in phase estimates than CBT. When modeling indirect markers of the circadian pacemaker, it is important for researchers to be cognizant of potential accuracy limitations even using different analyses of the same biological marker (Klerman, *et al.*, 2012).

The molecular mechanism generating circadian rhythms in the SCN and the peripheral oscillators, is based on a network of transcriptional – translational feedback loops (TTFLs) (Takahashi, 2017). Circadian clock genes also are involved in non-clock physiology. Experimental studies reveal that a 5–20% of the genes involved in physiological functions have circadian oscillation (Takahashi, 2017). For example, a majority of the pathways regulated by the core circadian genes *Clock* and *Bmal1* contribute to normal metabolic regulation, and disruption in core clock genes *Cry1*; *Cry2* and *Bmal1* alters sleep patterns (Ehlen *et al.*, 2017; Takahashi, Hong, Ko, & McDearmon, 2008). Circadian rhythms also control cell-cycle related genes (Matsuo *et al.*, 2003), and play important roles in tissue homeostasis (Bratsun, Merkuriev, Zakharov, & Pismen, 2016). In addition, shift work, which causes misalignment of both peripheral circadian clocks and of the master circadian clock from environmental time (Roenneberg & Merrow, 2016), is associated with abnormal cell growth and tumor formation (Bratsun, *et al.*, 2016; Kubo *et al.*, 2006; Megdal, Kroenke, Laden, Pukkala, & Schernhammer, 2005; Sack *et al.*, 2007; Schernhammer, Kroenke, Laden, & Hankinson, 2006; Schernhammer *et al.*, 2001). Dysregulation of circadian rhythms may also be involved in the development of a variety of neurological diseases such as depression, posttraumatic stress disorder, and neurodegenerative diseases (Rosenwasser, 2010; VIdenovic, Lazar, Barker & Overeem, 2014), metabolic diseases such as diabetes (Marcheva *et al.*, 2010), and other disorders (Kim & Duffy, 2018; Abbott, Reid & Zee, 2015).

Mathematical modeling - principles

Mathematical modeling is an essential and powerful tool to study and analyze complex physiological systems. Given the inherently complex structure that includes feedback and nonlinearities of the circadian clock at specific scales (organism, cellular, molecular, or genetic) or hierarchical levels (central clocks or peripheral clocks), modeling provides a valuable quantitative and mechanistic approach to understanding different aspects of circadian physiology.

Mathematical modeling complements "wet-lab" *in vivo* and *in vitro* experimental approaches and can also be used to design experiments. We recommend integrating modeling and experimental validations via an iterative process (Figure 1) as in (D'Alessandro *et al.*, 2017; Forger, Jewett, & Kronauer, 1999; Jewett, Kronauer, & Czeisler, 1994; Kronauer, Forger, & Jewett, 1999; St Hilaire, Dean, & Klerman, 2007; Zhou, Kim, Eng, Forger, & Virshup, 2015). Modeling also can be used to manipulate the system *in silico* with specificity that cannot be easily achieved using experimental methods for cost, time, or other reasons.

There are three main approaches to constructing models. While these three approaches are fundamentally different, they are not mutually exclusive, and a model can be constructed using a combination of these approaches. The first two are mathematical dynamic approaches and the last is a statistical approach; these terms will be discussed further below

(i)   Modeling the physiology of the system, including its detailed components.—The aim of this approach is to faithfully reproduce the underlying physiology and reproduce the available experimental data. Therefore, this aim begins with equations representing the system based on knowledge of the system. This mechanistic approach to modeling has been employed to particularly notable effect in chronobiology (Bechtel & Abrahamsen, 2010). The Forger and Peskin model of circadian rhythms (Forger & Peskin, 2005), and the Grandi *et al.*, model of cardiac cells (Grandi, Pasqualini, & Bers, 2010) are examples of this type of modeling. These models are often complicated, with many variables, and difficult to analyze mathematically. Their advantage is that their variables have physiological meaning. A model that is based on the physiology of the biological system can be more directly linked to the experimental data, and could be more useful for providing insights into the underlying physiology and for translational or clinical applications than a simplified model.

(ii)   Using mathematical principles to match the underlying behavior of the system.—In this approach, a class of mathematical model with the dynamical properties of the observed system is chosen, without necessarily linking these properties directly to physiology. These models can be considerably simpler than physiology-based models in terms of numbers of equations or parameters, yet they retain the essential features of the system. Examples of this type of modeling include (Kronauer, *et al.*, 1982; Pittendrigh & Bruce, 1957; Van Der Pol, 1926; Wever, 1965b). In the case of models that describe physical or biological oscillations, there are three common classes (Figure 2): (i) self-sustained oscillations (i.e., reaches a steady state closed trajectory called a "limit cycle" that describes the periodic behavior of the system, and to which it returns after any small perturbation; (ii) damped oscillations (i.e., the system can be induced to oscillate by an input, but the oscillation decays away over time as the system attracts to a stable fixed point); and (iii) excitable oscillations (i.e., the system has one globally attracting steady-state point, but a sufficiently large perturbation from the steady state causes one cycle of an oscillation before returning to the steady state). Most models of the circadian clock are self-sustained oscillatory systems, reflecting this fundamental required characteristic of endogenous circadian rhythms. In certain circumstances damped oscillator models have also been used to generate circadian rhythms in the presence of noise, since the noise input can enable persistent oscillations (Westermark, Welsh, Okamura, & Herzel, 2009).

(iii)   Data-driven modeling or statistical fitting of the data.—In this approach, statistical methods such as curve-fitting, an explicit model statement, or a nonparametric statistical formulation are applied to available data from the biological system to estimate parameters and variables of the model. Of note, the choice of curve to be fit or explicit model statement requires a mental "model" of the system. Some applications of this method include *a priori* selection of the equation type to be fit (e.g., a sinusoid for circadian

rhythms). The Brown and Luithardt model of circadian rhythms (Brown & Luithardt, 1999) and Klerman *et al.* model of human growth hormone (Klerman, Adler, Jin, Maliszewski, & Brown, 2003), are examples of data-driven modeling. The model can be statistically analyzed to (i) determine if the number of variables is too few (i.e., oversimplified model) or too many (i.e., nonessential variables are in the model); and (ii) determine the performance of the model system and measures its robustness when its parameter values are perturbed (i.e., sensitivity analysis) (Stelling, Sauer, Szallasi, Doyle, & Doyle, 2004). Sensitivity analysis can reveal the limitations of the model relative to a specific parameter as well as identifying parameter regions in the model that may cause minimal or maximal interventional effect (Abel & Doyle, 2016). If information about the model's parameters prior to the study is not available, the parameters of the model could be estimated via maximum-likelihood analysis (Brown & Luithardt, 1999).

Mathematical modelers should follow robust criteria for constructing their model, similar to the principles that biologists follow in designing their experiments (Klerman & St Hilaire, 2007). Thus, developing a hypothesis, choosing the mathematical model system, specifying variables to be modeled, choosing techniques for analyzing the variables and their interactions within the system, and methods for testing the models must all be considered. Figure 3 illustrates a general schematic description of one method for developing a mathematical model, revised from the schema in (Brown & Luithardt, 1999; Klerman & St Hilaire, 2007).

MATHEMATICAL MODELING – REPRESENTATION OF THE CIRCADIAN SYSTEM

Mathematical and computational modeling of the circadian system is a vibrant area in this multidisciplinary research field, with more than 600 published modeling papers in the last five decades. Several publications have reviewed the circadian modeling field at different levels (e.g., at the intracellular level (Forger, Gonze, Virshup, & Welsh, 2007), for organism behavior and performance (Klerman & St Hilaire, 2007)), or emphasizing the significance of modeling (Beersma, 2005; Forger *et al.*, 2003; Roenneberg, Chua, Bernardo, & Mendoza, 2008).

It is helpful to divide the above mathematical approaches into two main categories: dynamical models [above sections 1.2.1 and 1.2.2)] and statistical models [above section 1.2.3].

Dynamical models use differential or difference equations (i.e., equations that define how the rate of change of each variable depends on each other variable) to describe how a system evolves dynamically in time (or space). Statistical models do not use differential equations; they use regression or other analysis (to fit data), descriptive statistics (to define properties of the dataset), and/or inferential statistics (to perform null hypothesis testing).

Dynamical vs. statistical modeling

Dynamical modeling—Dynamical models describe the state of a system as a function of time and usually are represented by differential or difference equations. These models may

be "deterministic" or "stochastic". Deterministic models usually consist of ordinary or partial differential equations (ODEs or PDEs) and do not contain statistical noise. Stochastic models include statistical noise and can be comprised of stochastic differential equations (SDEs) or the probabilistic chemical master equation (CME). Table 1 provides a summary and description of some deterministic and stochastic models of circadian rhythms in animals.

Deterministic models for circadian rhythms

Ordinary differential equation (ODE) models have frequently been used to describe and assess the dynamic properties of a circadian pacemaker. The van der Pol oscillator is one example of an ODE that produces self-sustained oscillations with a stable limit cycle. These models have the form of

$$\frac{d\boldsymbol{x}}{dt} = \boldsymbol{f}(\boldsymbol{x}, \boldsymbol{c}, u(t)), \quad \text{Eqn. 1}$$

where, $\boldsymbol{f}$ is the rate of change for states $\boldsymbol{x}$, and depends on a set of parameters $\boldsymbol{c}$, and $u(t)$ is an external signal such as light. In general, systems of the form Eqn. 1 can approach either steady state or sustained oscillations, depending on their parameters. When a system approaches a sustained oscillation (i.e., limit cycle), it returns to its original state after time τ, therefore $\boldsymbol{x}(t + \tau) = \boldsymbol{x}(t)$. While these models are useful in understanding the dynamics of circadian rhythms, they cannot capture the intrinsic fluctuations of the circadian clock at the cellular level, since individual components of the circadian system are considered "sloppy" due to stochastic noise (Herzog, Aton, Numano, Sakaki, & Tei, 2004).

Stochastic models of circadian rhythms

In biological systems, randomness and noise are usually present (Herzog, Aton, Numano, Sakaki, & Tei, 2004). For instance, circadian clocks can be relatively accurate at a macroscale level but are noisy at a microscale level. For example, the circadian period in individual SCN neurons has much larger cycle-to-cycle variation than the circadian period of that entire organism's behavior (e.g., activity, feeding) probably due to both molecular noise or intrinsic stochasticity within a single cell and coupling between cells (Herzog, Aton, Numano, Sakaki, & Tei, 2004). When statistical noise is a significant part of the signal, stochastic models are used. Stochastic noise may be divided into extrinsic (caused by differences between cells or within the environment), or intrinsic (caused by low copy numbers of biochemical species and/or the random nature of reaction events).

A common technique for modeling intrinsic noise is to use SDEs of the following form:

$$dX(t, w) = f(t, X(t, w))dt + g(t, X(t, w))dW(t, w), \quad \text{Eqn. 2}$$

where function f corresponds to the deterministic part of the SDE and is called the drift; function g is the diffusion coefficient; and $dW(t, w)$ represents the noise term. Alternatively, stochasticity may be accounted for by use of the chemical master equation (CME), where

biochemical species occur in discrete units and reactions occur probabilistically. Stochastic models of circadian rhythms may be simulated using approaches such as a Monte Carlo scheme and Gillespie algorithms (Abel, Widmer, St. John, Stelling, & Doyle, 2015; Forger & Peskin, 2005). Noise in the circadian system has been studied extensively using SDEs (Westermark, *et al.*, 2009) or the CME (Abel, *et al.*, 2015; Forger & Peskin, 2005; Gonze, Halloy, & Goldbeter, 2002).

While intrinsic noise usually has been studied using SDEs or the CME, extrinsic variability (such as differences between cells, or within the local environment) may be captured by varying parameterization of each cell within a multicellular model. For example, this technique was used in (To, *et al.*, 2007) to create variability within a multicellular model of the SCN.

Statistical modeling/curve fitting—Using markers (e.g., CBT, melatonin), some rhythmic properties of the circadian system, such as the period, amplitude, and phase, can be extracted via statistical models. One simple, commonly used approach is the use of regression analysis to fit a fixed curve to the data, such as a sinusoid function or a skewed sine wave (Daan & Beersma, 1984). For example, the general sinusoid function is given by $f(x) = a\ sin(\omega x + c)$, with amplitude a, angular frequency ω (and period $\frac{2\pi}{\omega}$), and phase c.

When using regression methods, it is vital to calculate goodness-of-fit metrics to obtain the model that summarizes the principal data features with the minimum number of parameters. Examples of goodness-of-fit methods are log-likelihood, the estimated error variance, the signal-to-noise-ratio (i.e., the ratio of the data variance explained by the model divided by the estimated error variance), and the Akaike Information Criterion (AIC) that adds a "cost function" related to the number of parameters in the model. It is also vital (for most statistical methods) that the data set being fit is truly circadian or has statistically independent circadian and other factors (Klerman *et al,* 1999)

There are several limitations associated with a regression modeling approach. (i) Representing the circadian process by a sinusoidal equation implies a static 1-dimensional phase-only system (Klerman & St Hilaire, 2007) and therefore cannot reproduce the Type 0 resetting that has been experimentally observed in humans and other animals (e.g., (Jewett, Kronauer, & Czeisler, 1991)) or shifting between limit cycles, as in Drosophila (Peterson, 1980). This is because Type 0 resetting, sometimes referred to as "strong" resetting, mechanistically includes amplitude reduction (and therefore a 2-dimensional system). (ii) A fixed curve assumes the circadian waveform is not changing between cycles. This assumption holds only under entrained conditions or in controlled laboratory experiments: it assumes that in response to a stimulus, the whole curve shifts (e.g., to a later time), and that following a transient, there is no change in the shape of this function (e.g., there is change only in phase but not amplitude, period, or shape). Consequently, this technique is not appropriate for predicting the effects of most stimuli, especially since changes in the shape of the circadian waveform can affect the response to a subsequent stimulus (Klerman & St Hilaire, 2007; Mallis, Mejdal, Nguyen, & Dinges, 2004). Therefore, in circumstances in which the circadian system is changing (e.g., phase shifts or non-entrained conditions, such as jet lag or rotating shiftwork), dynamical models are needed. Some studies have

compensated for this by fitting a three-parameter damped sinusoid to specific types of experimental data; this captures the known time-dependent decreasing amplitude after some stimuli, for improved calculation of phase and amplitude and is therefore a common approach to describing populations of cellular circadian bioluminescent reporters. For instance, Westermark *et al.* (Westermark, *et al.*, 2009) employed two mathematical models to quantify circadian rhythms within a single cell. In their approach, the descriptive parameters of each cell, such as noise intensity, damping rate, and frequency, were extracted from bioluminescence data of Per gene expression in mouse SCN neurons that were fit with both a damped oscillator driven by noise and a self-sustained noisy oscillator to test hypotheses about which physiological mechanism was involved.

For ease-of-computation and model parsimony reasons, fixed-curve representations of the circadian waveform have been used in models whose purpose is predicting other metrics besides dynamics of the circadian system. For instance, since changes in phase of the human circadian pacemaker impact the timing and content of sleep, objective neurobehavioral performance, and subjective alertness (Goel, Basner, Rao& Dinger, 2013; McHill et al, 2018), many models of these variables include a fixed-curve representation of the circadian system (Klerman & St Hilaire, 2007; Mallis, *et al.*, 2004). More detailed examples of these models are included in the **Application** section, below.

As an alternative to regression-based methods, time series for circadian markers can also be analyzed using spectral methods such as Fourier analysis, periodograms, spectrograms, wavelet-based methods, autocorrelation, and Hilbert transforms (Klerman, Wang, Phillips, & Bianchi, 2017; Leise, 2015; Leise, Indic, Paul, & Schwartz, 2013). Other less common methods such as Bayesian spectral analysis (Cohen, Leise, & Welsh, 2012) and detrended fluctuation analysis (Hu, Scheer, Ivanov, Buijs, & Shea, 2007) also have been used to analyze circadian data. These can be used to track changes in phase or amplitude of circadian processes over time, including before and after an intervention.

Statistical models can also enable analysis of additional data features, such as thermoregulatory system involvement in the evoked effects of protocol-specific activity on CBT (Brown & Luithardt, 1999; Klerman, *et al.*, 1999). CBT circadian phase and amplitude can be defined as a signal-plus-correlated-noise model where the data series is described by a combination of a harmonic-regression model (describing the rhythmicity of the periodic signal)-and correlated noise (capturing perturbation from non-circadian physiological processes such as physical activity and the data-recording system) (Brown & Czeisler, 1992). The model can be formulated in a Bayesian framework, in which the posterior probability density for calculating parameter values combines the prior information of the parameters with the information derived from the data (Brown & Czeisler, 1992).

Physiological levels of modeling

Organism level—Mathematical models of circadian rhythms at the organism level were first developed in mid-twentieth century using a single oscillator (Pittendrigh & Bruce, 1957), or multiple oscillators (Pittendrigh, 1960; Pittendrigh & Bruce, 1959), to reproduce many of the experimentally-observed characteristics of circadian rhythms. In one of the earliest examples of circadian models, Wever developed a 1-dimensional oscillator model

capable of being entrained by an environmental stimulus, such as exogenously applied light cycles (Wever, 1962, 1964, 1965a). In 1967, Winfree demonstrated that a 2-dimensional limit cycle oscillator also captured amplitude and phase dynamics of circadian rhythms (Winfree, 1967). Winfree's work was highly influential, and modelers began to widely adopt 2-dimensional limit cycle oscillators, such as the van der Pol oscillator (Van Der Pol, 1926), to simulate circadian behavior (Kronauer, *et al.*, 1982; Wever, 1966).

Models of two or more interacting circadian oscillators were later developed to explain transients and resetting phenomena in Drosophila (Pittendrigh & Daan, 1974), the "splitting" phenomenon in free-running activity rhythms in rodents (Daan & Berde, 1978; Pittendrigh & Daan, 1976), and to simulate re-entrainment after perturbation of the circadian system by stimuli (Daan & Beersma, 1992). Kronauer and collaborators in 1982 (Kronauer, *et al.*, 1982) proposed an alternative two-oscillator model, with oscillatory in rhythms in both CBT and rest-activity. The oscillators in this model affected each other by velocity-type coupling (rather than the phase-type coupling in other models), and each oscillator was itself 2-dimensional (e.g., characterized by both phase and amplitude). Variations on the model have been used to study the effect of different stimulus (*zeitgeber*; a stimulus that entrains a biological rhythm) strength on human circadian rhythms (Gander, *et al.*, 1984; Jewett & Czeisler, 1992; Jewett, *et al.*, 1991, 1994; Kronauer & Czeisler, 1993; Kronauer, Jewett, & Czeisler, 1993). Further details are included in the **Applications** section of this article.

While these models provided insight into the mathematical structure of the human circadian system's response to light, they had limitations. First, in some cases, the circadian oscillator was described 1-dimensionally (by phase only). A multidimensional state space (e.g., analogous to latitude and longitude instead of only longitude) is necessary to produce some circadian phenomena, such as Type 0 resetting. Second, the external stimulus driving model entrainment was often not reflective of physiology. In some cases, the external stimulus affected only one of the oscillator populations (Pittendrigh & Daan, 1974), or the stimulus was shaped to reflect human perception of its effect or for simplicity (e.g., a daily light environment was represented as a square wave). These two limitations were partially addressed in a later model of the human circadian pacemaker's response to light stimuli (Kronauer, *et al.*, 1999); the model included a "Process L" in which light is converted into a dynamic stimulus, and a 2-dimensional limit-cycle "Process P" that describes the pacemaker (i.e., circadian oscillator).

Biochemical and molecular level clocks—Parallel to the development of organism-level models of the circadian system, models were developed to describe the biochemical and molecular machinery underlying the clock. In 1965, Goodwin (Goodwin, 1965) proposed the first biochemical limit-cycle oscillator model, which included the production and degradation rate of protein at the molecular level in a negative feedback loop. The Goodwin oscillator has been used to simulate circadian feedback loops at the molecular and genetic level (Goldbeter, 1995; Leloup & Goldbeter, 1998) and to investigate circadian temperature compensation (Ruoff, Vinsjevik, Monnerjahn, & Rensing, 2001). Another oscillator model that captured enzymatic reactions in Drosophila was proposed by Pavlidis (Pavlidis, 1967) as part of a study of the effects of the light on circadian oscillators in that organism. The Pavlidis oscillator model was extended to include temperature effects on

phase (Pavlidis, Zimmerman, & Osborn, 1968), but unlike the Goodwin oscillator, did not gain popularity amongst modelers. In the 1990s, when the transcriptional-translational negative feedback loop at the core of the circadian clock in Drosophila and Neurospora was discovered, Goldbeter (Goldbeter, 1995) proposed a biochemical model for circadian oscillations in *period* protein (PER). Further discussion of these models is below.

At the molecular level, circadian oscillations are generated by a set of genes that form a regulatory feedback loop. Since the specific genes involved in generating self-sustained circadian oscillation may vary by species, deterministic models of the molecular basis of circadian rhythms have been proposed for Drosophila and Neurospora (Goldbeter, 1995; Leloup & Goldbeter, 1998; Leloup, Gonze, & Goldbeter, 1999; Smolen, Baxter, & Byrne, 2001), and for mammals (Forger & Peskin, 2003; Hirota *et al.*, 2012; Leloup & Goldbeter, 2003; Mirsky, Liu, Welsh, Kay, & Doyle, 2009).

The detailed nature of these models causes their parameterization to be an open challenge, as available experimental data frequently under-specifies parameter values. Deterministic models have been used to predict the parameter values for which the gene regulatory network of the clock can produce sustained oscillations of the limit cycle type (Leloup & Goldbeter, 2003). For example, Forger and Peskin (Forger & Peskin, 2003) employed mass action kinetics and developed a detailed model that predicted the phase of entrainment and the amplitude of oscillation, and was robust to parameter changes. A model of the regulatory structure of the intracellular circadian clock in mice (Mirsky, *et al.*, 2009) successfully reproduced the experimentally observed cell-autonomous circadian phenotypes of gene knockout animals. A detailed model developed by Kim and Forger (Kim & Forger, 2012) accurately predicted the phenotype of some known mutations of the mammalian circadian clock; they found that the mutations that cause the average ratio of the concentration of repressor genes to that of activator genes over one circadian cycle (i.e., stoichiometry) to be too high or too low, yielded arrhythmic phenotypes (Hannay, Forger, & Booth, 2017).

Stochastic models of varying complexity have studied the effects of molecular noise on the circadian clock. Stochastic noise due to extrinsic variability or molecular fluctuations is known to affect circadian period in individual cells (Hastings & Herzog, 2004). Forger and Peskin (Forger & Peskin, 2005) showed that gene duplication causes more promoters to interact with transcription factors and increase the number of binding targets, thereby increasing robustness to stochastic noise and oscillatory precision. The resistance to noise was found to enable long-term synchrony in a population of synthetic oscillators, and the presence of molecular noise has been shown to change the oscillatory behavior of single uncoupled cells (Westermark, *et al.*, 2009); for example, damped oscillatory behavior in a deterministic single-cell model near a Hopf bifurcation can transition to sustained oscillatory behavior (Abel, *et al.*, 2015; Westermark, *et al.*, 2009).

Multicellular level—Researchers have also employed multicellular models of the mammalian circadian clock to explore interactions between cellular oscillators, especially those in the mammalian SCN. For example, modeling has been used to study the roles of the neuropeptide vasoactive intestinal polypeptide (VIP) and the neurotransmitter γ-aminobutyric acid (GABA) (DeWoskin *et al.*, 2015). Both GABA and VIP are known to

affect circadian oscillations. To *et al.* (To, *et al.*, 2007) and Vasalou *et al.* (Vasalou, Herzog, & Henson, 2009) confirmed the role of VIP in SCN synchrony, by connecting models of a single circadian neuron, using physiologically-accurate mathematical descriptions of intercellular communication. Later, DeWoskin *et al.* (DeWoskin, *et al.*, 2015) explained the role of GABA as a critical factor in both synchronizing and desynchronizing SCN circadian rhythms: their modeling predicted that large doses of VIP can reduce the amplitude of circadian rhythms by reducing synchrony among neurons, a prediction confirmed by experiment (An *et al.*, 2013).

Multicellular models have been used to study emergent phenomena at the network level. For instance, DeWoskin *et al.* (DeWoskin, Geng, Stinchcombe, & Forger, 2014) developed a multicellular model by extending an intracellular signaling model (Kim & Forger, 2012) and subsequently used this model to study the interactions between cells in the SCN network. Their modeling results, in agreement with experimental data, showed that coupling between cells makes the SCN more resistant to perturbations and increases the amplitude of rhythms.

Modelers also have integrated the core molecular clock, electrophysiology, neurotransmitter signaling, and network structure, into one model to (i) examine the presence of circadian rhythms in intracellular ion calcium concentration (Noguchi *et al.*, 2017); (ii) study the role of electrical activity in generating and synchronizing circadian rhythms in SCN neurons (Antle, Foley, Foley, & Silver, 2003), as well as their entrainment to external zeitgebers (Antle, Foley, Foley, & Silver, 2007; Beersma, van Bunnik, Hut, & Daan, 2008; Gonze, Bernard, Waltermann, Kramer, & Herzel, 2005); and (iii) to show how dynamics of the SCN network arise from multicellular coupling (Diekman & Forger, 2009).

Peripheral level—Many non-SCN tissues including lung, liver, and skeletal muscle tissues also exhibit circadian oscillations (Nagoshi, Brown, Dibner, Kornmann, & Schibler, 2005; olde Scheper, Klinkenberg, Pennartz, & van Pelt, 1999). Modeling of peripheral oscillators can be used to understand the relationships among circadian tissues within an organism. The SCN and other inputs such as feeding, entrain other oscillatory tissues in the body, but these tissues may realign at different rates or respond differentially to external cues, causing internal desynchrony (Nagano *et al.*, 2003; Nakamura, Yamazaki, Takasu, Mishima, & Block, 2005). One multistage mathematical model that explains the temporary desynchrony of such a system is described in (Leise & Siegelmann, 2006). The components of their multistage circadian system were modeled using the equations developed in (olde Scheper, *et al.*, 1999). They investigated the effects of phase shifts and predicted that prolonged desynchrony of tissues within the system worsens organism-level jet lag symptoms. Abraham *et al.* (Abraham *et al.*, 2010) compared entrainment characteristics of simulated SCN clocks vs. simulated lung cell clocks, and Mavroudis *et al.,* (Mavroudis, Scheff, Calvano, Lowry, & Androulakis, 2012) investigated the dynamics of entrainment of peripheral clocks by cortisol using a modeling approach. The relationships between the SCN and peripheral clocks, and among peripheral clocks, are still being determined experimentally. Models of these relationships are relatively few and new, and more are expected soon.

APPLICATIONS OF CIRCADIAN MODELS

Here, we summarize a few examples of how mathematical models of circadian rhythms have been used.

Reconciling contradictory results

Mathematical modeling can reconcile contradictory results or contribute to debates in the field. For instance, Klerman *et al.* (Klerman, Dijk, Kronauer, & Czeisler, 1996) simulated experimental protocols to investigate whether the endogenous period of the human circadian pacemaker was ~24.2 hours, as calculated in some experimental protocols, or 25 hours, as calculated from other experimental protocols. They showed that simulations with *endogenous* periods of ~24.2 hours could produce results with *observed* periods of ~25 hours in some protocols. However, simulations with *endogenous* periods of ~25 hours could not match results with observed periods of ~24.2 hours in other protocols. Another example of using models to reconcile apparently contradictory results is in (Forger & Peskin, 2004): inconsistency between model predictions and experimental results motivated new experiments whose results matched the model's predictions (Gallego, Eide, Woolf, Virshup, & Forger, 2006). As a third example, Phillips *et al.* (Phillips, Chen, & Robinson, 2010) helped to resolve a debate over which factors influence chronotype; the modelling suggested that chronotype is both a circadian-driven trait and influenced by non-circadian factors.

Effects of light on the human circadian pacemaker

Although light has long been known to entrain circadian rhythms in non-human species, the idea that lower levels of light also affect the human circadian clock was at first controversial. In the 1990s, it was conclusively shown that exposure to light before and after the minimum of CBT induces phase delays and phase advances, respectively, and light exposure near the CBT minimum suppresses the amplitude of the human circadian pacemaker (reviewed in (Duffy & Czeisler, 2009)). The effects of timing and duration of light on human circadian amplitude, observed period, and phase have been studied using the Kronauer model and its variations (Achermann & Kunz, 1999; Beersma & Daan, 1992; Dijk, Borbély, Beersma, & Daan, 1988; Klerman, *et al.*, 1996; Kronauer, 1990; Kronauer & Czeisler, 1994; Kronauer, *et al.*, 1999). Later versions of these models included fitting to intermittent light stimuli and non-photic effects on circadian oscillations (Forger, *et al.*, 1999) (Jewett, Forger, & Kronauer, 1999) (Jewett, *et al.*, 1994) (Kronauer, *et al.*, 1999) (Nakao, Yamamoto, Honma, Hashimoto, & Honma, 2002) (St Hilaire *et al.*, 2007).

Other uses of the Kronauer model have included studying human circadian dynamics under different protocols that include different lighting patterns. One example is the forced desynchrony (FD) protocol that causes desynchronization of the endogenous circadian rhythm from the rest-activity cycle by placing an individual in a non-entrainable light-dark (LD) cycle. Modeling using 20–30- hour cycles (Klerman, *et al.*, 1996) and ultradian cycles (e.g. 7 hours) (Stack, Barker, Carskadon, & Diniz Behn, 2017) has been performed. The models can be used to assess the influence of study design on the estimation of endogenous period in these FD protocols (Klerman, *et al.*, 1996; Stack, *et al.*, 2017)

Photic input to the circadian system also has been modelled by Rea and collaborators (Rea, Figueiro, Bullough, & Bierman, 2005). They developed a mathematical model based on human circadian phototransduction neurophysiology of the retina, predicted the experimental data on melatonin suppression of nocturnal under light simulation, and quantified light input to the circadian system for different light spectral power distributions.

Entrainment of circadian system—Winfree's very influential study showing that limit cycle oscillator models are able to reproduce both weak (Type 1) and strong (Type 0) phase resetting in terms of a phase singularity (i.e., a point in phase space at which phase is undefined) precipitated a rapid growth in the mathematical study of entrainment stimuli (Winfree, 1967). Mathematical models of the circadian oscillator have been used to study the stability of entrainment to zeitgebers (Pavlidis, 1967; Pittendrigh, 1981; Wever, 1966), and later, these models were also used to investigate how to achieve optimal entrainment by adjusting properties of the external stimulus such as phase and period (Beersma, Daan, & Hut, 1999). Variability in environmental signals and day-to-day fluctuations are considered in the Beersma *et al.* model (Beersma, *et al.*, 1999), in which they investigated how the precision of the entraining cues determine the stability of the entrainment.

Modelers have used three general methods for predicting how entrainment to a given stimulus will occur: (i) phase response curves (PRCs) that describe the relationship between timing of the stimulus and change in the phase of circadian pacemaker (Daan & Pittendrigh, 1976; Pittendrigh & Minis, 1964); (ii) velocity response curves that describe a change in the clock's endogenous period in response to stimuli (Daan & Pittendrigh, 1976; Jiao, Lee, & Rusak, 1999); and (iii) dynamical changes in time of the phase in a differential equation model (Jewett, *et al.*, 1999; Comas, *et al.*, 2006, 2007, 2008), or equivalently the integrated change in oscillator cycle length (Roenneberg, Hut, Daan, & Merrow, 2010), in response to a pattern of stimuli. The third approach is the most general and can be used to derive PRCs, although it does not describe the empirical observation of plasticity in intrinsic period (Daan & Pittendrigh, 1976; Scheer, Wright, Kronauer, & Czeisler, 2007). Recent work, however, suggests that plasticity may be an emergent property of a multi-oscillator system, rather than a velocity response of a single oscillator (Beersma, Gargar, & Daan, 2017).

Optimal lighting interventions have also been designed using models to find the best schedule to rapidly re-entrain the circadian system under conditions such as jet lag (Serkh & Forger, 2014); shift human circadian rhythms to a desired new phase (Dean, Adler, Nguyen, & Klerman, 2014); and to strengthen the circadian rhythms of patients in intensive care units and reduce the delirium rates in hospitals by improving their light environments (Barroso & den Brinker, 2013).

Sleep-wake regulatory networks

The timing of sleep-wake behavior is regulated by circadian rhythms as well as the length of time awake. Borbély (Borbély, 1982) proposed a very influential two-process model of sleep regulation, postulating that the timing of sleep and waking is determined by a homeostatic process (S) – which increases during waking and decays during sleep – and a circadian process (C). Conceptual models (Daan & Beersma, 1984), as well as physiologically based

models (Phillips & Robinson, 2008; Rempe, Best, & Terman, 2010; Robinson, Phillips, Fulcher, Puckeridge, & Roberts, 2011), have incorporated this approach.

These sleep-wake regulatory models often define the circadian drive as a sinusoidal function (Fleshner, Booth, Forger, & Diniz Behn, 2011) or a skewed sinusoidal function (Rempe, *et al.*, 2010). Dynamical circadian pacemaker equations such as the Kronauer model (Kronauer, 1990), have also been employed to predict the timing and content of sleep, and its dependence on physiology and environment (Phillips, *et al.*, 2010; Skeldon, Phillips, & Dijk, 2017; Swaminathan, Klerman, & Phillips, 2017). This topic deserves its own review; we recommend (Booth & Diniz Behn, 2014).

Human performance

One major application of circadian models is to predict performance and alertness (e.g., (Hursh *et al.*, 2004; Manfredini *et al.*, 2002)) for operational reasons. Since circadian and homeostatic components affect objective performance and subjective alertness, the two-process model of sleep regulation (Borbély, 1982) has also influenced mathematical models of human fatigue and performance (Hursh, Redmond, *et al.*, 2004; Klerman & St Hilaire, 2007; Mallis, *et al.*, 2004; Roach, Fletcher, & Dawson, 2004); these models predict fatigue or performance instead of sleep timing and content. Van Dongen *et al.* (Van Dongen & Dinges, 2003) used a statistical mixed-effects version of a two-process model with a fixed-curve circadian waveform to investigate possible interactions between circadian and homeostatic processes on waking neurobehavioral performance.

Some models of objective performance and subjective alertness also include sleep inertia. Sleep inertia is the decreased alertness and poor performance immediately following awakening that can last several hours. Three-process models (Folkard & Åkerstedt, 1987, 1989, 1992), with sleep inertia as the third process, have been used for predicting performance and alertness (Belyavin & Spencer, 2004) and in fatigue risk assessment in transportation (Dijk & Larkin, 2004; Moore-Ede *et al.*, 2004).

One model of fatigue predictions that has been used by industrial and governmental organizations (Hursh, Balkin, Miller, & Eddy, 2004; McCormick *et al.*, 2013), is the Fatigue Avoidance Scheduling Tool (FAST) (Fatigue avoidance scheduling tool (FAST), 2001) derived from the Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) model (Hursh & Fanzone, 2008). The SAFTE simulation is a three-process model of human cognitive effectiveness. The model integrates (i) circadian rhythms in metabolic rate; (ii) cognitive performance rate (i.e., recovery during sleep and decline with wakefulness), and (iii) cognitive performance associated with sleep inertia. In the SAFTE model, a circadian drive influences cognitive effectiveness and sleep regulation, where cognitive effectiveness depends on the current balance of the sleep regulation process, the circadian process, and sleep inertia, and sleep regulation depends on hours of sleep, hours of wakefulness, current sleep debt, the circadian process and awakenings during a sleep period.

Mathematical models of the circadian system can also be used to explore the effect of extended work shift and circadian misalignment on individuals and to find the optimal timing of work shifts and/or light exposure to reduce these adverse effect (Patriarca,

Postnova, Braun, Hernandez-Garcia, & Toral, 2012; Postnova, Robinson, & Postnov, 2013). For example, Postnova *et al.* integrated a sleep wake cycle model (Phillips & Robinson, 2007) with a human circadian pacemaker model (St Hilaire, Klerman, *et al.*, 2007) to predict entrainment and sleepiness on different shift work schedules and in different light conditions (Patriarca, *et al.*, 2012; Postnova, Postnov, Seneviratne, & Robinson, 2014; Postnova, *et al.*, 2013). Klerman *et al.* modeled the effects of different work schedules on teams of medical residents rather than individuals (Klerman, Beckett, & Landrigan, 2016).

Circadian rhythms and cardiac electrophysiology

Circadian rhythms regulate the electrical activity of the heart by altering ionic currents in cardiac myocytes, which leads to changes in the morphology and dynamics of cardiac action potentials (APs). In cardiac tissues, a subunit for the inactivating voltage-gated potassium current (i.e., potassium channel interacting protein 2 (KChIP2) expression), contributes to the regulation of several cardiac ion channels and has circadian rhythmicity (Jeyaraj *et al.*, 2012). Fotiadis and Forger (Fotiadis & Forger, 2013) developed the first mathematical model to study cardiac circadian rhythms by investigating the effects of circadian rhythms of KChIP2 expression on the dynamics of human and murine ventricular APs, as well as the duration of depolarization and repolarization phases (the QRS and QT intervals) in electrocardiograms (ECGs). They modified the ionic currents in two published models of electrophysiology of human (Grandi, *et al.*, 2010) and murine (Pandit, Clark, Giles, & Demir, 2001) ventricular myocytes, as a function of KChIP2 expression concentration. Circadian rhythmicity of KChIP2 expression was implemented by setting the concentration of KChIP2 to be a sinusoidal function and the ionic current to be dependent on this function. Their modeling results showed that altering KChIP changes the APs, and QRS and QT intervals; this suggests that KChIP2 is a key regulator of circadian rhythms in the electrical activity of the heart. Their findings agreed with experimental results showing that QT interval is controlled by a circadian clock and it reaches its maximum duration during the first hours of the day (Jeyaraj, *et al.*, 2012). This has clinical implications since alteration of the regular expression of KChIP2 can lead to channelopathy diseases and cardiac arrhythmias (Guo & Stein, 2003; Jeyaraj, *et al.*, 2012; Portaluppi & Hermida, 2007).

Circadian rhythms and tumor growth in epithelial tissue

Disrupted circadian rhythms are implicated in gene deregulation and cancerous tumor formation (Bratsun, *et al.*, 2016). Circadian rhythm disruption also (i) changes the mechanical properties of cancer cells such that they stop exchanging signals with healthy cells, and (ii) accelerates experimental and clinical cancer processes (Levi, Okyar, Dulong, Innominato, & Clairambault, 2010) and tumor formation (Clairambault, Michel, & Perthame, 2006). Mathematical modeling provides the opportunity to combine circadian rhythm models with models of tumor growth and investigate links between rhythm disruption and the occurrence of cancer. Bratsun *et al.* (Bratsun, *et al.*, 2016) proposed a multiscale model of cancer tumor growth induced by circadian rhythm disruption and quantified the effects of rhythm disruption on the desynchronization of cell activity in the epithelial tissue and occurrence of the cancerous state. Their model incorporates each cell's dynamics with its gene regulation. Therefore, potential future directions of this modeling

could be (i) to simulate targeted pharmacological therapies for different type of cancers, and (ii) to expand the model and investigate the effect of other mechanisms on tumor growth.

Circadian rhythms and drug delivery (chronotherapy)

Control of circadian rhythms—Studying properties of the circadian clock provides both better understanding of complex inter-related physiological systems and facilitates the development of more efficient pharmacological or behavioral treatments. Manipulating circadian phase and amplitude to reduce negative health outcomes associated with circadian disruption is an important translational goal of circadian modeling (Hirota & Kay, 2015; Zhao *et al.*, 2016). Mathematical models are required for developing algorithmic control approaches to manipulate the circadian system to a desired new state. In a feedback control approach, the state of the system is observed (sensor), a control path is calculated through an algorithm (controller), and the calculated control input is applied (actuator). A common feedback strategy for calculating the control input, called model predictive control (MPC), has also gained particular attention for its strong error tolerance (Abel & Doyle, 2016; Bagheri, Stelling, & Doyle, 2008).

Modeling has been used to identify small molecules that modulate circadian clock components (Hirota, *et al.*, 2012) that may in turn be dosed using control theory for manipulation of clock phase, amplitude, and entrainment (Abel & Doyle, 2016; Serkh & Forger, 2014; St John, Hirota, Kay, & Doyle, 2014; St John, Taylor, *et al.*, 2014). A control theory approach to delivering pharmaceuticals that affect the clock may enable treatment of circadian disorders or chrono-disruption.

Open-loop control (without feedback) has also been notably applied to calculate optimal light schedules for achieving a desired phase shift. Open-loop control, for example, is used in the app "Entrain" to assist in resetting circadian rhythms following jet lag (Walch, Cochran, & Forger, 2016).

Circadian effects on pharmaceuticals—Nearly 50% of the currently most popular pharmaceuticals target gene products under circadian regulation (Anafi, Francey, Hogenesch, & Kim, 2017). Approximately, half of these have short half-lives of 6h or less. Therefore, the circadian phase at which many common pharmaceuticals are taken likely affects the efficacy of their action. These effects are only now receiving attention, and much work remains to be done in either developing techniques for delivering commonly-used drugs at the proper circadian phase, or finding effective drugs that have never been used due to unrealized circadian gating of their effects. Mathematical models that explicitly include pharmacokinetics and pharmacodynamics (e.g., (Breslow, Phillips, Huang, St Hilaire, & Klerman, 2013) for melatonin) will be necessary for choosing optimal timing of dosages.

Cancer treatment—Circadian rhythms control many cellular and intracellular functions associated with cancer, including cell cycles, DNA repair, apoptosis, drug metabolism, and detoxification (Kubo, *et al.*, 2006; Megdal, *et al.*, 2005; Sack, *et al.*, 2007; Schernhammer, *et al.*, 2006; Schernhammer, *et al.*, 2001). Most healthy tissues have persistent circadian entrainment and some tumors have poor circadian entrainment (Levi, *et al.*, 2010). Treatment timing in experimental models and cancer patients affects both the tolerability and

the efficacy of anticancer drugs (Bernard, Cajavec Bernard, Levi, & Herzel, 2010; Innominato *et al.*, 2014; Levi, *et al.*, 2010). Circadian regulation of cancer treatments can be modeled and optimized using mathematical and computational modeling. For example, Bernard *et al.* adopted a population model of cell proliferation (Burns & Tannock, 1970), to include a sinusoidal circadian function. They used the model to simulate circadian regulation for normal cell and tumor growth and established an optimal treatment schedule based on differences in cell cycle dynamics between healthy and cancerous cells. They investigated the role of the growth rate of the tumor, on the timing of the best and worst treatment outcomes and identified important biological parameters in designing a chronotherapy strategy (Bernard, *et al.*, 2010). There is much interest in this clinically important application.

Circadian rhythms and metabolism

Entrainment of peripheral clocks uses a different mechanism than entrainment of the SCN; therefore, separate models are required. For example, peripheral clocks are primarily entrained by feeding-fasting cycles rather than light-dark cycles (Damiola *et al.*, 2000; Saini *et al.*, 2013). Perturbed feeding-fasting cycles (i.e., meal timing or high-fat diets) disrupt peripheral clock rhythms and possibly contribute to metabolic diseases (Eckel-Mahan *et al.*, 2013; Hatori *et al.*, 2012). This is an area of active investigation and a review of these models of circadian peripheral clocks will soon be needed.

Mathematical models have been developed to study the entrainment of peripheral clocks by metabolic factors. Woller *et al.*, (Woller, Duez, Staels, & Lefranc, 2016) developed a mathematical model of the liver clock that incorporated molecular sensors of metabolites nicotinamide adenine dinucleotide (NAD^+) and adenosine monophosphate (AMP) as metabolic inputs to the clock (Huang, Ramsey, Marcheva, & Bass, 2011). The NAD^+-dependent sensor that regulates many metabolic pathways is SIRT1 (Chang & Guarente, 2014), and the sensor that is activated by shortage of energy, is AMPK (Hardie, Ross, & Hawley, 2012). The model utilized various temporal patterns of AMPK activation to mimic the effects of a regular diet, fasting, and a high-fat diet. The authors showed that the liver clock is entrained by variations in AMPK activity, and they identified altered AMPK signaling as a mechanism leading to clock disruption and its associated metabolic effects. This model also reproduced the damped clock gene expression and NAD+ rhythms previously reported for mice on a high-fat diet (Hatori, *et al.*, 2012), and suggested pharmacological interventions may rescue these effects.

While photoperiod (light-dark cycle) and nutrition (feeding-fasting cycle), both influence the dynamics of the peripheral clock; peripheral clock phase is entrained by the latter signal when these cues are out-of-phase (Damiola, *et al.*, 2000), (Saini, *et al.*, 2013). To study the circadian dynamics of the peripheral clock in the presence of both of these environmental cues (i.e., feeding-fasting and light-dark cycles), Bae and Androulakis (Bae & Androulakis, 2017) developed a mathematical model of circadian rhythms of human liver cells. Their model (Bae & Androulakis, 2017) considered the peripheral clock genes in the liver cells to be entrained (i) by light-dark cycle via the cortisol-receptor complex, and (ii) by feeding-fasting cycle via NAD+ and SIRT1. Using the model, they studied the interactions between

SIRT1, NAD+, and peripheral clock genes under various light-dark and feeding-fasting phase relations and intensities, and predicted that the peripheral clock genes could be entrained entirely to feeding-fasting cycle, independent of the light-dark cycle. Moreover, their model predicted the phase relation between these two cues is a critical factor in determining the oscillation amplitude for the peripheral clock genes, suggesting that controlling the dynamics of SIRT1 may restore the oscillations of the peripheral clock machinery. The Bae and Androulakis (Bae & Androulakis, 2017) model was used to explore the effect of circadian disruption on hepatic gluconeogenesis, and to investigate various nonpharmacological methods to overcome the effects of circadian disruption (Bae & Androulakis, 2018). Their model predicted that by imposing modifications to the feeding time relative to the light-dark cycle, high level of fasting gluconeogenesis could be reduced to a wild-type level.

CONCLUSION

This article has been written to classify and distinguish circadian models based on their type and application, with a goal to providing a helpful primer for researchers to identify kinds of models and tools for their work. Modeling of different aspects of circadian rhythms is shifting towards more mathematically complex and realistic models that incorporate components with physiological meaning. Detailed models have provided insight into an understanding of the circadian system at different scales. Innovative modeling approaches at the gene regulatory network level, cellular, and multicellular levels, and at the organism and human behavioral level, have provided new insights into physiology and ways of altering it. Controlling the phase and period of circadian rhythms, and developing tools to optimize performance, are now major translational foci of circadian researchers. In the new era of precision medicine, further work is needed to enable the models to predict individual, rather than group, outcomes. This may require a combination of modeling and real-time data collection, since models currently do not include all known (and unknown) influences on circadian clocks and their outputs (e.g., objective performance). The widespread use of wearable biosensors may enable characterization of circadian function in the general population. New models and modeling approaches will be needed in the future for interpreting and utilizing these data.

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CIRCADIAN MODELING

Circadian clocks are present within individual cells, and communication among multiple cells gives rise to emergent properties at the tissue level. In mammals, both the master circadian clock in the suprachiasmatic nucleus and tissue-level peripheral clocks have major effects at the organism level on numerous key physiological functions, including sleep/wake cycles, metabolism, cardiovascular function, reproduction, immune function, neurobehavioral performance, and mood. Misalignment between the master clock and peripheral clocks within an organism, or misalignment between an organism's clocks and its external environment, has adverse physiological consequences. When circadian interventions are needed to improve physiological function, a multiscale understanding of circadian rhythmicity therefore is essential to accurately manipulate this complex oscillatory system.

Mathematical modeling is an essential tool to study and analyze complex physiological systems. It has been used to provide insight into the circadian system at multiple levels (i.e., organism, multi-cellular, cellular, molecular, genetic), to design new experiments, and to manipulate and control the components of the system *in silico* with specificity that cannot be easily achieved using *in vivo* and *in vitro* experimental methods for cost, time, or other reasons. Applications include shifting circadian timing or amplitude after jet lag or for shift work, and for choosing optimal timing and doses of drugs or other therapies to increase effectiveness and decrease side effects.
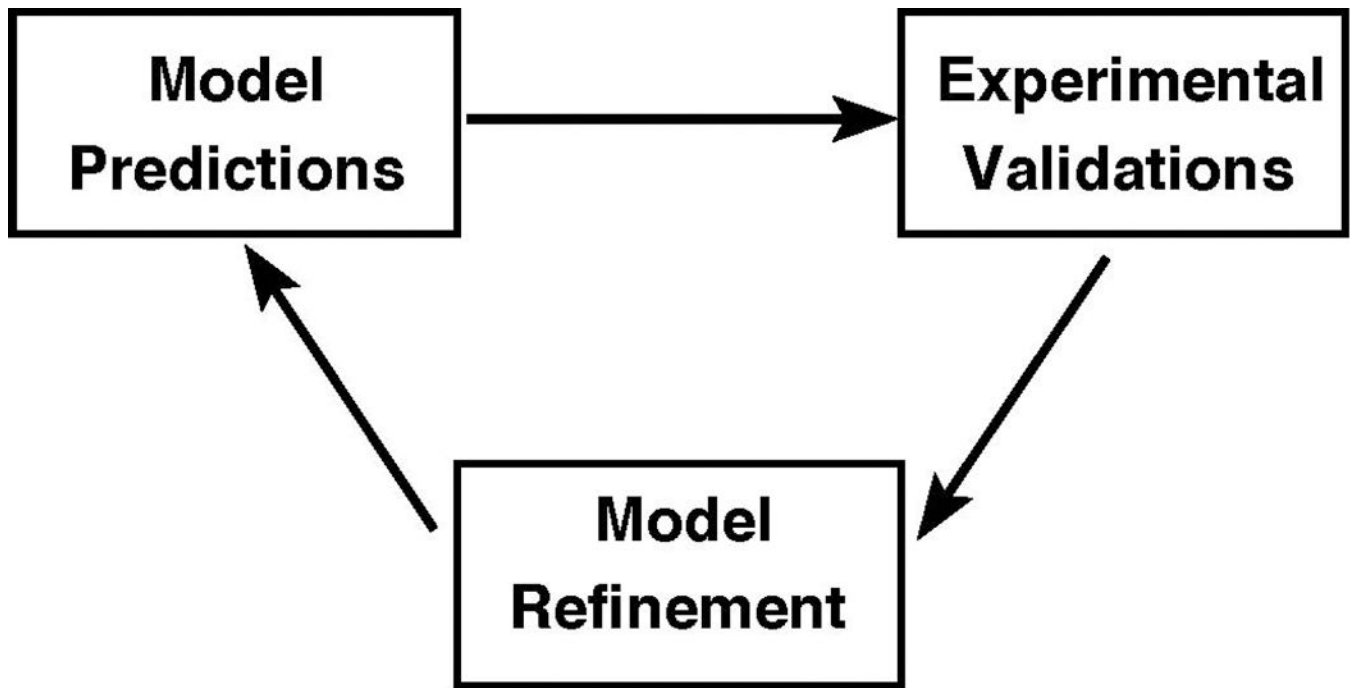
Fig.1.
An iterative process of model validation.
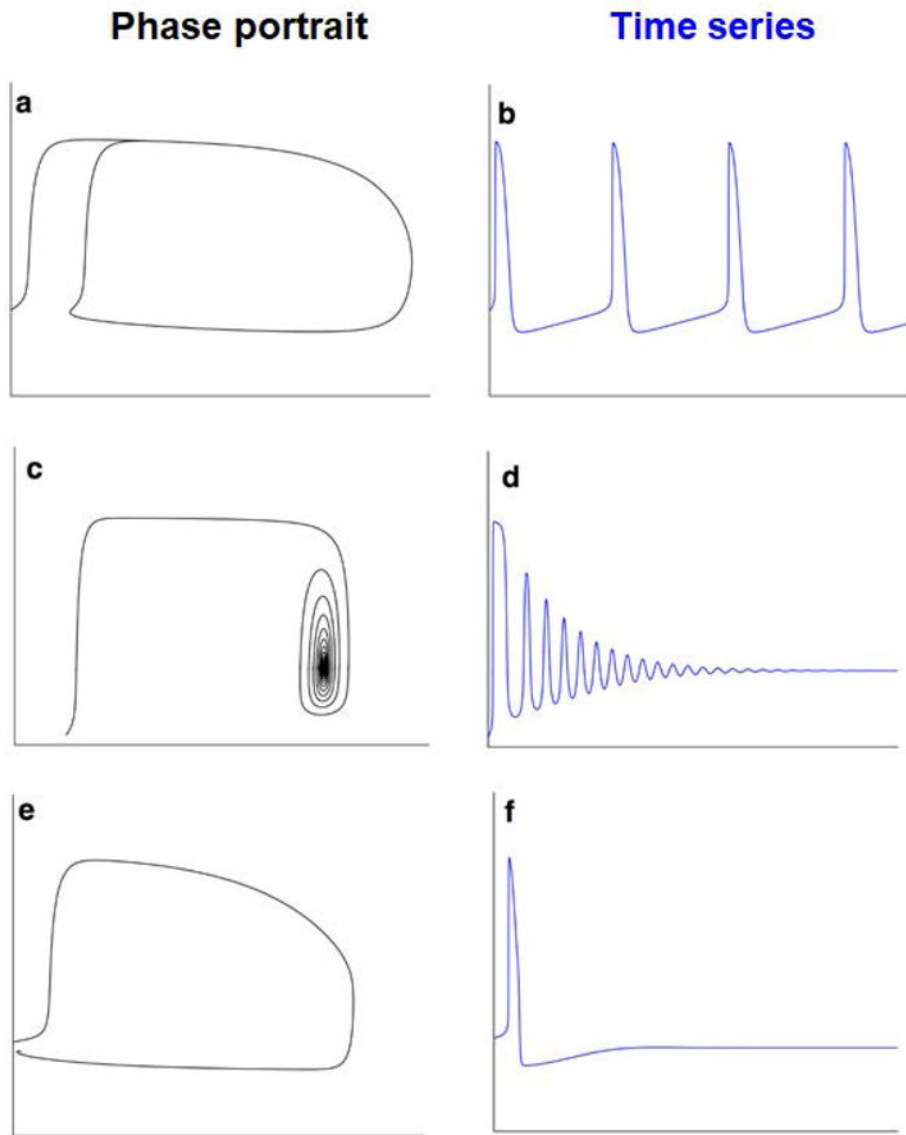
Phase portrait   Time series

Fig.2.
Illustrative examples of self-sustained (a & b), damped (c & d), and excitable (e & f) oscillations for the Hodgkin-Huxley model of a neuron, with variation in the potassium channel conductivity parameter. The left column shows the phase portraits (i.e., how 2 variables evolve in time with respect to each other. Note that time is an implicit variable), while the right column shows how one variable (voltage) changes with time. For the self-sustained oscillator (a, b), the model evolves to a closed limit cycle with a periodic output. For the damped oscillator (c, d), the model evolves to a steady state as the amplitude of the oscillation decays. For the excitable oscillator (e, f), a single cycle can be evoked, but the system thereafter returns to the steady state.
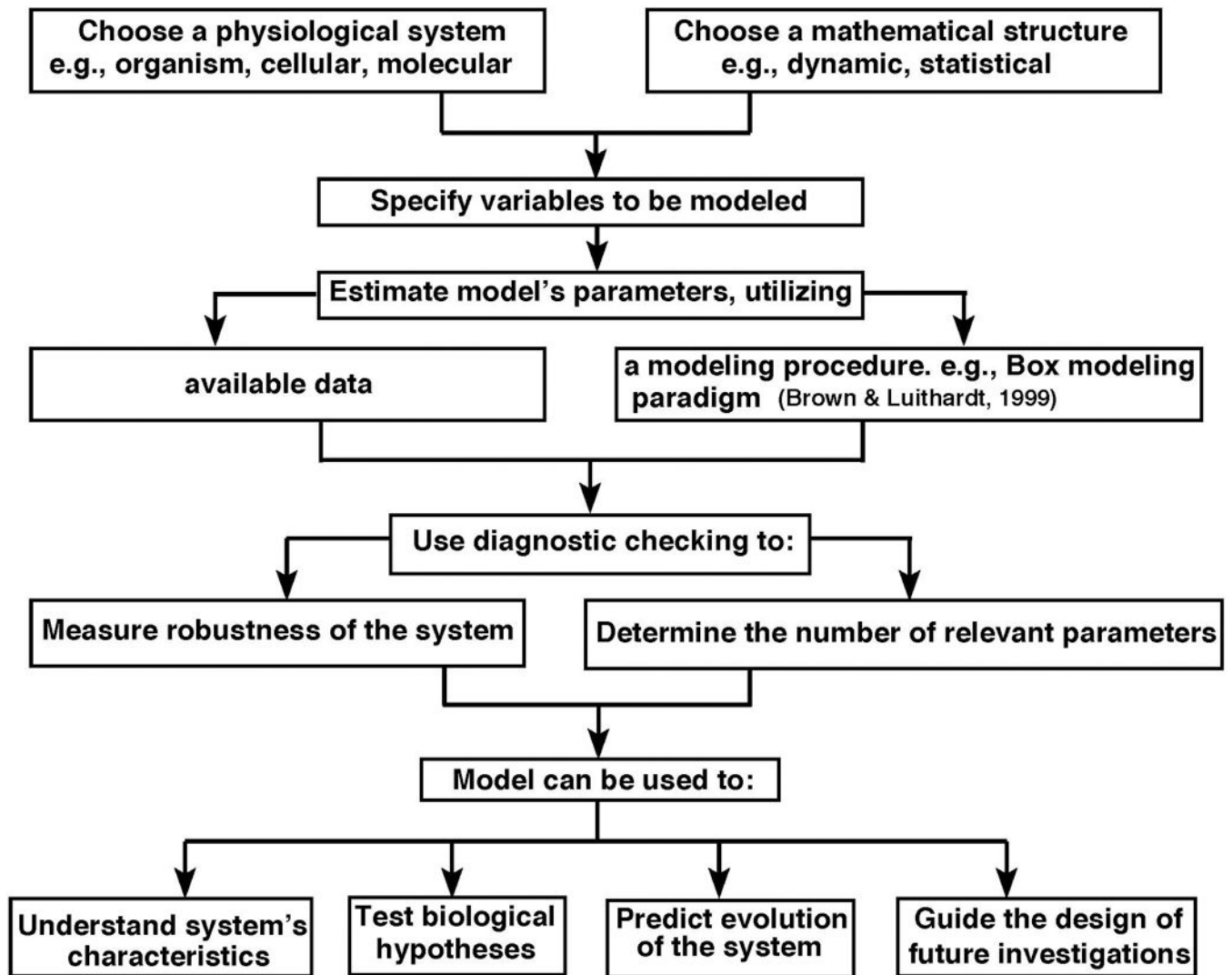
Choose a physiological system
e.g., organism, cellular, molecular

Choose a mathematical structure
e.g., dynamic, statistical

Specify variables to be modeled

Estimate model's parameters, utilizing

available data

a modeling procedure. e.g., Box modeling
paradigm (Brown & Luithardt, 1999)

Use diagnostic checking to:

Measure robustness of the system

Determine the number of relevant parameters

Model can be used to:

Understand system's
characteristics

Test biological
hypotheses

Predict evolution
of the system

Guide the design of
future investigations

Fig. 3.
A schematic description of one method for developing a mathematical model. (Revised from
the schema in (Brown & Luithardt, 1999; Klerman & St Hilaire, 2007).

Table 1.

Some deterministic and stochastic models of circadian rhythms in animals.

Model	Type	Level	Organism	No. of Dynamical variables
Gander, Kronauer, Czeisler, & Moore-Ede, 1984; Kronauer, Czeisler, Pilato, Moore-Ede, & Weitzman, 1982	ODE oscillator with external stimuli	Organism	Human	2–3
Daan & Berde, 1978	ODE oscillator	Organism	Human	2
Daan & Beersma, 1984	ODE oscillator	Organism	Human	2
To, Henson, Herzog, & Doyle, 2007	Mechanistic ODE model	Multicellular	Mammalian	17
Goodwin, 1965	Biochemical oscillator	Molecular	Drosophila	5
Leloup & Goldbeter, 2003	Mechanistic ODE model	Molecular	Mammalian	16
Forger & Peskin, 2003	Ordinary differential equations (ODEs)	Molecular	Mammalian	74
Forger & Peskin, 2005; Mohawk, et al., 2012; Yoo et al., 2004	Discrete stochastic chemical master equation (CME)	Molecular	Mammalian	73
Kim & Forger, 2012; Takahashi, 2017	Mechanistic ODE model	Molecular	Mammalian	181