Published in final edited form as:

Crit Rev Biomed Eng. 2016 ; 44(3): 193–211. doi:10.1615/CritRevBiomedEng.2017019658.

Asymmetry in Signal Oscillations Contributes to Efficiency of Periodic Systems

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Abstract

Oscillations are an important feature of cellular signaling that result from complex combinations of positive- and negative-feedback loops. The encoding and decoding mechanisms of oscillations based on amplitude and frequency have been extensively discussed in the literature in the context of intercellular and intracellular signaling. However, the fundamental questions of whether and how oscillatory signals offer any competitive advantages—and, if so, what—have not been fully answered. We investigated established oscillatory mechanisms and designed a study to analyze the oscillatory characteristics of signaling molecules and system output in an effort to answer these questions. Two classic oscillators, Goodwin and PER, were selected as the model systems, and corresponding no-feedback models were created for each oscillator to discover the advantage of oscillating signals. Through simulating the original oscillators and the matching no-feedback models, we show that oscillating systems have the capability to achieve better resource-to-output efficiency, and we identify oscillatory characteristics that lead to improved efficiency.

Keywords

PER; Goodwin; encoding; decoding; oscillating signals

I. INTRODUCTION

A. Oscillators Allow for Self-Regulation and Response to the Environment

Living systems respond to internal and external cues to self-regulate and adapt to changes in environment via activation of appropriate signals.¹ Oscillations, and their characteristics, in biological signals are effective mediators of this response. For example, hormone levels (such as for melatonin and cortisol) are known to vary rhythmically throughout the day and communicate with core clock genes to modulate the pace of important biological functions, including immune response^{2,3} and metabolism.^{4,5} These patterns of activity are often related to anticipatory modulations. For example, they may precede periods of activity and feeding:

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time periods that accompany intense energy needs and place an organism at the greatest risk of infection.³ In that respect, Curtis et al. surmise that “if the immune system needs to be poised for attack, just as the [organism] enters the activity and feeding phase, a clock might then allow for the enhancement of immune function.”³ In their 2008 review describing the design principles of biochemical oscillators, Novak and Tyson share Curtis’s conviction, concluding that oscillatory systems evolved because they likely provided some mechanism of evolutionary advantage over their alternative counterparts,⁶ which we interpret as nonoscillatory counterparts. Energy homeostasis has also been hypothesized to have a critical role in the emergence and persistence of rhythmic patterns of biological and physiological function.^{7,8}

Oscillatory communication is observed in various physiological systems. For example, the cardiac pacemaker is a classic example of a biological oscillator, comprised of a coupled ion-channel membrane oscillator and intracellular calcium oscillator for synchronization.⁹ Other biological oscillators that have been extensively studied include the following:

- **Neural conduction:** The neurons of the mammalian forebrain can individually resonate and oscillate at multiple frequencies, ranging from 0.05 to 500 Hz.¹⁰ This suggests that “precise timing of [neuron] activity within neuronal networks could represent information,”¹⁰ meaning that frequency (freq) encoding in neuronal signals generates different brain states.¹⁰ Each neuron class is defined by an eigenfrequency, leak conductance, capacitance of the neuronal membrane, and resting membrane potential, parameters that together define the neuron as a band-pass or band-stop filter.¹⁰ Neuron classes of similar resonance are associated with competing brain states.¹⁰ Multiple rhythms can exist within the same neuronal network simultaneously and interact with one another.¹⁰ Even neuronal networks designed from nonoscillating pyramidal neurons can generate sustained oscillations.¹⁰
- **Brain-wave activities:** “The default state of the unperturbed sleeping brain is a complex system of numerous self-governed oscillations.”¹⁰ In early studies of brain-wave activities using scalp electrodes, the conscious brain was observed to exhibit desynchronized patterns, whereas the sleeping brain exhibited clear oscillations.¹⁰ Neuronal activity is a measurement of the change in membrane potential of a single or group of neurons, encompassing action potentials and local field potentials (LFPs).¹¹ LFPs “represent a population measure (spatial average across many neurons)” and oscillate as a function of the concert of behavior from a neuron group.¹¹ The freq of LFP oscillations varies, generating different downstream events in neurons and other tissues.¹¹ Neuronal unit desynchronization is associated with many neuropsychiatric disorders including epilepsy, schizophrenia, dementia, and Parkinson’s disease¹¹; The characteristic tremor and loss of motor control suffered by patients of Parkinson’s disease is associated with the lack of synchronization within and among brain regions including the basal ganglia (a region of the brain critical to motor control) thalamocortical loop, cerebellothalamocortical loop, cortical motor, and sensory areas.¹¹ High-freq stimulation is used to treat Parkinson’s tremors and is believed

to be effective because the high-freq stimulation overrides the abnormal oscillatory communication among neuronal groups.¹¹

- p53 tumor suppressor/mouse double minute 2 (MDM2) oncogene protein activity in stress response:** In response to radiation stress,^{12,13} the p53 tumor suppressor is transcribed, triggering pathways that stimulate the production of p21, which binds to cdk2 to arrest cell division.¹⁴ The gene *mdm2* is transcriptionally regulated by p53, and protein MDM2 functions to inhibit the arrest initiated by p53 by targeting this and other tumor suppressors for proteasome degradation.^{12,15} In this way, radiation stress triggers a feedback loop in which sustained oscillations are observed.^{12,13} The oncogene MDM2 and tumor suppressor p53 are observed to oscillate in response to gamma irradiation of isogenic cells.¹³ In a Geva-Zatorsky et al. analysis, before irradiation, oscillations are not observed.¹³ Postirradiation, oscillations are with inconsistent amplitude (amp) but with a consistent period of 5.5 hr and a 2-hr delay of MDM2 following p53 (oscillations sustained during the entire 3-d experiment).¹³ The greater the radiation dose (0.3–10 Gy gamma radiation), the more cells were observed to oscillate, with 60% of the population oscillating at the same freq after undergoing the highest dose at 10 Gy.¹³ In their analysis, Geva-Zatorsky et al. observed that the remaining cells exhibited minor, if any, oscillations that readily decayed.¹³
- Nuclear factor (NF)- κ B transcription factor activity:** NF- κ B refers to a collective of transcription factors integral to “inflammation, immunity, cell proliferation/differentiation and regulation of anti-apoptotic signals.”¹⁶ Members of the NF- κ B family (RelA, RelB, RelC) exist as heterodimers or homodimers in the cytoplasm, eventually entering the nucleus when the dimer is released from an inhibiting factor (such as inhibitor of the NF- κ B [$\text{I}\kappa\text{B}$] family), in response to extracellular stimuli triggering a signaling cascade.^{16,17} NF- κ B exhibits oscillations in nucleus-cytoplasm localization, movement that is prevented with increased transcription of inhibitors such as $\text{I}\kappa\text{B}\alpha$.¹⁶ Other inhibitors including $\text{I}\kappa\text{B}\beta$ and $\text{I}\kappa\text{B}\epsilon$ also mediate NF- κ B oscillations via intermediate $\text{I}\kappa\text{B}$ kinase signaling.¹⁶
- Cytosolic calcium levels:** Extracellular stimuli including temperature change, mechanical stress, “mitogens, cytokines, hormones and neurotransmitters ... differentially affect Ca^{2+} channel, pumps and binding proteins,” altering the calcium concentration in the cytoplasm and causing it to oscillate.¹⁸ Various decoding elements resonate as specific calcium signal frequencies (f). Dolmetsch et al. demonstrate the effect of modulating the calcium signal period (τ) from 100 to 1800 s on “gene expression driven by the proinflammatory transcription factors NF-AT, Oct/OAP, NF- κ B,”¹⁹ as well as interleukin 2 (IL-2) and IL-8.¹⁹ Their results indicate that high-freq calcium signals ($\tau < 400$ s, $f > 2.5$ mHz) trigger gene expression of NF-AT, Oct/OAP, and NF- κ B, whereas only NF- κ B expression continues for $\tau > 400$ s and $f < 2.5$ mHz¹⁹ Similarly, IL-2 and IL-8 are both sensitive to low frequencies. ($\tau < 250$ s, $f > 4$ mHz); however, only IL-8 remains sensitive to greater τ /less f .¹⁹

- **Hormones, cytokines, and metabolism:** Rhythmic variability in terms of inflammatory and metabolic mediators has also received increased attention. The time of day and seasonal dependence of mediators of inflammation, physiological markers of stress, as well as the potential for reentrainment of those rhythms have been extensively studied. Particularly worth mentioning are modeling analyses aimed at establishing the design principles and boundaries of operation for those rhythmically varying mediators to establish functional dependencies and/or implications of loss of rhythmicity in the context of system robustness.^{20–32} Particularly prominent is the role of circadian rhythmicity in chronic inflammatory diseases.^{33–37}

The oscillators described above are responsible for myriad physiological tasks, depend on coordinated interactions of multiple factors or cell groups, and manifest emergent system properties.^{38,39} Ultimately, these factors function to receive external stimuli, translate them into an actionable cellular message, and induce intracellular changes to maintain homeostasis. Many factors, such as basal ganglia neurons or NF- κ B, act as both decoders and encoders of signals, reading and rewriting signal parameters discussed further below.

B. Mechanisms of Encoding and Decoding Information in Oscillatory Systems

Encoding and decoding mechanisms of oscillation have been discussed in the context of intercellular and intracellular signaling and are used to communicate different information via modulating oscillatory characteristics including chemical messenger, freq, amp, peak duration, and absolute concentration.^{1,40–42} Recommended reviews on the established field include Purvis and Lahav⁴² and Sonnen and Aulehla.⁴³ Molecular intermediates frequently overlap in their roles of encoding and decoding information. Although most signaling mechanisms in physiological systems have complicated modes of modulation, it is often possible to identify the key molecules in any given pathway and discover the driving mechanism.⁴¹

Modulation by oscillation amp is perhaps the easiest to identify among oscillatory characteristics. Amp-to-amp modulation is receptor mediated and effects change via an all-or-nothing or dose-response manner.^{1,44} For example, the mitogen-activated protein kinase (MAPK) pathway controls cell fate decisions in yeast and mammalian cells and exhibits dose-response behavior for certain functions. In *Saccharomyces cerevisiae*, the MAPK protein Fus3 responds to extracellular pheromone concentration and triggers a graded downstream response for its substrates via a negative-feedback control mechanism.⁴⁵ In *Xenopus* oocytes, MAPK signaling exhibits a switch-like, on/off behavior when exposed to a threshold of progesterone.⁴⁴ This dose-response behavior is evolutionarily conserved in mammalian cells, specifically, Swiss 3T3 fibroblasts, which exhibit graded MAPK signaling response in response to graded extracellular signal-related (ERK) input.⁴⁴

Similar to amp modulation, magnitude of a resource also communicates downstream effects but is itself the result of other signal parameters. Cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling is responsible for regulating multiple independent pathways involved in metabolism, gene regulation, cell growth/differentiation, and others.⁴⁶ PKA influences the translocation of the downstream transcription factor Msn2⁴⁰ that

regulates various gene expression patterns depending on the organism's needs. In their investigation into Msn2-modulated gene expression, Hao and O'Shea demonstrate that maximum expression increases with increasing Msn2 magnitude (specifically, the area under the curve [AUC] of nuclear-translocated Msn2). In this example, magnitude increases by increasing the freq of Msn2 pulses of identical duration and amp.⁴⁰ Therefore, freq modulation allows PKA to exhibit spatiotemporal control over substrate phosphorylation.⁴⁷

As discussed above, cytosolic calcium concentration oscillates with modulating freq that initiates unique responses in downstream effectors,¹⁸ achieving diverse signals and a spectrum of cellular functions. Dolmetsch et al.'s analysis uses the aforementioned calcium clamping technique to demonstrate decoder sensitivity to Ca^{2+} oscillations in Jurkat cells.¹⁹ Freq modulation is also observed when translating extracellular calcium concentration via the calcineurin-responsive zinc finger transcription factor Crz1.⁴⁸ Crz1 exhibits resting concentration in the cytoplasm.⁴⁸ After stimulation of the cell with calcium, calcineurin dephosphorylates Crz1, allowing it to translocate to the nucleus in a series of regularly repeating bursts.⁴⁸ The greater the concentration of calcium, the more frequent the bursts of Crz1 in the nucleus.⁴⁸ Thus, freq is decoded from an elevated amp or magnitude calcium signal. Cai et al. demonstrate that the *Crz1* gene targets exhibit transcription proportional to burst freq, with different targets remaining proportional to each other as extracellular calcium concentration is varied.⁴⁸

Additionally, signal encoding/decoding parameters include a signal's robustness to noise⁴³; in cellular communication noise is understood as general fluctuations in signals due to such abiotic factors as pH or temperature.⁴³ Sonnen and Aulehla note that signal freq and fold change are more resistant to information loss than are encoding parameters such as amp.⁴³ Signal or peak duration is also identified as an encoding/decoding parameter.^{43,49}

C. Role of Oscillatory Systems

Oscillatory systems are expected to control more than 10% of the genome of a mammal.² They are hypothesized to have evolved in aerobic organisms for the purpose of anticipating changes in environmental oxygen levels, thus offering a competitive advantage by allowing organisms to efficiently use their limited resource of oxygen supply and increase their survival chances.^{2,3} Because biological oscillations are hypothesized to have evolved for optimizing control of resources such as oxygen supply² and are observed to communicate messages specifically by means of aforementioned signal characteristics, the question arises as to whether periodicity in biological signals is merely a result of oscillating resource or an evolutionary advantage exists in providing the resource to a system in an oscillatory manner, as opposed to a constant manner, motivating our modeling investigation below.

In their review, Novak and Tyson discuss the ubiquity of sustained oscillations and illustrate four requirements for sustained oscillations: (1) negative feedback, (2) sufficiently delayed feedback communication, (3) nonlinear kinetic rate laws to describe interactions (hypersensitivity), and (4) temporally coordinated reactions such that oscillations can be maintained.⁶ All chemical oscillators are constructed with some method of negative-feedback, ensuring that "if the concentration of [a variable] gets too large, it will eventually decrease, and if it gets too small it will eventually increase."⁶ In their conclusion, Novak and

Tyson provide insight into the evolutionary origin of oscillatory systems in their description of the likelihood that “biochemical oscillations have arisen repeatedly from basic, homeostatic, negative-feedback loops by serendipitous genetic changes that destabilized the steady state and generated sustained oscillations.”⁶ Going further, they explain that although maladaptive oscillations are lost by natural selection, adventitious oscillations would be selected and it is likely that “mechanisms of circadian rhythms evolved many times independently in this way.”⁶

This defines the contemporary convention that oscillations provide some evolutionary advantage over alternative nonoscillatory systems. Existing within an external environment subject to a circadian structure (Earth’s revolution around the sun), organisms may have evolved to oscillate because systems capable of this type of temporal coordination use available resources most effectively.

D. Investigation into Oscillatory Characteristics and Resource Use

If oscillations in resource availability are advantageous over constant resource availability, what oscillatory characteristics of the resource signal contribute to the improved use of resources? As previously discussed, amp and freq of periodic signals contribute to signal specificity and magnitude. However, some signals deliver information via oscillatory characteristics other than, or in combination with, freq and amp modulation. Manipulating cumulative peak duration of calcium signals regulates NF- κ B transcriptional activity, phosphorylation of I κ B α , and calcium-dependent gene expression, indicating that cumulative peak duration defines signaling specificity independently of freq modulation.⁴⁹ Another feature of the periodic profile may need identification and characterization to explain the degree of resource use. Therefore, we ask the following questions in this study: (1) Do oscillating systems provide advantages in resource utilization and (2) does the way in which resource is presented to the system affect the efficiency of resource use? We hypothesize that oscillating systems offer advantages in terms of resource use efficiency, that is, the ratio of output to input and indication of the system’s ability to optimally use its input to generate output. We argue that in addition to improving specificity and inducing discrete on/off outputs, oscillating resources likely maximize output over time, when compared against the output generated by an equivalent nonoscillating resource.

We investigated the behavior of original versions of two classic negative-feedback models, namely, the Goodwin and PER oscillators, and created corresponding no-feedback nonoscillatory counterparts for each. We then supplied the corresponding models with identical time-averaged synthesized resource and compared their outputs to evaluate their relative system efficiency. The models were analyzed for efficiency in an effort to understand whether and why oscillatory systems maximize resource use. Freq and amp alone were found to be insufficient for complete characterization of system efficiency. Our investigation identified a characterizing parameter proportional to efficiency in both the Goodwin and PER models. We used statistical skewness, a calculation of the third moment of a dataset,⁵⁰ to describe the shape of the resource profile and to quantify how resource is presented the system. Its correlation with resource use efficiency provided evidence for nature’s preference of oscillatory systems over nonoscillatory systems.

II. METHODS

This study was designed to evaluate the efficiency of oscillating systems against complementary nonoscillating systems. We selected the Goodwin oscillator and the PER oscillator to serve as exemplary oscillating systems, because both Goodwin^{51–53} and PER^{54–57} are well-characterized tools that demonstrate negative-feedback control at the level of gene transcription. We created corresponding no-feedback nonoscillating systems for each model and supplied the original and modified models with identical synthesized resource over time to compare outputs. We hypothesized that oscillating systems have an advantage over nonoscillating systems in terms of resource use. To test this hypothesis, 10,000 parameter sets were generated using the Latin hypercube sampling (LHS) method and analyzed to discover the driving force behind efficiency in resource use.

A. Goodwin Oscillator

The Goodwin oscillator generically models periodic behavior that results from enzymatic reactions that incorporate autoregulation of a protein at the transcription level.^{1,58} Smith^{59,60} made one of the first adaptations of the Goodwin model to biological oscillation in a description of an endocrine regulatory circuit. Now termed the Goodwin–Smith model, it describes the testosterone regulation in males involving the gonadotropin-releasing hormone and luteinizing hormone and the negative-feedback effect of testosterone on the gonadotropin-releasing hormone. With a simple negative-feedback control mechanism, the Goodwin oscillator has been modified and extended for different purposes. The Goodwin–Smith model has been further modified to include impulsive control in an attempt to explain the observed chaos in testosterone regulation and has been closely studied with added delays and extra feedback.^{61–63} The modified Goodwin oscillator with Michaelis–Menten kinetics has proved to be useful for describing the central control mechanisms for circadian oscillators in the hypothalamic-pituitary-adrenal (HPA) axis in *Neurospora*, *Drosophila*, and mammals.^{26,52,53} As these examples show, the Goodwin oscillator is a simple yet versatile model with a negative feedback that can provide mechanistic insight into periodic biological phenomena.

Mathematically, the Goodwin oscillator consists of three differential Eqs. (1–3), featuring linear synthesis and degradation terms, and a Hill function to describe the negative feedback. Together, these equations describe the autoregulation of mRNA (X), enzyme (Y), and product (Z), where the product represses the transcription of messenger RNA (mRNA) and drives periodicity of the system. As a prototypical oscillatory system, the Goodwin oscillator demonstrates the effects of negative feedback and indirect inhibition in sustaining a dynamic steady state for a genetic oscillator.⁵¹ A schematic of the Goodwin oscillator is shown in Fig. 1(A).

$$\frac{dX}{dt} = \frac{a}{K + kZ^n} - bX, \quad (1)$$

$$\frac{dY}{dt} = \alpha X - \beta Y, \quad (2)$$

$$\frac{dZ}{dt} = \gamma Y - \delta Z. \quad (3)$$

To ensure that the design space is comprehensively represented, we chose LHS⁶⁴ as the sampling method for creating 10,000 samples each of the original oscillating systems. The LHS sampling method with uniform distribution was used to generate parameter values for the Hill function in Eq. (1). Thus, samples with varying resource profiles were generated, and the parameters defining the remainder of the model remained identical parameters in Eqs. (2,3). The constants α , K , and k were sampled between 50% and 150% of the original values (listed in Table 1). The Hill coefficient n , which determines the strength of negative feedback, was sampled between 8 and 24 and rounded to the nearest integer for the simulations. A Hill coefficient value of <8 was not considered, because such values yielded profiles that were incapable of generating oscillations. All other parameters retained the original values listed in Table 1.⁵¹

For each sample set generated, a simulation using the original oscillatory model was first performed. The steady-state region of output was tested for sustained oscillations to ensure that the resource profile was periodic when using the following algorithm. First, the output profile was tested for the existence of regularly repeating minima and maxima over a range of the final 2000 time steps in the simulation's profile. If regularly repeating peaks were detected, the maxima were analyzed for signal decay by taking the derivative of the values of the maxima within that same interval. Finally, the resource profile was converted into the freq domain to identify the frequencies present in this signal. If the freq peaks were identifiable in this domain (peaks above 1% intensity), the set was accepted; otherwise, the resource profile was considered nonoscillatory and rejected.

Once a sample was screened for sustained oscillation, a simulation in the corresponding no-feedback, nonoscillating model was performed, using an identical parameter set. The corresponding nonoscillatory model was created by removing the inhibitory effect of Z on X , visualized as the red cross in Fig. 1(A). To achieve this, Eq. (1) of the original oscillator was replaced with Eq. (4), where a 0th-order synthesis term V_s was introduced in place of the Hill function. Equations (2) and (3) from the original Goodwin oscillator remained identical in the modified model. The value of the constant synthesis term V_s was determined with Eq. (5), where the integral of the synthesis term of X from Eq. (1) is calculated over one period of the X profile included, described by the domain (t_1, t_2) , and then normalized by the period of X . In essence, the term V_s represents the average synthesis rate of X , each period, for a particular profile. Calculating V_s in this way ensured that for each parameter set, the no-feedback system experienced an identical amount of resource over time, as did the original oscillatory model. The no-feedback system was simulated alongside the original

oscillating system, so that output production could be compared. The simulation algorithm is summarized in Fig. 2.

$$\frac{dX}{dt} = V_s - bX, \quad (4)$$

$$V_s = \frac{\int_{t_1}^{t_2} \frac{a}{K + kZ^n}}{\text{period}(X)}. \quad (5)$$

Representative samples of the oscillating and nonoscillating models are shown in Fig. 3(A) and (B), respectively. The results show that all components X , Y , and Z exhibit periodicity from the oscillating model, whereas all components show constant values from the nonoscillating model. Once the outputs were obtained from both the oscillating and nonoscillating models, several key results were compared, including system efficiency and amp, freq, and skewness of the resource profiles.

Amp and freq carry the standard definitions of the distance from minimum to maximum for a certain component profile and the inverse of the time duration for one period, respectively. In this analysis, all amp and freq values are of the X profile and of the oscillating model, unless otherwise noted.

Skewness was used to quantify the shape of the oscillation profiles, using third-moment calculation, for resource X from the oscillating system. To test the hypothesis that the way in which the resource is available to the system affects the output, we first described the shape of the resource profile quantitatively. Skewness was selected to perform this role, because it describes how a period of oscillation deviates from a standard deviation curve, that is, deviations from a symmetrical curve. Qualitatively, skewness allows for the comparison of multiple resource profiles that share the same temporal average but differ in curvature and moment characteristics. Skewness of value 0 describes perfect symmetry, negative skewness corresponds to slow ascension and rapid descension with the peak located on the right-hand side of the center of a standard deviation curve, and positive skewness corresponds to rapid ascension and gradual descension with the peak located on the left-hand side of a standard deviation curve. Figure 4 provides examples of PER model resource (M) profiles sharing identical temporal average but different skewness; similar curves can also be created with the Goodwin model. Equation (6) was used to calculate skewness of the resource profile.⁶⁵ In this equation, x represents simulated data points over a complete period of the resource X profile, $\bar{x}$ and represents the time-average resource during that period.

$$\text{skew} = \frac{\sum (x - \bar{x})^3}{\left(\sum (x - \bar{x})^2 \right)^{\frac{3}{2}}}. \quad (6)$$

Relative efficiency (eff) compares the average output (i.e., Z) of the original oscillating system against the corresponding nonoscillating system, as defined by Eq. (7). This comparison can be made because the paired oscillating and nonoscillating systems experience identical amounts of synthesized resource. Efficiency also demonstrates whether the output of the oscillatory system is superior ($eff > 0$), inferior ($eff < 0$), or generates the same magnitude of output ($eff = 0$).

$$eff = \frac{\text{mean output of original model at steady state} - \text{mean output of corr. no - feedback model}}{\text{mean output of corr. no - feedback model}}.$$

(7)

B. PER Oscillator

Goldbeter developed the period protein (PER) model to demonstrate the mechanism of circadian oscillations in *Drosophila*.⁵⁴ The PER protein was identified to oscillate between the nucleus and the cytosol, exhibiting a circadian rhythm whose oscillations were reinforced by negative feedback exerted by PER on *per* transcription, that is, via posttranslational modifications.⁵⁴ It was observed that cells that lost this rhythm were the only cells whose repression was compromised, resulting in overproduction of PER protein.⁵⁴ The period protein is present in many organisms, including mammals, having been included in the many orthologous genes relevant to circadian regulation that derived from a common ancestor to insects and mammals 600–700 million years ago.⁶⁶ Because of PER's historical prevalence, the PER model is a useful tool for investigating clock regulatory mechanisms. Goldbeter's PER oscillator incorporates Michaelis–Menten kinetics and captures both the linear and plateau regimes of the enzymatic reaction.⁶⁷ The PER model is described by Eqs. (8–12), and its schematic is shown in Fig. 1(B). The PER oscillator model describes the translation of *per* mRNA (M) to native PER protein (P_0). PER protein is phosphorylated twice (P_1 is phosphorylated once and P_2 is phosphorylated twice) before translocating to the nucleus (P_N). Then, the nuclear PER (P_N) exerts inhibition on the transcription of its own mRNA (M) with a Hill-type function that drives the sustained periodicity of this system. In addition to simply describing transcription–translation negative-feedback control of the *period* gene, this system has been studied elsewhere as a model circadian oscillator. It was studied to assess the robustness of circadian oscillations in the presence of molecular noise^{55,56} and to explore the temperature compensation on circadian rhythms.⁶⁸

Similar to the Goodwin model, LHS⁶⁴ was used to create 10,000 samples of the original PER model. LHS with uniform distribution was used as the sampling method for the parameters in Eq. (8) to create samples with varying resource profiles, with the rest of the model Eqs. (9–12) identical. For the PER model, the constants v_s , K_p , v_m , and K_m were sampled between 50% and 150% of the original values⁵⁴ (listed in TABLE 1). The cooperativity coefficient n was sampled between 2 and 12 and rounded to the nearest integer for performing the simulations. All other constants held their original values.

Simulations were performed for the PER model using each parameter set generated via the above method. The steady-state output was tested for sustained oscillations, as with the Goodwin model. First, the output for the resource M profile was tested for the existence of regularly repeating minima and maxima from the steady-state portion of the simulation's time profile, the final 200 time steps. If regularly repeating peaks were detected, the maxima were analyzed for signal decay by taking the derivative of the values of the maxima within that same interval. The M profile was converted to the freq domain to analyze the sample for defined freqs, indicating oscillations. If irregular freqs were detected, this was considered to be noise, and the sample set was eliminated.

$$\frac{dM}{dt} = v_s \frac{K_i^n}{K_i^n + P_N^n} - v_m \frac{M}{K_m + M}, \quad (8)$$

$$\frac{dP_0}{dt} = k_s M - V_1 \frac{P_0}{K_1 + P_0} + V_2 \frac{P_1}{K_2 + P_1}, \quad (9)$$

$$\frac{dP_1}{dt} = V_1 \frac{P_0}{K_1 + P_0} - V_2 \frac{P_1}{K_2 + P_1} - V_3 \frac{P_1}{K_3 + P_1} + V_4 \frac{P_2}{K_4 + P_2}, \quad (10)$$

$$\frac{dP_2}{dt} = V_3 \frac{P_1}{K_3 + P_1} - V_4 \frac{P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - v_d \frac{P_2}{K_d + P_2}, \quad (11)$$

$$\frac{dP_N}{dt} = k_1 P_2 + k_2 P_N. \quad (12)$$

For parameter sets exhibiting sustained oscillation, a simulation with the no-feedback nonoscillating system corresponding to the PER model was performed. The corresponding model was created by removing the inhibitory effect of P_N on M , represented by the red cross in Fig. 1(B). To achieve this, Eq. (8) of the original oscillator was replaced with Eq. (13), where a 0th-order synthesis term V_s was introduced in place of the Hill-type function. Equations (9–12) from the original PER oscillator remained identical for the modified model. The value of the constant synthesis term V_s was determined with Eq. (14), where the area under the synthesis rate of M over one period was computed over (t_1, t_2) and normalized by the period of M ($period[M]$). The period was determined from the freq domain conversion during the sustained oscillation-screening step. The no-feedback system was simulated alongside the original oscillating system, and the outputs were compared.

$$\frac{dM}{dt} = V_s - v_m \frac{M}{K_m + M}, \quad (13)$$

$$V_s = \frac{\int_{t_1}^{t_2} v_s \frac{K_i^n}{K_i^n + P_N^n}}{\text{period}(M)}. \quad (14)$$

A representative sample of the oscillating and nonoscillating PER models are shown in Figs. 3(C) and (D), respectively. The results show that all variables exhibit periodicity within the oscillating model, whereas constant values are generated within the nonoscillating model. Once the outputs were obtained from both the oscillating and nonoscillating models, several key results (identical to the Goodwin model) were compared: system efficiency and amp, freq, and skewness of the resource profiles. Amp and freq were found for the oscillating resource M profile. Skewness was computed using Eq. (6). Relative efficiency was computed for each sample using profiles of P_2 and Eq. (7).

III. RESULTS

A. Efficiency Distribution with Various Output Parameters

The efficiency distribution with various parameters for all simulated results is shown in Fig. 5. The left-hand column with Figs. 5(A), (C), and (E) shows the efficiency distribution with respect to skewness, amp, and freq for the Goodwin model. Next, the right-hand column with Figs. 5(B), (D), and (F) shows the same distribution for the PER model. From Fig. 5(A), we observe that in the case of the Goodwin model, most of the simulated results exhibited skewness >0 . Simulated results from the PER model (Fig. 5[B]) contained both negative and positive skewness. In the PER model, skewness had a positive correlation with efficiency. This was not true for the Goodwin model; instead, the efficiency range increased with skewness, allowing the system to achieve more flexible efficiency with highly skewed resource profiles. In contrast, the efficiency for PER model was always above 0.

Amp correlated to efficiency similarly to skewness. For the Goodwin model, higher amp corresponded to increased flexibility in achievable efficiency (Fig. 5[C]), whereas for the PER model, amp positively correlated with efficiency (Fig. 5[D]). Freq behaved to the opposite of amp and skewness in the Goodwin model; the efficiency range was higher at lower freqs (Fig. 5[E]). Lower freqs corresponded to higher flexibility in efficiency for the PER model as well (Fig. 5[F]).

B. Efficiency Variability for Similar Resource and Freq

Although considering the simulated data as a whole has merit for uncovering the separate behaviors of the two representative systems, there is also value in uncovering common relationships that encompass both the Goodwin and PER models. To ensure that no systematic error occurred due to the resource presented to the system, data sharing a narrow

range of the average synthesized resource were selected. Supplementary Fig. A1 in the Appendix shows the histograms for the AUC of synthesis of X and the AUC of synthesis of M for all simulated data exhibiting sustained oscillations. On the basis of these histograms, the range (0.54, 0.56) was selected for the AUC of synthesis of X and the range (10.25, 10.35) was selected for the AUC of synthesis of M , for all following analyses, because these were the most recurrent values from the simulations. Then, the data were screened again for identical freq to ensure that the final sets experienced a similar resource during the similar time span. For the Goodwin model, a freq of 0.2 was selected, and for the PER model, a freq of 0.042 was selected for accurate analysis. After screening, efficiency–skewness–amp relationships were analyzed and are shown in Fig. 6. Fig. 6(A) shows that skewness correlates positively to efficiency for the Goodwin model. Fig. 6(B) shows the same trend for the PER model, although the slope of correlation (0.24) is much lower than the Goodwin model (4.2). In this dataset, amp also correlates positively to system efficiency for both the Goodwin model (Fig. 6[C]) and PER model (Fig. 6[D]). Finally, the amp of the resource profile increases as skewness increases, in both the Goodwin model (Fig. 6[E]) and PER model (Fig. 6[F]).

IV. DISCUSSION

In this study, we examined the hypothesis that an oscillating resource provides an advantage in its use, and the way in which the resource is presented to the system affects the degree of superiority for an oscillating system over the corresponding nonoscillating system. Examining the distribution of efficiency in both models (Fig. 5) tells us that a periodically behaving resource indeed provides an advantage in terms of resource use. For the PER model, efficiency was always >0 , implying that within the parameter range explored in this study, an oscillating resource always produces output greater in magnitude than that of the constant resource, given identical average resource concentration. The results indicate that the oscillating resource optimizes resource use, providing more average output (P_2) using the same amount of resource (M) over time. For the Goodwin model, efficiency ranged from negative to positive values. The range of efficiency increased with increasing skewness (Fig. 5[A]), increasing amp (Fig. 5[C]), and decreasing freq (Fig. 5[E]). For the PER model, efficiency values increased with increasing skewness (Fig. 5[B]) and increasing amp (Fig. 5[D]). Decreasing freq in the PER model increased the range of efficiency (Fig. 5[F]). All of these trends indicate that system efficiency correlates with various characteristics of resource dynamics, suggesting that the way in which a resource is supplied to the system affects the efficiency of resource use.

Common trends of both Goodwin and PER simulations are shown in Fig. 6. Data presented in this figure have a narrow range of synthesized resource and freq (selection was based on Supplementary Fig. 1), to remove any unknown bias due to the extremely high or extremely low resource available to the system. All frequencies and synthesized resource concentrations selected yielded the same directionality of correlations among the three output parameters, although the magnitude of slope did change for some pairs (data not shown). From the analysis of the screened data, two common factors that affect system efficiency were identified: skewness and amp. For both Goodwin and PER models, increasing skewness and amp in the resource profile increased efficiency (Fig. 6[A]–[D])

when the average synthesized resource and its freq were held constant. Amp increased with skewness in both models (Fig. 6[E] and [F]). Negatively skewed high-amp resource profiles tend to exhibit higher efficiency for both the Goodwin and PER model, given an identical temporal concentration of resource.

In addition to revealing that oscillating systems have the capability of exhibiting better efficiency, we also identified the correlation between resource curve shape and system efficiency. The concept of a “starved system” is introduced to rationalize the observations made from this study. In a “starved system,” the resource increases gradually and decreases quickly. Its counterpart is an “unstarved system,” where the resource increases quickly and decreases gradually. This study revealed that if the average resource concentration is identical, an unstarved system is more likely to achieve higher output, and therefore higher efficiency, compared to a starved system. Additionally, an unstarved system usually achieves higher amp, compared to a starved system. To find the cause of the increased efficiency of a highly skewed, greater amp, unstarved system, the Goodwin model profiles were analyzed in closer detail. We observed that amp characteristic was preserved within the resource (i.e., X parameter), intermediate (Y parameter), and output (Z parameter) profiles. However, the skewness characteristic was lost as the system progressed from profile X to Y to Z (see sample simulation results in Fig. 4[A]). To investigate the reason why the skewness decreased during the progression, a sample resource profile of the Goodwin model was obtained, and Y and Z profiles were obtained while altering the ratio between synthesis and degradation of intermediate Y . In other words, the ratio between α and β from Eq. (2) was

varied, the default condition for which is $\frac{a}{b} > 1$. Decreasing the ratio $\frac{a}{b}$ resulted in a loss of amp and magnitude, increased positive skewness for Y and Z , and lower efficiency. Therefore, in an ideal oscillator, the amp and skewness of the resource profile must be maximized concurrently, and downstream reactions must exhibit higher synthesis rates than their degradation rates, to convert the skewness characteristic from the resource to higher output values.

Goodwin and PER models limited to the same freq range were analyzed to answer the question of what acted to maximize amp and skewness; specifically, to find the correlation among feedback strength, skewness, and efficiency. For the PER model, the feedback parameters of the resource generation term in Eq. (8) are v_s , K_i , and n , where n is the cooperativity parameter. The term v_m is not directly indicative of feedback but exhibits interesting characteristics with relation to the starved/unstarved system concept. Polynomial regression analysis of these terms with skewness revealed that first-order variation of n and K_i with skewness have high correlation, producing an R^2 value of 0.7918. Increasing n and decreasing K_i were associated with stronger negative feedback and correlated with increasing skewness and efficiency. For the Goodwin model, analogous findings followed. The feedback parameters α , K , k , and n , from the generation term of Eq. (8), were correlated with skewness using a polynomial regression. A third-order variation on K and first-order variation on n yielded the best fit, producing an R^2 value of 0.5795. An increase in n and decrease in K led to more positive skewness. Increasing n is indicative of stronger negative feedback, as in the PER model analysis. Decreasing K yields more weight of the denominator to the effect of parameter n , again increasing negative-feedback strength.

Observations from this analysis are consistent with the behavior seen in the unstarved system: stronger negative feedback leads to higher skewness and efficiency.

Also observed in this analysis are the correlations between v_m , n , and skewness of the PER model. As v_m decreased and K_i or n increased, statistical skewness increased with correlations of $R^2 = 0.7605$ and $R^2 = 0.7918$, respectively. These results indicate that for an elevated consumption of resource M (increased v_m), efficiency and skewness decrease. When the system has a high demand for signal M , v_m will also be high, and skewness and efficiency will decrease.

Comparing the original and modified Goodwin and PER oscillators indicates that oscillatory systems are able to be more resource efficient, compared to the corresponding no-feedback systems. In addition, the efficiency changes corresponding to changing oscillatory characteristics of the resource profile were explored in detail. The advantage of oscillating biological signals has been mainly reviewed in the literature from a signal-specificity perspective and the capability of achieving on/off behavior.^{19,42,49} In this study, we examined the periodic nature of signals and offered a new perspective: resource efficiency. We accomplished this by creating complementary no-feedback nonoscillating systems for two classic oscillators using negative-feedback mechanisms, Goodwin and PER models, by removing the inhibitory action of the output on the resource. Each pair of original oscillating system and the corresponding nonoscillating system was input with the identical average synthesized resource. Therefore, we were able to directly compare the level of output and determine the efficiency of the oscillating system as compared to the nonoscillating system. Moreover, we showed that system efficiency depends on how the resource is presented, which is characterized by statistical skewness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

I.P.A. acknowledges support from National Institutes of Health grant GM 024211. S.B. and A.A. acknowledge support from National Science Foundation Graduate Research Fellowship (DGE-1433187) and the National Institute of General Medical Sciences of the National Institute of Health (T32 GM008339).

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FIG. 1. Schematics of the representative systems. (A) The *X* region is removed to block inhibition on mRNA by the metabolite in the Goodwin oscillator, creating the corresponding nonoscillating system. (B) Similarly, inhibition on *per* mRNA by nuclear PER is removed from the PER oscillator to create a corresponding nonoscillating system.

FIG. 2.

Simulation method for calculating resource efficiency and characterizing component time profiles. First, parameters in the differential equation for the resource are sampled, and then the time profiles for each sample is calculated. Then, the AUC of the resource for one period is calculated, and this is used to compute the synthesis rate for the no-feedback model. Using the new synthesis rate, time profiles of each component for the no-feedback model are calculated and the output parameters are then computed using profiles from both the oscillating and no-feedback models. AUC, Area under the curve

FIG. 3.

Sample simulation results for classic negative-feedback oscillators ([A] Goodwin; [B] PER) and their corresponding nonoscillating models. All of the constants used to generate this figure were taken from the original literature,^{51,54} and the values are listed in Table 1. (A) Oscillating Goodwin model; (B) nonoscillating Goodwin model; (C) oscillating PER model; (D) nonoscillating PER model.

FIG. 4. Sample resource (M) concentration profiles exhibiting different skewness, ranging from positive to negative values. The peak moves from right to left as skewness increases. The graphs were created using the PER model.

FIG. 5.

Efficiency distribution for various parameters revealing comparative range of possible efficiency. (A) Efficiency distribution for skewness, Goodwin model; (B) efficiency distribution for skewness, PER model; (C) efficiency distribution for amp of resource X, Goodwin model; (D) efficiency distribution for amp of resource M, PER model; (E) efficiency distribution for freq of resource X, Goodwin model; (F) efficiency distribution for freq of resource M, PER model.

FIG. 6.

Efficiency–skewness–amp correlations when system freq and synthesized resource are similar. (A) Goodwin model, efficiency dependence on skewness; (B) PER model, efficiency dependence on skewness; (C) Goodwin model, efficiency dependence on amp of resource X; (D) PER model, efficiency dependence on amp of resource M; (E) Goodwin model, amp of resource X dependence on skewness; (F) PER model, amp of resource M dependence on skewness.

TABLE 1

List of simulation parameters

Model	Number	Parameter	Original values	Simulation range
Goodwin oscillator	1	a	360	240–480
	2	K	43	21.5–64.5
	3	k	1	0.5–1.5
	4	n	n/a	8–24
	5	b	1	1
	6	α	1	1
	7	β	0.7	0.7
	8	γ	1	1
	9	δ	0.8	0.8
PER oscillator	10	v_s	0.76	0.38–1.14
	11	K_i	1	0.5–1.5
	12	n	4	2–12
	13	v_m	0.65	0.325–0.925
	14	K_m	0.5	0.25–0.75
	15	k_s	0.38	0.38
	16	V_1	3.2	3.2
	17	K_1	1	1
	18	V_2	1.58	1.58
	19	K_2	1	1
	20	V_3	5	5
	21	K_3	2	2
	22	V_4	2.5	2.5
	23	K_4	2	2
	24	k_1	1.9	1.9
	25	k_2	1.3	1.3
	26	v_d	0.95	0.95