Modeling Circadian Clock Regulation of Immune System Response to SARS-CoV-2 Infection and Antiviral Treatment

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Abstract

Circadian clocks regulate the immune system, rendering humans more susceptible to infections at certain times of the day. Circadian modulation of SARS-CoV-2 infection has not yet been clearly established, nonetheless the circadian control of other respiratory viruses such as influenza A makes apparent the need to study the interaction between circadian rhythms and COVID-19 disease progression. We incorporated circadian oscillations into a mechanistic model of SARS-CoV-2 dynamics and immune response fit to viral load data from COVID-19 patients. The model predicts that circadian variation of parameters associated with the innate immune response and viral death rate lead to faster clearance of the virus, whereas circadian variation of parameters representing the susceptible cell infection rate, the viral production rate, and the adaptive immune response lead to slower clearance of the virus. We then used a model of remdesivir to simulate antiviral therapy. Our model simulations predict that the effectiveness of the treatment depends on the time of day the drug is administered. Based on our proof-of-concept modeling results, we advocate for experimental and clinical studies to assess the impact that dosing time of day may have on the efficacy and toxicity of current COVID-19 antiviral drugs.

1 Introduction

Circadian rhythms are daily biological oscillations that serve to align human physiology and behavior with 24-hr environmental cycles. The central circadian pacemaker, the suprachiasmatic nucleus (SCN), is located in the hypothalamus and is capable of producing oscillations with a period near 24 hrs in the absence of external input. The SCN entrains to environmental light-dark cycles through the retinohypothalamic tract. The output of the SCN clock is a daily rhythm in electrical activity. This timing signal is sent to other parts of the brain and the endocrine system to control the release of hormones that circulate via the bloodstream and regulate circadian rhythms in peripheral tissues and organs [7].

The molecular basis of the circadian clock is a transcriptional/translational feedback loop. The protein products of certain "clock" genes inhibit their own production, forming a negative feedback loop. Mathematically, negative feedback can produce oscillations. The timescales associated with transcription, translataion, degradation, and other biochemical processes confers a period of approximately 24 hours to the oscillations in clock gene expression and protein abundance. This molecular timekeeping mechanism is found not just in SCN neurons, but in cells throughout the body, including cells in the cardiovascular system, metabolic system, and immune system [27, 30, 31, 32].

The circadian oscillations generated by these peripheral clocks are entrained and coordinated by the SCN. These rhythms have important implications for physiology and behavior, as well as for pathophysiology and the treatment of disease [50]. For example, cells exhibit a circadian rhythm in their ability to repair DNA damage. This suggests there may be value in a *chronotherapeutic* approach that administers cancer treatment at the optimal time of day to maximize effectiveness or minimize side effects. A recent study found that progression-free survival and overall survival for female patients with diffuse large B cell lymphoma that received chemotherapy mostly in the morning was significantly shorter compared to patients that received chemotherapy mostly in the afternoon [24].

Circadian rhythms in the immune system have received increasing interest in recent years, but their discovery goes back decades to a study on bacterial toxins. The body's response to endotoxins relies on the innate immune system, which is considered the first line of defense against infection [45]. Franz Halberg, who coined the term circadian in 1959, showed that the survival rate of mice injected with the endotoxin *E. Coli* depends on the time of day that it is injected [17]. It is now known that monocyotes and macrophages, cells central to the innate immune response, contain

molecular circadian clocks. Clock genes also exist within B and T cells, and the role of circadian rhythms in the later-stage adaptive immune response has become increasingly recognized [12].

Although viruses do not exhibit intrinsic circadian rhythms of their own, the host's circadian clock can affect the ability of viral pathogens to propagate within the host and modulate the progression of a viral infection [37]. For example, replication of herpes virus was 10 times higher in mice infected at the start of their resting phase (analogous to late evening for humans) than in mice infected at other circadian phases [13]. Replication of human immunodeficiency virus 1 (HIV-1) also exhibits circadian oscillations due to regulation by the host's clock machinery [3]. Furthermore, a relationship between infection time of day and viral pathogenesis has also been demonstrated for influenza [44]. Mice infected just prior to their active phase had enhanced inflammation, more severe lung injury, and worse survival outcomes than animals infected just before the onset of their rest phase. However, differences in viral titers these two groups did not emerge until after 4 days post-infection, leading Sengupta et al. to conclude that viral replication was not affected by the time of infection. Instead, they attributed the observed time-of-day effects to circadian regulation of viral clearance [51].

The time-dependent regulation of a respiratory virus like influenza motivates the investigation of circadian regulation of the immune response to SARS-CoV-2 infection. Intriguingly, a preliminary retrospective study of COVID-19 patients treated with a single daily dose of the antiviral medication darunavir-ritonavir for seven days showed a significantly stronger reduction in C-reactive protein levels in patients dosed in the morning versus those dosed in the evening [9]. In this paper, we develop a computational model linking the circadian and immune systems and use it to explore how circadian variation of immune system parameters affects SARS-CoV-2 infection dynamics and the response to antiviral therapy administered at different times of day.

2 Methods

In this section we describe the models we used for circadian rhythm generation and the immune system response to SARS-CoV-2 infection.

Circadian pacemaker model. We used the Forger-Kronauer-Jewett (FJK) model to describe the circadian pacemaker [14]. The FJK model is a modified version of the classic Van der Pol oscillator. In this model, self-sustained limit cycle oscillations arise from positive and negative feedback interactions between two internal clock state variables, C and A [8]. The pacemaker is driven by the external light-dark cycle through a third state variable, n. The FJK model consists of three ordinary differential equations:

$$\frac{dC}{dt} = \frac{\pi}{12}(A+B) \tag{1}$$

$$\frac{dA}{dt} = \frac{\pi}{12}\left(\mu\left(A - \frac{4}{3}A^3\right) - C\left(\left(\frac{24}{0.99669\,\tau_c}\right)^2 + \kappa B\right)\right) \tag{2}$$

$$\frac{dn}{dt} = \lambda\left(\alpha[\zeta]f(t)\,(1-n) - \eta n\right) \tag{3}$$

where

$$B = G\alpha[\zeta]f(t)(1-n)(1-0.4C)(1-0.4A) \tag{4}$$

and

$$\alpha[\zeta] = \alpha_0\left(\frac{\zeta}{\zeta_0}\right)^p. \tag{5}$$

The variable C represents core body temperature, n models the phototransduction pathway through which light drives the circadian system, B models circadian modulation of the oscillator's sensitivity to light, and A is a phenomenological auxiliary variable. We used the following parameter values: $\mu = 0.23$, $\tau_c = 24.2$, $\kappa = 0.55$, $\lambda = 60$, $\eta = 0.0075$, $G = 33.75$, $\alpha_0 = 0.05$, $\zeta = 1000$, $\zeta_0 = 9500$, and $p = 0.5$. The parameters of the FJK model and its precursors were determined based on laboratory experiments measuring how the phase and amplitude of the human circadian system respond to light input [25, 14, 26, 23]. These models have been extensively validated under a variety of laboratory and field conditions [46, 10].

We note that τ_c determines the period of the oscillator in constant darkness and ζ represents light intensity. To simulate alternating periods of light and dark we take $f(t)$ to be a square wave with a period of 24 hours and a duty cycle of 0.5, i.e. $f(t) \equiv 1$ for 12 hours of light and $f(t) \equiv 0$ for 12 hours of darkness. We consider Zeitgeber Time (ZT) 0 to be sunrise at 7 AM and ZT 12 to be sunset at 7 PM.

Immune system model. We used the Goyal et al. [16] model to describe the immune system response to SARS-CoV-2 infection. It consists of six ordinary differential equations:

$$\frac{dS}{dt} = -\beta V S \tag{6}$$

$$\frac{dV}{dt} = \pi I - \gamma V \tag{7}$$

$$\frac{dI}{dt} = \beta V S - \delta I^k I - m\frac{E^r}{E^r + \phi^r} I \tag{8}$$

$$\frac{dM_1}{dt} = \omega I M_1 - q M_1 \tag{9}$$

$$\frac{dM_2}{dt} = q(M_1 - M_2) \tag{10}$$

$$\frac{dE}{dt} = q M_2 - \delta_E E \tag{11}$$

where S are susceptible cells, V are SARS-CoV-2 viral particles, I are SARS-CoV-2-infected cells, M are precursor immune cells, and E are effector immune cells. SARS-CoV-2 virions replicate inside infected cells with rate π and die with rate γ. SARS-CoV-2 enters susceptible cells and converts them into infected cells with rate βV, triggering a two-stage immune response comprised of an early innate response and a late acquired response. In the first stage, SARS-CoV-2-infected cells are cleared by the innate immune response with a density-dependent rate δI^k. In the second stage, infected cells are cleared by the acquired immune response with rate $mE^r/(E^r + \phi^r)$. The development of the slower acquired response is modeled by proliferation of precursor cells M_1 with rate ωI, which differentiate with rate q into precursor cells M_2 and then ultimately into effector cells. The effector cells die with rate δ_E.

Goyal et al. [16] used nonlinear mixed-effects modeling to fit the parameters of the immune system model to viral shedding data from 25 untreated COVID-19 patients. The data consisted of viral load measurements taken over several days from SARS-CoV-2 infected people in Singapore, Germany, South Korea, and France. They obtained maximum likelihood estimates of the population median and standard deviation for each model parameter using a stochastic approximation version of the expectation-maximization algorithm. Their parameter estimation procedures yielded patient-specific values for six of the parameters (β, δ, k, π, m, and ω) and set the remaining five parameters to the same value for all patients ($\gamma = 15$, $r = 10$, $\phi = 100$, $q = 2.39 \times 10^{-5}$, and $\delta_E = 1$). The patient-specific parameter values for the three patients that we simulated (patients S18, S12, and G2) are provided in Table 1.

Model of antiviral therapy. The action of remdesivir, an antiviral drug approved by the FDA for the treatment of COVID-19, was also modeled by Goyal et al. [16]. They used a two-compartment model to capture the pharmacokinetic data of remdesivir, where the first compartment (C_p) represents the amount of drug in the plasma and the second compartment (C_a) represents the amount of drug in its active form in peripheral blood mononuclear cells (PBMCs).

$$\frac{dC_p}{dt} = -k_{pa} C_p - k_c C_p \tag{12}$$

$$\frac{dC_a}{dt} = k_{pa} C_p - k_a C_a \tag{13}$$

where k_{pa} is the rate at which remdesivir is metabolized into its active form, k_c is the rate at which it is eliminated from the plasma, and k_a is the rate at which the active form is eliminated from PBMCs. Although PMBCs are blood cells rather than lung cells, they are commonly used as a surrogate for lung tissue in clinical studies of remdesivir [6, 18, 21].

The antiviral efficacy (ε) of remdesivir was modeled as a function of the concentration of drug in its active form:

$$\varepsilon = \frac{C_a/V_2}{C_a/V_2 + \mathrm{EC}_{50}} \tag{14}$$

Parameter	Patient S18	Patient S12	Patient G2
β	5.8917×10^{-8}	5.9149×10^{-8}	5.9680×10^{-8}
δ	3.1471	3.1362	3.1212
k	0.0784	0.0780	0.0775
π	389.2781	391.5886	396.2050
m	3.1973	3.2621	3.2083
ω	2.7652×10^{-5}	2.7766×10^{-5}	2.7878×10^{-5}

Table 1: Values of the patient-specific parameters used in this study, taken from [16].

where V_2 is a conversion factor based on the volume of the second compartment and the molar mass of remdesivir in its active form, and EC_{50} is the half-maximal effective concentration. Goyal et al. [16] assumed that remdesivir inhibits the viral production rate by a factor $(1-\varepsilon)$, thus Eqn. (7) becomes

$$\frac{dV}{dt} = \pi(1-\varepsilon)I - \gamma V. \tag{15}$$

For the simulations in this paper, we set $k_{pa} = 21, k_c = 29, k_a = 12, V_2 = 0.12$, and $EC_{50} = 0.8$, based on the half-life of remdesivir and Goyal et al.'s fitting of the two-compartment model to pharmacokinetic data from non-human primates [22, 49, 28]. Goyal et al. considered three different scenarios for the potency of remdesivir: high ($EC_{50} = 0.8$), medium ($EC_{50} = 8$), and low ($EC_{50} = 80$). The high potency value was based on the EC_{50} estimate of 0.77 μM obtained by Wang et al. [47] for in vitro measurements of remdesivir's antiviral activity against a clinical isolate of SARS-CoV-2 in Vero E6 cells. The medium and low potency scenarios represented hypothetical in vivo values. Pruijssers et al. [38] also tested remdesivir against SARS-CoV-2 in vitro, and estimated $EC_{50} = 1.65$ μM in Vero E6 cells and $EC_{50} = 0.28$ μM in Calu3 2B4 cells. Pruijssers et al. then evaluated the efficacy of remdesivir in vivo and measured $EC_{50} = 0.01$ μM in human lung cells and primary human airway epithelial cultures. They attributed the weaker activity in Vero E6 cells to their low capacity to metabolize remdesivir. Thus, for our simulations, we used the high potency value from Goyal et al., rather than the medium and low potency hypothetical in vivo values.

Circadian regulation of immune model. To model circadian regulation of the various components of the immune system, we assumed that the main variable of the circadian pacemaker (C) modulates parameters of the immune model. Specifically, we scaled the waveform of C to be in the range [0,1] and performed simulations with scaled C driving circadian variation in each of the 11 parameters of the Goyal model using the following equation:

$$x(t) = x_0\left(0.1 + 1.8\left(\frac{C(t)+1.13}{2.26}\right)\right) \tag{16}$$

where $x(t)$ represents $\beta(t)$, $\delta(t)$, $k(t)$, $\pi(t)$, $m(t)$, $\omega(t)$, $q(t)$, $\gamma(t)$, $r(t)$, $\phi(t)$, and $\delta_E(t)$, and x_0 is the original value of each parameter (as specified in Table 1 or the "Immune system model" section of the Methods). This leads to a circadian oscillation in each parameter from 0.1 to 1.9 times its original value, corresponding to a 19-fold difference from peak to trough. Circadian peak-to-trough differences of more than 20-fold have been observed in a variety of contexts, such as expression of REV-ERBα in macrophages [33], PPARγ in the aorta [48], and tubules in the kidney [53].

Numerical Simulations. We performed simulations use 'ode15s', a variable-order stiff solver built-in to MATLAB. The initial conditions we used for the 11 state variables of the model are as follows: $A(0) = 1.08$, $C(0) = -0.18$, $n(0) = 0.0031$, $S(0) = 1 \times 10^7$, $V(0) = \pi/\gamma$, $I(0) = 1$, $M_1(0) = 1$, $M_2(0) = 0$, $E(0) = 0$, $C_p(0) = 0$, and $C_a(0) = 0$.

In our simulations of antiviral therapy, we simulated daily administration of remdesivir at two different timepoints (ZT0 or ZT12) beginning on Day 5 or Day 6. To assess the efficacy of treatment, we used numerical integration with 'trapz' to compute the area under the curve (AUC) of the number of infected cells from Day 7 until the virus was cleared. MATLAB code for the model simulations is available on GitHub at https://github.com/diekmanc/circ-immune-antiviral.

3 Results

We implemented the Goyal et al. [16] model of the immune system response to SARS-CoV-2 infection (Eqns. 6–11) in MATLAB. First, we performed simulations of the model with the parameters that Goyal et al. fit to viral load data from a COVID-19 patient in Singapore (patient S18). Figure 2A shows the simulated viral load (V) time course for patient S18, beginning with initial conditions of a single infected cell ($I_0 = 1$) and $V_0 = 26$ virions. The peak viral load of $V = 1.80 \times 10^7$ occurs after 2.9 days (at this time there are $I = 6.95 \times 10^5$ infected cells), after which the immune system begins to clear the virus. Throughout this study, we deem the virus to have been cleared once there is again just a single infected cell, and terminate the simulations at that point. For the simulation shown in Fig. 2A, the virus is cleared after 21.3 days.

To explore how circadian regulation of the immune system may affect SARS-CoV-2 dynamics, we coupled a circadian pacemaker model (Eqns. 1-5) to the Goyal model (Fig. 1). The circadian oscillator model entrains to periodic forcing by the light-dark cycle and thus exhibits rhythms with a 24-hour period. To couple the models, we assume that the parameters of the Goyal model are modulated by the circadian clock variable C. We performed simulations with circadian variation in each of the 11 parameters of the Goyal model. We found that circadian rhythms in different parameters had different effects on the viral load time course, with circadian variation in some parameters leading to faster clearance of the virus and circadian variation in other parameters leading to slower clearance of the virus (see Fig. 2B-F). For example, for patient S18, circadian variation in the innate immune response parameter δ and the virus death rate γ, resulted in clearance times of just 7.2 days and 6.7 days, respectively (Figs. 2B,C). On the other hand, circadian variation in the susceptible cell infection rate β (Fig. 2B), the viral reproduction rate π (Fig. 2C), and the acquired immune response parameter ω (Fig. 2D) resulted in a clearance time of greater than 25 days (63.8, 83.9, and 39.1 days, respectively). Circadian variation in some other parameters, such as the effector cell death rate δ_E and the acquired immune response parameter m, do not have a significant effect on the clearance time (Figs. 2B,D). We focused primarily on patient S18 because it is one of the few patients in the Goyal et al. dataset for which viral load was measured during the early stages of the infection, while the viral load was still increasing. However, we observed the same trends in 4 other patient models (patients S5, S12, S14, and G2), with δ and γ leading to faster clearance and β and π leading to slower clearance. Simulation results for patients S12 and G2 are shown in Figs. 2E and 2F, respectively.

All the simulations discussed above were for untreated SARS-CoV-2 infections. Next, we investigated how the efficacy of antiviral therapy may be affected by circadian rhythms in the immune system. We focused on circadian variation in the parameter π that represents the viral replication rate. Circadian oscillations in this parameter could represent circadian clock regulation of the interferon system. Interferons are proteins produced by the immune system that "interfere" with viral replication [35] and are believed to play a key role in the response to SARS-CoV-2 infection [41]. In mathematical models of influenza and hepatitis C infections, the interferon response has been modeled by a decrease in the parameter representing the viral production rate [52, 1, 34]. For antiviral drug therapy, we used the pharmacodynamic model of of remdisivir (Eqns. 12-15) that was developed by Goyal et al. [16] based on data from nonhuman primates. We simulated a single daily dose of antiviral therapy beginning on Day 5 and administered to patient S18 either in the morning (ZT0) or the evening (ZT12). Figures 3A and 3B show that the number of infected cells decreases more rapidly when the treatment begins at ZT0 rather than ZT12. We then simulated the same 2 administration times, but began treatment on Day 6 instead of Day 5. Again we see that beginning treatment earlier (at ZT0 on Day 6) is more effective than beginning treatment later in that same day (at ZT12 on Day 6). However, the more interesting finding is that beginning treatment at ZT0 on Day 6 is also more effective than beginning treatment 12 hours earlier, i.e. at ZT12 on Day 5. This demonstrates that the effectiveness of daily antiviral therapy may depend on the time of day that it is administered. In these simulations, when treatment begins on either Day 5 or Day 6, the integrated number of infected cells from Day 7 until when the virus is cleared is at least 90% lower than no treatment when the dosing time is ZT0, but only 67% lower when the dosing time is ZT12. We observed the same phenomenon for patient G2 (Figs. 3C,D), with antiviral therapy again being more effective when the dosing time is ZT0 (at least 89% less infected cells than with no treatment) than when the dosing time is ZT 12 (64% less infected cells than with no treatment).

4 Discussion

Our model simulations provide a proof-of-concept that circadian regulation of the immune system to SARS-CoV-2 infection may cause the effectiveness of antiviral therapy to depend on the time of day it is administered. The plausibility of this hypothesis is supported by the results of a small-scale retrospective study of an antiviral drug administered to 33 COVID-19 patients (9 with morning administration, and 24 with evening administrated) early in the pandemic [9]. We call for a large-scale retrospective or prospective study of current antiviral COVID-19 treatments (e.g. Paxlovid or molnupiravir) to assess the impact that dosing time of day may have on the efficacy or side effects of these medications.

Further support for the notion that circadian rhythms and chronotherapy are worthwhile considerations in the context of COVID-19 [2, 4, 5, 15, 19, 29, 36, 40, 42, 43] is provided by a recent study showing that less breakthrough infections occurred in patients that received COVID-19 vaccination in late morning/early afternoon compared to evening vaccination [20, 39]. Since a mechanistic model of immune response to COVID-19 vaccines has been developed [11], future work incorporating circadian regulation into this model as a tool for vaccination timing optimization is warranted.

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References

[1] Prasith Baccam, Catherine Beauchemin, Catherine A Macken, Frederick G Hayden, and Alan S Perelson. Kinetics of influenza a virus infection in humans. Journal of virology, 80(15):7590–7599, 2006.

[2] Helene Borrmann, Jane A McKeating, and Xiaodong Zhuang. The circadian clock and viral infections. Journal of Biological Rhythms, 36(1):9–22, 2021. PMID: 33161818.

[3] Helene Borrmann, Görkem Ulkar, Anna E Kliszczak, Dini Ismed, Mirjam Schilling, Andrea Magri, James M Harris, Peter Balfe, Sridhar Vasudevan, Persephone Borrow, et al. Molecular components of the circadian clock regulate hiv-1 replication. Iscience, 26(7), 2023.

[4] WJ Bryson. Circadian rhythm sleep-wake disorders and the covid-19 pandemic, 8 2020.

[5] Nicolas Cermakian and Mary E. Harrington. Chronobiology in response to covid-19. Journal of Biological Rhythms, 36(1):3–3, 2021. PMID: 33543668.

[6] Jessica M Conway and Pia Abel zur Wiesch. Mathematical modeling of remdesivir to treat covid-19: can dosing be optimized? Pharmaceutics, 13(8):1181, 2021.

[7] Robert Dallmann, Steven A Brown, and Frédéric Gachon. Chronopharmacology: new insights and therapeutic implications. Annual review of pharmacology and toxicology, 54:339–361, 2014.

[8] Amritam Das, Thomas Chaffey, and Rodolphe Sepulchre. Oscillations in mixed-feedback systems. Systems & Control Letters, 166:105289, 2022.

[9] A De Giorgi, F Fabbian, E Di Simone, S Greco, R De Giorgio, G Zuliani, A Passaro, E Caselli, and R Manfredini. Morning vs. evening administration of antiviral therapy in covid-19 patients. a preliminary retrospective study in ferrara, italy. Eur Rev Med Pharmacol Sci, pages 8219–8225, 2020.

[10] Dennis A Dean, Adam Fletcher, Steven R Hursh, and Elizabeth B Klerman. Developing mathematical models of neurobehavioral performance for the "real world". Journal of biological rhythms, 22(3):246–258, 2007.

[11] Prashant Dogra, Carmine Schiavone, Zhihui Wang, Javier Ruiz-Ramírez, Sergio Caserta, Daniela I Staquicini, Christopher Markosian, Jin Wang, H Dirk Sostman, Renata Pasqualini, et al. A modeling-based approach to optimize covid-19 vaccine dosing schedules for improved protection. JCI insight, 8(13), 2023.

[12] Polly Downton, James O. Early, and Julie E. Gibbs. Circadian rhythms in adaptive immunity, 12 2020.

[13] Rachel S. Edgar, Alessandra Stangherlin, Andras D. Nagy, Michael P. Nicoll, Stacey Efstathiou, John S. O'Neill, and Akhilesh B. Reddy. Cell autonomous regulation of herpes and influenza virus infection by the circadian clock. Proceedings of the National Academy of Sciences of the United States of America, 113:10085–10090, 2016.

[14] Daniel B. Forger, Megan E. Jewett, and Richard E. Kronauer. A simpler model of the human circadian pacemaker. JOURNAL OF BIOLOGICAL RHYTHMS, 14(6):533–537, 1999.

[15] Allan Giri, Ashokkumar Srinivasan, and Isaac Kirubakaran Sundar. Covid-19: Sleep, circadian rhythms and immunity–repurposing drugs and chronotherapeutics for sars-cov-2. Frontiers in neuroscience, 15:674204, 2021.

[16] Ashish Goyal, E Fabian Cardozo-Ojeda, and Joshua T Schiffer. Potency and timing of antiviral therapy as determinants of duration of sars-cov-2 shedding and intensity of inflammatory response. Sci. Adv, 6, 2020.

[17] F Halberg, E Johnson, B Brown, and J Bittner. Susceptibility rhythm to e. coli endotoxin and bioassay. Proc Soc Exp Biol Med, 103:142–144, 1960.

[18] Patrick O Hanafin, Brian Jermain, Anthony J Hickey, Alexander V Kabanov, Angela DM Kashuba, Timothy P Sheahan, and Gauri G Rao. A mechanism-based pharmacokinetic model of remdesivir leveraging interspecies scaling to simulate covid-19 treatment in humans. CPT: pharmacometrics & systems pharmacology, 10(2):89–99, 2021.

[19] Jeffrey Haspel, Minjee Kim, Phyllis Zee, Tanja Schwarzmeier, Sara Montagnese, Satchidananda Panda, Adriana Albani, and Martha Merrow. A timely call to arms: Covid-19, the circadian clock, and critical care. Journal of Biological Rhythms, 36(1):55–70, 2021. PMID: 33573430.

[20] Guy Hazan, Or A Duek, Hillel Alapi, Huram Mok, Alex Ganninger, Elaine Ostendorf, Carrie Gierasch, Gabriel Chodick, David Greenberg, Jeffrey A Haspel, et al. Biological rhythms in covid-19 vaccine effectiveness in an observational cohort study of 1.5 million patients. The Journal of clinical investigation, 133(11), 2023.

[21] Rita Humeniuk, Kavita Juneja, Shuguang Chen, Scott Ellis, Olena Anoshchenko, Deqing Xiao, Aaron Share, Matthew Johnston, Santosh Davies, Adam DeZure, et al. Pharmacokinetics, safety, and tolerability of inhaled remdesivir in healthy participants. Clinical and Translational Science, 16(11):2276–2288, 2023.

[22] Rita Humeniuk, Anita Mathias, Huyen Cao, Anu Osinusi, Gong Shen, Estelle Chng, John Ling, Amanda Vu, and Polina German. Safety, tolerability, and pharmacokinetics of remdesivir, an antiviral for treatment of covid-19, in healthy subjects. Clinical and translational science, 13(5):896–906, 2020.

[23] Megan E Jewett, Daniel B Forger, and Richard E Kronauer. Revised limit cycle oscillator model of human circadian pacemaker. Journal of biological rhythms, 14(6):493–500, 1999.

[24] Dae Wook Kim, Ja Min Byun, Jeong-Ok Lee, Jae Kyoung Kim, and Youngil Koh. Chemotherapy delivery time affects treatment outcomes of female patients with diffuse large b cell lymphoma. JCI insight, 8(2), 2023.

[25] RE Kronauer. A quantitative model for the effects of light on the amplitude and phase of the deep circadian pacemaker, based on human data. Sleep, 90:306–309, 1990.

[26] Richard E. Kronauer, Daniel B. Forger, and Megan E. Jewett. Quantifying human circadian pacemaker response to brief, extended, and repeated light stimuli over the photopic range. JOURNAL OF BIOLOGICAL RHYTHMS, 14(6):501–515, 1999.

[27] Nathalie Labrecque and Nicolas Cermakian. Circadian clocks in the immune system, 8 2015.

[28] E Leegwater, DJAR Moes, LBE Bosma, TH Ottens, IM van der Meer, C van Nieuwkoop, and EB Wilms. Population pharmacokinetics of remdesivir and gs-441524 in hospitalized covid-19 patients. Antimicrobial Agents and Chemotherapy, 66(6):e00254–22, 2022.

[29] Zulian Liu, Sharlene Ting, and Xiaodong Zhuang. Covid-19, circadian rhythms and sleep: from virology to chronobiology. Interface Focus, 11(6):20210043, 2021.

[30] Ryan W. Logan and Dipak K. Sarkar. Circadian nature of immune function, 2 2012.

[31] Kevin Man, Andrew Loudon, and Ajay Chawla. Immunity around the clock. Science, 354:999–1003, 2016.

[32] Atsuhito Nakao. Temporal regulation of cytokines by the circadian clock, 2014.

[33] Atsuhito Nakao. Temporal regulation of cytokines by the circadian clock. Journal of immunology research, 2014(1):614529, 2014.

[34] Avidan U Neumann, Nancy P Lam, Harel Dahari, David R Gretch, Thelma E Wiley, Thomas J Layden, and Alan S Perelson. Hepatitis c viral dynamics in vivo and the antiviral efficacy of interferon-α therapy. Science, 282(5386):103–107, 1998.

[35] Jacqueline Parkin and Bryony Cohen. An overview of the immune system. The Lancet, 357(9270):1777–1789, 2001.

[36] Keshav Raj Paudel, Saurav Kumar Jha, Venkata Sita Rama Raju Allam, Parteek Prasher, Piyush Kumar Gupta, Rahul Bhattacharjee, Niraj Kumar Jha, Sukriti Vishwas, Sachin K Singh, Jesus Shrestha, et al. Recent advances in chronotherapy targeting respiratory diseases. Pharmaceutics, 13(12):2008, 2021.

[37] James Alexander Pearson, Alexander Christopher Voisey, Kathrine Boest-Bjerg, F Susan Wong, and Li Wen. Circadian rhythm modulation of microbes during health and infection. Frontiers in Microbiology, 12:721004, 2021.

[38] Andrea J Pruijssers, Amelia S George, Alexandra Schäfer, Sarah R Leist, Lisa E Gralinksi, Kenneth H Dinnon, Boyd L Yount, Maria L Agostini, Laura J Stevens, James D Chappell, et al. Remdesivir inhibits sars-cov-2 in human lung cells and chimeric sars-cov expressing the sars-cov-2 rna polymerase in mice. Cell reports, 32(3), 2020.

[39] Laura J Rasmussen-Torvik et al. Time of day for covid vaccine administration linked to clinical effectiveness. The Journal of Clinical Investigation, 133(11), 2023.

[40] Sandipan Ray and Akhilesh B. Reddy. Covid-19 management in light of the circadian clock. Nature Reviews Molecular Cell Biology, 21:494–495, 2020.

[41] Charles E Samuel. Interferon at the crossroads of sars-cov-2 infection and covid-19 disease. Journal of Biological Chemistry, 299(8), 2023.

[42] Shaon Sengupta, Thomas G. Brooks, Gregory R. Grant, and Garret A. FitzGerald. Accounting for time: Circadian rhythms in the time of covid-19. Journal of Biological Rhythms, 36:4–8, 2 2021.

[43] Shaon Sengupta, Louise Ince, Francesca Sartor, Helene Borrmann, Xiaodong Zhuang, Amruta Naik, Annie Curtis, and Jane A. McKeating. Clocks, viruses, and immunity: Lessons for the covid-19 pandemic. Journal of Biological Rhythms, 36(1):23–34, 2021. PMID: 33480287.

[44] Shaon Sengupta, Soon Y. Tang, Jill C. Devine, Seán T. Anderson, Soumyashant Nayak, Shirley L. Zhang, Alex Valenzuela, Devin G. Fisher, Gregory R. Grant, Carolina B. López, and Garret A. FitzGerald. Circadian control of lung inflammation in influenza infection. Nature Communications, 10:1–13, 2019.

[45] George A. Timmons, James R. O'Siorain, Oran D. Kennedy, Annie M. Curtis, and James O. Early. Innate rhythms: Clocks at the center of monocyte and macrophage function. Frontiers in immunology, 11:1743, 2020.

[46] Hans Van Dongen. Comparison of mathematical model predictions to experimental data of fatigue and performance. Aviation, space, and environmental medicine, 75(3):A15–A36, 2004.

[47] Manli Wang, Ruiyuan Cao, Leike Zhang, Xinglou Yang, Jia Liu, Mingyue Xu, Zhengli Shi, Zhihong Hu, Wu Zhong, and Gengfu Xiao. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-ncov) in vitro. Cell research, 30(3):269–271, 2020.

[48] Ningning Wang, Guangrui Yang, Zhanjun Jia, Hui Zhang, Toshinori Aoyagi, Sunhapas Soodvilai, J David Symons, Jurgen B Schnermann, Frank J Gonzalez, Sheldon E Litwin, et al. Vascular pparγ controls circadian variation in blood pressure and heart rate through bmal1. Cell metabolism, 8(6):482–491, 2008.

[49] Travis K Warren, Robert Jordan, Michael K Lo, Adrian S Ray, Richard L Mackman, Veronica Soloveva, Dustin Siegel, Michel Perron, Roy Bannister, Hon C Hui, et al. Therapeutic efficacy of the small molecule gs-5734 against ebola virus in rhesus monkeys. Nature, 531(7594):381–385, 2016.

[50] Ray Zhang, Nicholas F Lahens, Heather I Ballance, Michael E Hughes, and John B Hogenesch. A circadian gene expression atlas in mammals: implications for biology and medicine. Proceedings of the National Academy of Sciences, 111(45):16219–16224, 2014.

[51] Li Zhao, Mei Liu, Jiayue Ouyang, Zheming Zhu, Wenqing Geng, Jinxiu Dong, Ying Xiong, Shumei Wang, Xiaowei Zhang, Ying Qiao, et al. The per-1 short isoform inhibits de novo hiv-1 transcription in resting cd4+ t-cells. Current HIV Research, 16(6):384–395, 2018.

[52] Carolin Zitzmann and Lars Kaderali. Mathematical analysis of viral replication dynamics and antiviral treatment strategies: from basic models to age-based multi-scale modeling. Frontiers in microbiology, 9:1546, 2018.

[53] Annie Mercier Zuber, Gabriel Centeno, Sylvain Pradervand, Svetlana Nikolaeva, Lionel Maquelin, Léonard Cardinaux, Olivier Bonny, and Dmitri Firsov. Molecular clock is involved in predictive circadian adjustment of renal function. Proceedings of the National Academy of Sciences, 106(38):16523–16528, 2009.

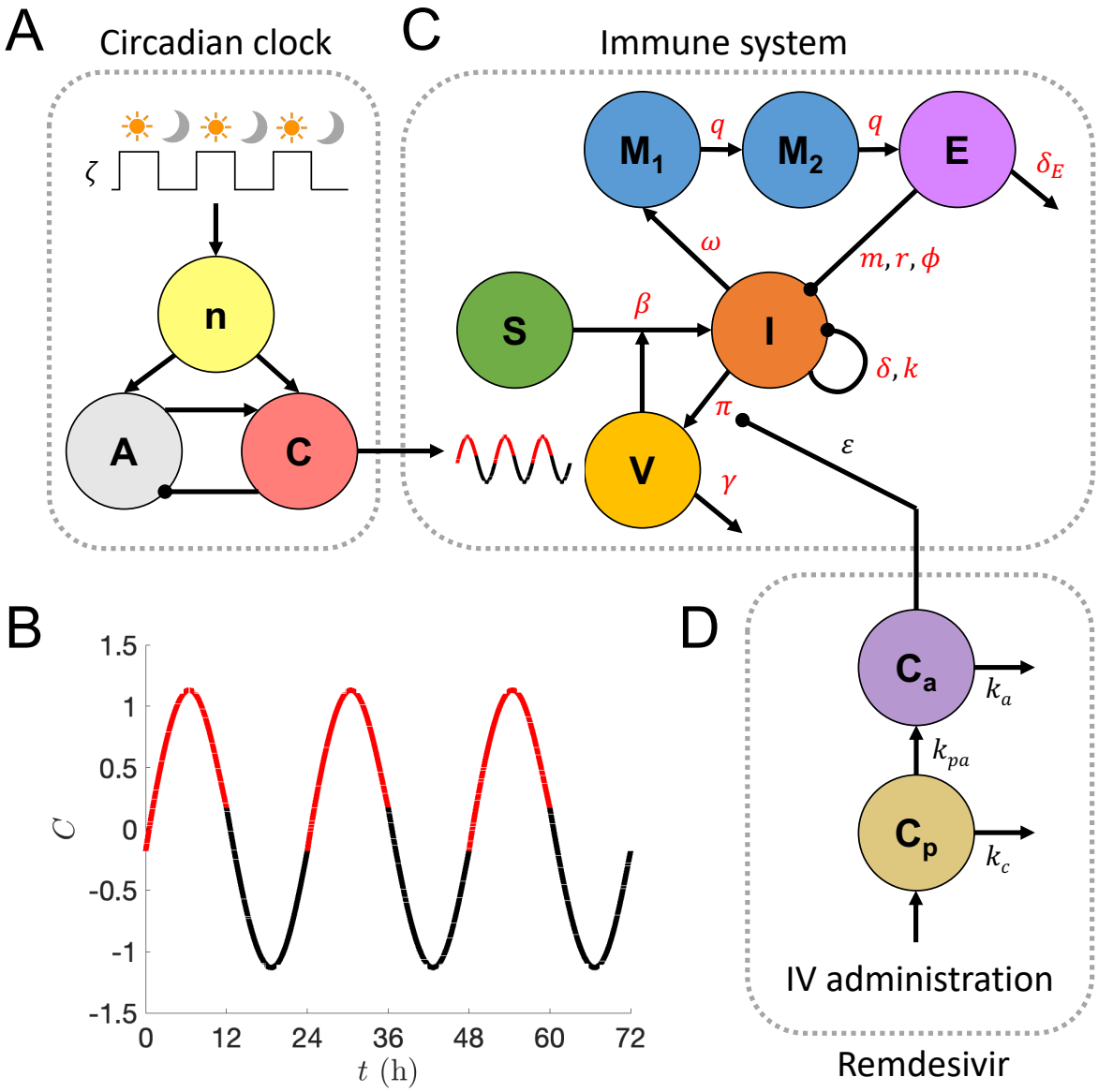

Figure 1: Schematic of our model coupling the circadian clock (variables n, A, C) to the immune system (variables V, S, I, M_1, M_2, and E) and treatment with the antiviral medication remdesivir (variables C_p and C_a). **A:** ζ represents the light-dark cycle and is an input to the circadian system. **B:** C represents the output of the circadian system that modulates the immune system dynamics. The red and black portions of the C waveform correspond to light and dark hours, respectively. **C:** We tested the effect of the clock variable C driving the 11 different immune system parameters shown in red: β, δ, k, m, r, ϕ, π, γ, ω, q, and δ_E. **D:** Treatment with the antiviral medication remdesivir reduces the viral replication rate by the factor $1-\varepsilon$. The meaning of each model variable and parameter is provided in the Methods section.

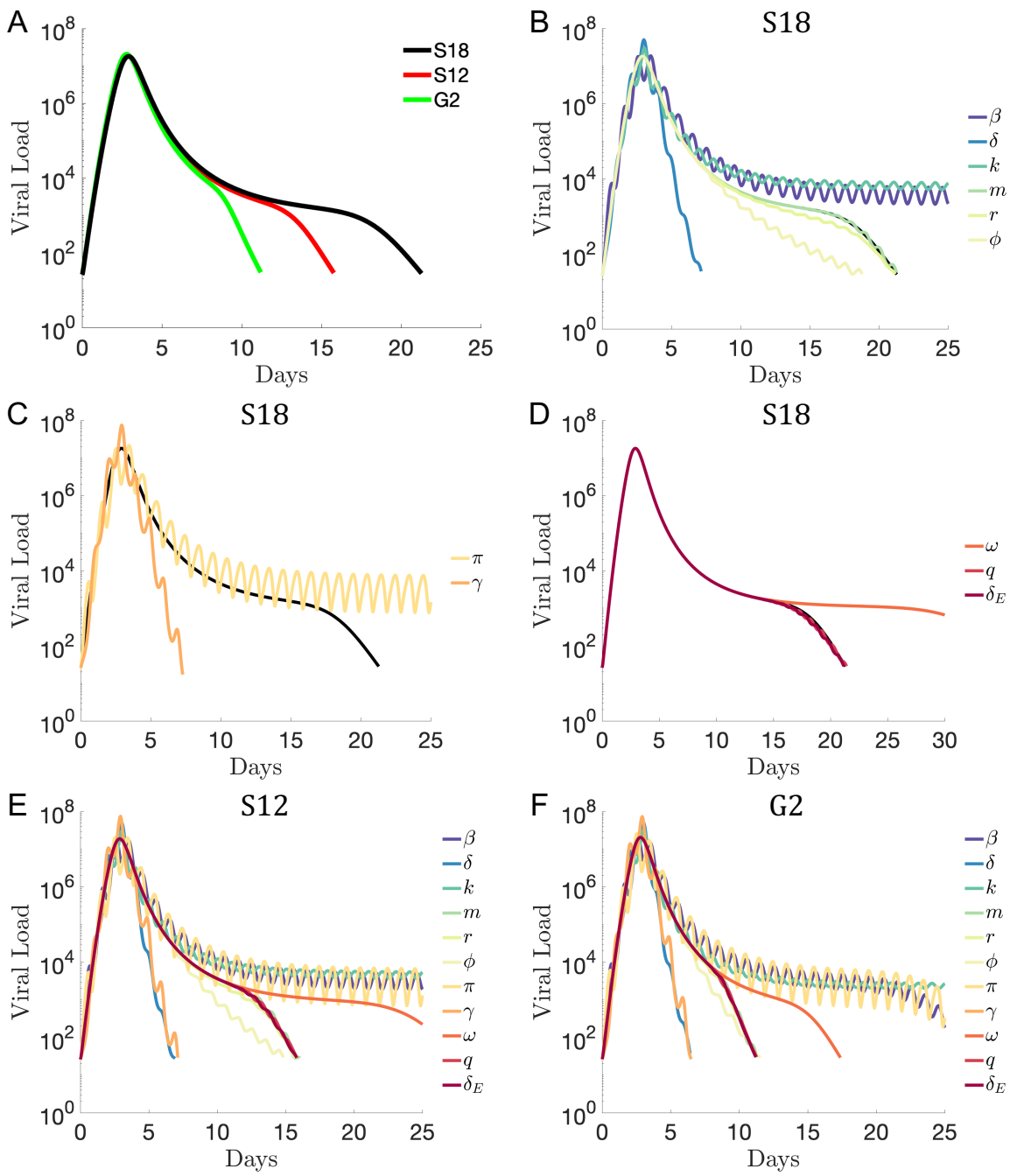

Figure 2: **Simulations of circadian regulation of the immune system response to SARS-Cov-2 infection. A:** Time course of viral load (V) for the model of patients S18, S12, and G2 from Goyal et al. [16] without circadian variation of parameters. Infection begins on Day 0. **B–D:** Time course of viral load (V) for the patient S18 with circadian variation in 11 different parameters associated with SARS-CoV-2 dynamics and the immune system response using the coupled circadian-immune model shown in Fig. 1. See the Methods section for interpretations of each parameter. **E:** Same as **B–D**, but for patient S12. **F:** Same as **E**, but for patient G2.

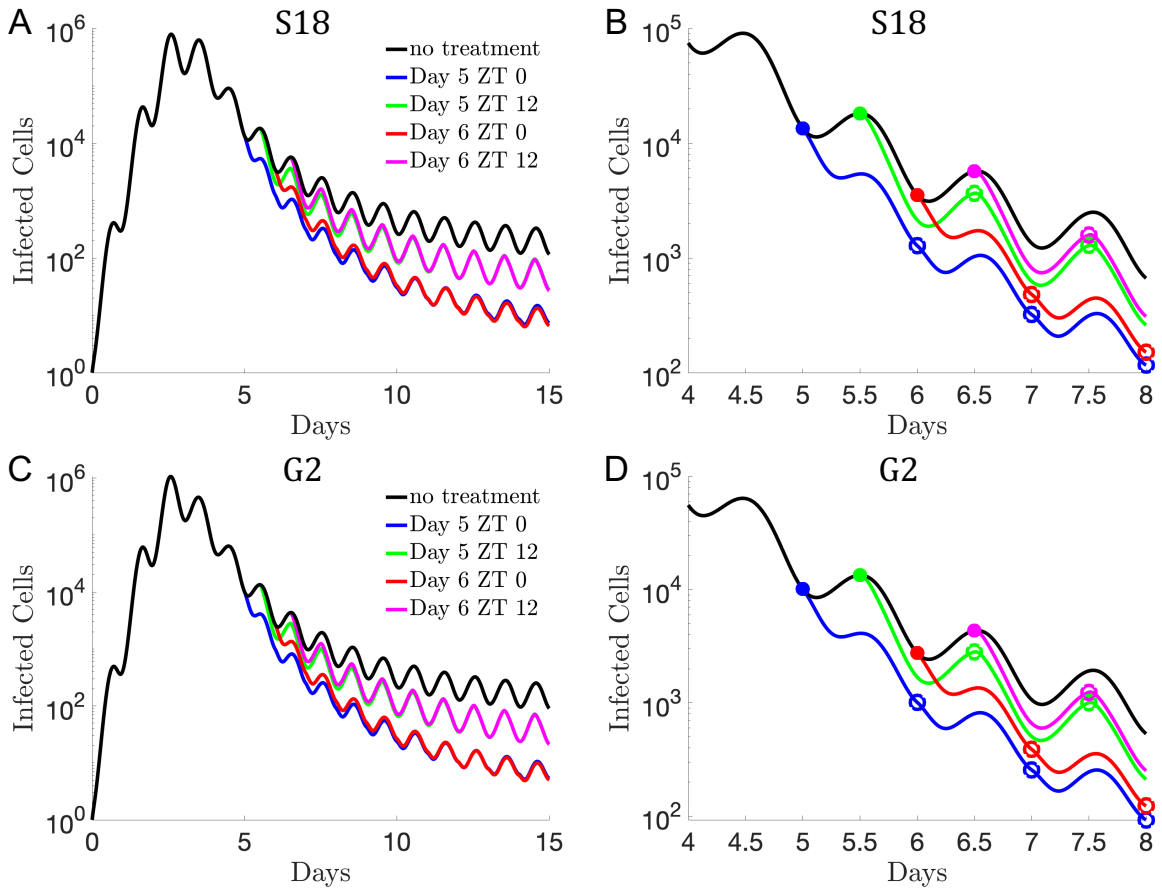

Figure 3: **Simulations of antiviral treatment of SARS-Cov-2 infection at different times of day. A:** Time course of the number of infected cells (I) for patient S18 with circadian variation in the viral replication rate (parameter π) and a single daily dose of antiviral therapy beginning on Day 5 or Day 6 administered in the morning (ZT0, blue and red curves) or administered in the evening (ZT12, green and magenta curves). Black curve corresponds to no antiviral therapy. **B:** Zoomed-in view of Days 4 through 8 from panel A. Solid dots indicate first treatment, open circles indicate subsequent daily treatments. **C-D:** Same as panels A-B, but for patient G2.