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Artificial Intelligence in Circadian Physiology: Predicting Biochemical and Hormonal Rhythms in Health and Disease

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Abstract

Circadian rhythms are intrinsic, approximately 24-hour cycles governing physiological and biochemical processes, including hormonal secretion, metabolic regulation, and sleep-wake patterns. Disruptions in these rhythms are implicated in a wide range of diseases, from metabolic and cardiovascular disorders to psychiatric and neurodegenerative conditions. Traditional methods for assessing circadian biology often rely on invasive sampling or require extended monitoring periods, posing challenges for clinical implementation. Recent advances in artificial intelligence (AI), particularly in time-series analysis and multimodal data integration, offer new opportunities to predict and model circadian dynamics with greater precision, scalability, and personalization.

This review explores the intersection of circadian physiology and AI, focusing on how machine learning and deep learning algorithms can decode and forecast biochemical and hormonal rhythms. We highlight key studies utilizing AI to model patterns of melatonin, cortisol, insulin, and other chronobiological markers in both health and disease. Applications span from sleep medicine and endocrinology to oncology and chronopharmacology, where AI-guided insights may improve diagnosis, disease monitoring, and therapeutic timing.

We also discuss the limitations of current models, including issues of data heterogeneity, interpretability, and ethical concerns related to privacy and continuous monitoring. Finally, we propose future directions for the integration of AI with chronobiological research, emphasizing its potential to revolutionize personalized medicine through real-time, circadian-aware healthcare strategies. By synthesizing current evidence, this review aims to provide a comprehensive foundation for researchers and clinicians seeking to harness AI in the study and application of circadian physiology.

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Introduction

Circadian physiology refers to the endogenous, entrainable oscillations that regulate a broad spectrum of biological functions across the 24-hour day-night cycle [1]. These rhythms are orchestrated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which serves as the master clock, synchronizing peripheral oscillators present in various organs.2 Through complex feedback loops involving core clock genes and environmental cues such as light, feeding, and activity, circadian rhythms govern fluctuations in hormone secretion, metabolic pathways, immune responses, and sleep-wake cycles [2]. Disruptions to these rhythms, whether due to lifestyle factors such as shift work or underlying pathophysiological conditions, are increasingly recognized as contributing to the onset and progression of a wide range of disorders, including obesity, type 2 diabetes, depression, cancer, and cardiovascular disease [3].

Despite the clinical significance of circadian biology, current approaches to assessing and monitoring circadian rhythms are limited by methodological constraints. Direct measurement of hormonal and biochemical rhythms often requires frequent sampling over 24-hour periods, which is invasive, resource-intensive, and impractical in most clinical settings. Moreover, individual variability in circadian phase and amplitude poses additional challenges for diagnosis and therapeutic optimization [4]. These limitations underscore the need for innovative tools that can capture, model, and predict circadian patterns in a personalized and scalable manner.

Artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL) techniques, has emerged as a promising approach to address these challenges. By leveraging large, multimodal datasets, including wearable biosensor data, electronic health records, omics profiles, and real-time physiological signals, AI systems can learn to identify patterns, predict circadian biomarkers, and simulate biological rhythms with high accuracy [5-7]. Such predictive capabilities hold immense potential for revolutionizing circadian medicine, from enhancing chronotherapeutic interventions to enabling early detection of rhythm disruptions and optimizing patient care according to circadian phase [7,8].

This review aims to comprehensively examine the integration of AI in circadian physiology, with a particular focus on the prediction and modeling of biochemical and hormonal rhythms in both health and disease. We explore the biological foundations of circadian regulation, the current limitations in its clinical monitoring, and the range of AI methodologies that have been employed to bridge these gaps. By synthesizing the latest developments across chronobiology, biomedical engineering, and computational sciences, this article seeks to provide a foundation for future research and translational applications in AI-enhanced circadian healthcare.

Biological Basis of Circadian Rhythms

Circadian rhythms are endogenous, self-sustaining cycles with a period of approximately 24 hours that regulate a wide array of physiological and behavioral functions. These rhythms are generated and maintained by a hierarchical system of clocks, with the central pacemaker located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [1,2]. The SCN receives direct input from photosensitive retinal ganglion cells via the retinohypothalamic tract, enabling it to synchronize the internal biological clock with the external light-dark cycle. This central clock coordinates subsidiary clocks found in peripheral tissues such as the liver, pancreas, heart, and adipose tissue, ensuring systemic temporal harmony [2,9].

At the molecular level, circadian rhythms are driven by interlocked transcription–translation feedback loops (TTFLs) involving core clock genes and proteins [10,11]. The primary loop includes the transcriptional activators CLOCK and BMAL1, which drive the expression of target genes such as PER (Period) and CRY (Cryptochrome) [10-12]. These proteins accumulate in the cytoplasm, dimerize, and translocate back into the nucleus where they inhibit their own transcription by repressing CLOCK–BMAL1 activity [10-12]. Secondary feedback loops involving nuclear receptors such as REV-ERBα and RORα regulate Bmal1 expression, contributing to rhythm robustness and stability [13]. This molecular machinery operates in nearly every cell, imparting circadian rhythmicity to diverse biological outputs.

Hormonal secretions are among the most well-characterized outputs of the circadian system. For instance, melatonin, secreted by the pineal gland, shows a distinct nocturnal peak and is tightly regulated by the SCN [14]. Cortisol follows a robust diurnal pattern, peaking in the early morning and declining throughout the day [15]. Insulin sensitivity and glucose metabolism also exhibit circadian variation, with important implications for metabolic homeostasis [16]. These rhythmic processes can be altered by aging, disease, or environmental disruptions, making them critical targets for both mechanistic understanding and clinical intervention [17].

Table 1 below summarizes key hormones and metabolites under circadian control, along with their physiological relevance and typical peak timing in healthy individuals.

Table 1: Key Circadian-Regulated Hormones and Biochemical Markers in Humans [14-16,18]

Biomarker	Origin/Organ	Circadian Peak Time	Physiological Role
Melatonin	Pineal gland	~02:00–04:00 (night)	Sleep regulation, antioxidant activity
Cortisol	Adrenal cortex	~06:00–08:00 (morning)	Stress response, glucose metabolism
Growth Hormone (GH)	Anterior pituitary	~23:00–01:00 (night)	Tissue growth, repair, lipolysis
Insulin	Pancreatic β-cells	Daytime meals (circadian sensitivity varies)	Glucose homeostasis
Glucose	Liver/blood	Lowest during early night	Energy substrate, influenced by feeding and insulin
Body Temperature	Hypothalamus	~17:00–19:00 (afternoon/evening)	Metabolic rate, thermoregulation

Challenges in Measuring and Modeling Circadian Rhythms

Despite the increasing recognition of circadian rhythms in health and disease, accurately measuring and modeling these biological cycles remains a significant challenge in both research and clinical contexts. Traditional methods for assessing circadian physiology, such as serial blood sampling for hormonal analysis, polysomnography for sleep cycles, and core body temperature recordings, are often invasive, labor-intensive, costly, and limited in temporal resolution [14-16]. These constraints not only reduce subject compliance but also restrict large-scale or long-term monitoring essential for understanding individual variability and population-level patterns.

One of the primary difficulties lies in the need for continuous or high-frequency sampling to capture the dynamic nature of circadian rhythms. Hormones like cortisol and melatonin exhibit sharp diurnal fluctuations, and missing even a few key timepoints can lead to inaccurate phase estimation [15-17]. Moreover, circadian rhythms vary significantly between individuals due to genetic polymorphisms in clock genes, age, sex, and lifestyle factors such as sleep habits, diet, and light exposure [19-20]. These inter-individual differences demand personalized approaches for modeling, rather than relying on generic population averages.

Environmental confounders pose an additional obstacle. External cues, referred to as “zeitgebers”, including light exposure, physical activity, social interactions, and meal timing, influence circadian phase and amplitude [19-21]. Failure to account for these variables may reduce the robustness of predictive models. Additionally, the internal desynchronization between central and peripheral clocks, often seen in disease states, further complicates data interpretation. For instance, metabolic organs like the liver may fall out of phase with the central clock in the SCN, leading to discordant rhythms that are hard to detect without multi-organ sampling [22].

From a computational perspective, modeling circadian rhythms requires time-aware algorithms capable of handling complex, nonlinear, and often noisy biological data [23,24]. Many conventional statistical models struggle with irregular sampling intervals, missing data, and the need for high temporal granularity. While AI and machine learning offer advanced tools for overcoming some of these issues, these methods also require large, well-labeled datasets and may suffer from interpretability challenges, particularly in clinical settings where transparency is essential [25,26].

To further illustrate the multifactorial nature of these challenges, Table 2 categorizes the primary difficulties associated with circadian rhythm assessment and modeling:

Table 2: Key Challenges in Measuring and Modeling Circadian Rhythms [17,19-22]

Challenge Category	Specific Issues	Impact on Modeling Accuracy
Sampling limitations	Invasive methods, low temporal resolution, patient burden	Incomplete or biased circadian profiles
Inter-individual variation	Genetic, age, sex, chronotype differences	Necessitates personalized models
Environmental confounders	Light, activity, feeding, social schedules	Causes masking or phase-shifting of rhythms
Internal desynchrony	SCN-periphery misalignment in disease states	Com plex multivariate modeling re-quired
Data quality & availability	Sparse or noisy datasets, lack of labeled timepoints	Limits training of machine learn-ing algorithms
Algorithmic constraints	Handling time-series, missing data, interpretability in AI models	Reduces clinical applicability and scalability

Overcoming these challenges will require interdisciplinary strategies that integrate robust biological understanding with advanced data science methods. This includes the use of non-invasive wearable sensors, multi-omics profiling, and AI-based chronobiological models capable of adjusting for personal and environmental variables in real-time [27,28]. Only by addressing these limitations can we move toward truly predictive and actionable models of circadian physiology.

AI Techniques for Circadian Rhythm Prediction

The integration of AI into circadian physiology research has opened new avenues for modeling and predicting complex biological rhythms with unprecedented precision and scalability. Unlike traditional statistical approaches, AI methods are capable of capturing nonlinear relationships, integrating heterogeneous data sources, and learning temporal dependencies across time-series data [25-27]. This is particularly valuable in chronobiology, where rhythmicity often manifests in multiscale patterns involving hormonal, metabolic, behavioral, and environmental signals [25-27].

A wide range of AI techniques have been employed to analyze circadian data, including supervised machine learning algorithms such as support vector machines (SVM), random forests, and gradient boosting decision trees [29-30]. These methods are particularly useful when large labeled datasets are available and the goal is to classify circadian phases, detect disruptions, or predict phase shifts based on input variables such as light exposure, activity patterns, and biomarker concentrations [31]. However, these models often rely on engineered features and may struggle to generalize across individuals with varying chronotypes or disease conditions.

Deep learning, particularly recurrent neural networks (RNNs) and their variants like long short-term memory (LSTM) networks, offers more advanced capabilities for circadian rhythm prediction [32,33]. These architectures are designed to handle sequential data and are capable of learning temporal dependencies across long time windows. LSTMs have been successfully applied to predict melatonin onset, sleep-wake cycles, and cortisol dynamics based on wearable sensor data, light levels, and heart rate variability [34]. Convolutional neural networks (CNNs), although traditionally used for image data, have also been adapted to detect rhythmic patterns in time-series or spectrogram-transformed circadian signals [34].

Chronobiology-specific models have also been developed, integrating domain knowledge into AI frameworks. For example, hybrid models combining mechanistic mathematical circadian oscillators with machine learning layers have been proposed to balance interpretability and predictive power. Bayesian models are increasingly used to manage uncertainty and inter-individual variability, while ensemble learning methods can improve robustness by aggregating predictions from multiple models [35].

The choice of AI model and data type significantly influences performance. Wearable-derived data such as actigraphy, body temperature, skin conductance, and heart rate are frequently used due to their non-invasive nature and continuous sampling [27,36]. Integration of multi-omics datasets, transcriptomics, proteomics, and metabolomics, has also begun to emerge, although these require complex preprocessing and substantial computational resources [37]. Electronic health records (EHRs), when temporally aligned, can provide valuable clinical context for rhythm prediction in disease states [38].

Table 3 summarizes key AI techniques used for circadian rhythm prediction, along with their strengths, limitations, and typical applications:

Table 3: Overview of AI Techniques for Circadian Rhythm Prediction [27,29-35]

AI Technique	Strengths	Limitations	Typical Applications
Support Vector Machine (SVM)	Effective for classification with limited features	Requires feature engineering; not ideal for time-series	Chronotype classification, sleep phase detection
Random Forest, XGBoost	High accuracy, interpretable feature importance	May overfit on small datasets; ignores time dependencies	Light-response modeling, biomarker-based phase prediction
LSTM (Long Short-Term Memory)	Captures temporal dependencies in sequential data	Computationally intensive; needs large data	Melatonin onset prediction, cortisol time-course modeling
CNN (adapted for 1D time-series)	Detects rhythmic patterns in transformed data	Less intuitive for sequential interpretation	Sleep staging from EEG, activity cycle classification
Bayesian Models	Incorporates uncertainty and prior knowledge	Computational complexity; slower training	Personalized rhythm modeling, prediction under missing data
Hybrid Mechanistic–AI Models	Integrates biological models with ML flexibility	Requires curated biological knowledge	Modeling molecular oscillators, circadian pharmacokinetics

These advanced algorithms offer a foundation for building predictive systems capable of estimating internal circadian phase in real-time, identifying rhythm disruptions, and guiding time-sensitive clinical interventions. Nonetheless, further work is needed to improve model interpretability, adapt models to diverse populations, and validate them in real-world clinical settings. The next stage of development will likely involve explainable AI (XAI) systems that preserve accuracy while providing actionable insight to researchers and clinicians alike [39].

Applications of AI in Circadian Biochemistry and Hormone Prediction

The application of AI in circadian biochemistry has ushered in a transformative shift in how hormonal and metabolic rhythms are analyzed, predicted, and utilized for clinical and research purposes. Traditional methods of evaluating biochemical circadian patterns, such as serial blood draws or saliva collection, are laborious, time-restricted, and often impractical in real-world settings [14-16]. AI offers a scalable alternative by enabling predictive modeling of circadian biomarkers using multimodal inputs, including wearable sensor data, behavioral logs, environmental exposure, and physiological time-series [27,29-35]. These applications are particularly impactful in the domains of endocrine regulation, metabolism, neurology, and chronopharmacology.

One of the most extensively studied hormones in this context is melatonin, a key circadian regulator secreted by the pineal gland. Its nocturnal rise and light-sensitive suppression make it a reliable marker of circadian phase. AI algorithms, especially recurrent neural networks (RNNs) and long short-term memory (LSTM) models, have been employed to predict melatonin onset and dim light melatonin onset (DLMO) based on light exposure, sleep timing, and activity data [17,32,33]. This allows for non-invasive circadian phase estimation without the need for repeated biological sampling. Similarly, cortisol, which follows a diurnal pattern with a peak in the early morning, can be predicted using machine learning models trained on heart rate variability, sleep stages, and even voice biomarkers, facilitating its use in stress physiology and adrenal health monitoring [15,32,33].

In metabolic regulation, insulin and glucose rhythms are strongly influenced by circadian processes [16]. AI techniques have enabled time-of-day–dependent modeling of postprandial glucose excursions and insulin sensitivity by integrating continuous glucose monitoring (CGM) data with sleep–wake cycles, meal timing, and physical activity [40].These models can improve the personalization of diabetes management and dietary interventions by identifying circadian windows of optimal metabolic efficiency. Moreover, predictive analytics based on AI can detect early signs of circadian misalignment in shift workers or individuals with metabolic syndrome by identifying rhythm disruptions in glucose and lipid profiles [29,31,41].

Neurologically relevant hormones, such as growth hormone (GH) and prolactin, which exhibit pulsatile nocturnal release, are now being modeled using deep learning frameworks that combine EEG-derived sleep data with other physiological markers [29,31,42]. These models are being explored to monitor growth disorders, pituitary dysfunction, and optimize timing for hormone replacement therapies.

AI is also increasingly integrated into chronopharmacology, where the timing of drug administration relative to endogenous circadian phase can significantly affect therapeutic outcomes [43]. By predicting an individual's hormonal profile and internal time, AI models can support personalized dosing schedules that align with biological rhythms, improving efficacy and minimizing adverse effects. For example, predictive modeling of cortisol and ACTH rhythms has been used to guide glucocorticoid therapy in adrenal insufficiency, while circadian-informed models of hepatic enzyme activity help refine dosing for drugs with narrow therapeutic windows [43].

Table 4 highlights representative applications of AI in predicting key biochemical and hormonal rhythms:

Table 4: Representative Applications of AI in Circadian Biochemistry and Hormonal Prediction [14-16,19,29-35,41-43]

Target Biomarker	AI Input Data	AI Method Used	Clinical/Research Application
Melatonin	Light exposure, actigraphy, sleep logs	LSTM, SVM	DLMO estimation, circadian phase prediction
Cortisol	HRV, sleep stages, acoustic biomarkers	Random Forest, LSTM	Stress monitoring, adrenal dysfunction detection
Insulin	CGM, meal logs, physical activity	Gradient Boosting, LSTM	Circadian metabolic modeling, diabetes management
Glucose	CGM, activity, sleep cycles	CNN, Time-aware RNNs	Detecting rhythm misalignment, optimizing meal timing
GH/Prolactin	EEG, sleep phase, HRV	Hybrid Deep Learning	Hormone therapy optimization, sleep-stage tracking
Drug metabolism	Clock gene expression, liver enzymes	Ensemble Models	Chronopharmacology, personalized dosing time prediction

These applications illustrate how AI is moving beyond theoretical modeling to become an actionable tool in clinical chronobiology. As wearable technology and biosensor fidelity continue to improve, AI-enabled systems will likely become central to the real-time monitoring and management of endocrine and metabolic health, especially in contexts where circadian rhythms are critical yet difficult to measure directly.

Clinical Implications and Translational Potential

The integration of artificial intelligence (AI) into circadian physiology carries profound implications for translational medicine, offering new possibilities for predictive diagnostics, personalized therapeutics, and real-time physiological monitoring [44]. Circadian rhythms regulate a wide array of biochemical and hormonal processes essential to homeostasis, yet clinical assessment of these rhythms remains rare outside of specialized research settings. AI systems capable of predicting circadian phase and hormonal fluctuations provide an opportunity to close this translational gap by embedding chronobiological insights into routine medical care [28-32].

One of the most promising clinical applications lies in chronotherapeutics, the tailoring of treatment timing to align with the body's internal clock. Numerous studies have shown that drug efficacy and toxicity can vary significantly depending on the time of administration. For instance, antihypertensive drugs, chemotherapy agents, and corticosteroids exhibit circadian variation in pharmacokinetics and pharmacodynamics [45]. AI-driven models that forecast circadian phase through passive monitoring (e.g., using wearable devices) allow clinicians to personalize dosing schedules to maximize therapeutic benefit while minimizing side effects [28,29,43]. In oncology, for example, machine learning-based circadian models have been used to time chemotherapy according to individual cortisol or melatonin rhythms, enhancing drug tolerability and reducing toxicity [46,47].

In diagnostics, AI-assisted prediction of circadian biomarkers enables early detection of rhythm-related pathologies. Circadian disruption is now recognized as a hallmark of many chronic diseases, including metabolic syndrome, depression, neurodegenerative disorders, and certain cancers [48]. AI algorithms trained on time-series data from physiological signals, hormone levels, or behavioral patterns can detect subtle abnormalities that may precede clinical symptoms. For instance, predictive modeling of cortisol dysregulation can aid in the diagnosis of Cushing's syndrome or adrenal insufficiency, while irregular melatonin secretion patterns may signal circadian rhythm sleep-wake disorders [49].

Moreover, remote patient monitoring is greatly enhanced by AI models capable of continuously assessing circadian health. By integrating data from wearables, mobile apps, and home sensors, clinicians can non-invasively track sleep-wake cycles, metabolic rhythms, and hormonal fluctuations in real time [27,31]. This has particular value in managing patients with chronic diseases, shift workers, or those undergoing treatment regimens that disrupt circadian stability. Additionally, AI can facilitate proactive interventions by predicting impending circadian misalignment or disease exacerbation [50].

In precision medicine, circadian-aware AI models allow clinicians to consider an individual's unique temporal biology as an essential component of their health profile. This expands the paradigm of personalization beyond genomics and lifestyle factors to include time-based biological variation [51]. In psychiatry, for example, AI algorithms can help tailor cognitive behavioral therapy for insomnia (CBT-I) or light therapy by identifying optimal intervention windows based on predicted circadian phase [52].

Table 5 summarizes key areas of clinical impact where AI-enabled circadian modeling is beginning to demonstrate translational utility:

Table 5: Clinical Applications and Translational Potential of AI in Circadian Physiology [45-52]

Clinical Domain	AI-Driven Application	Translational Benefit
Chronotherapeutics	Timing of drug administration based on predicted phase	Enhanced efficacy, reduced adverse effects
Diagnostic endocrinology	Detection of abnormal cortisol, melatonin, GH patterns	Early diagnosis of adrenal, sleep, and pituitary disorders
Psychiatry & Neurology	Prediction of circadian-related mood or sleep disturbances	Personalized timing of therapy and intervention
Metabolic diseases	Modeling insulin/glucose rhythms for shift workers or diabetics	Prevention of metabolic syndrome, improved glycemic control
Oncology	Time-based chemotherapy planning using rhythm predictors	Increased treatment tolerance, optimized tumor targeting
Remote health monitoring	Continuous tracking via wearables + AI	Real-time rhythm feedback, proactive care interventions

As these technologies advance, regulatory and ethical considerations will be vital to ensure patient privacy, model transparency, and equitable access to circadian-informed care. Nevertheless, the convergence of AI and chronobiology marks a critical evolution toward temporal precision medicine, where "when" becomes just as important as "what" or "how" in medical decision-making.

Limitations, Challenges, and Ethical Considerations

While the use of AI in circadian physiology holds great promise, several limitations and challenges must be critically addressed to ensure scientific rigor, clinical reliability, and ethical responsibility. These limitations span technical, biological, and societal domains, and their resolution is essential for transitioning AI-based circadian models from research settings to real-world medical applications.

One of the most significant technical limitations is the quality and quantity of circadian data. Accurate modeling of circadian rhythms requires high-resolution, time-stamped datasets that are often difficult to obtain, especially outside of controlled laboratory environments [53]. Many existing datasets lack sufficient temporal granularity or are collected under varying light, sleep, and lifestyle conditions that can confound circadian signals [53]. Furthermore, missing data, irregular sampling, and inter-device variability in wearable sensors can degrade model performance and generalizability. Deep learning models, in particular, require large volumes of annotated data, which are currently limited in circadian biology [38,54].

Biologically, inter-individual variability in circadian patterns poses a major challenge. Factors such as age, sex, genetic polymorphisms in clock genes, chronotype differences, comorbidities, and medication use can all influence circadian expression of hormones and biochemical markers [19,20]. Building models that are robust to this heterogeneity while still allowing personalized predictions requires advanced algorithms and large, demographically diverse training datasets, resources that are often unavailable.

Another major concern is the interpretability of AI models. Many high-performing AI approaches, especially deep neural networks, are often criticized as "black boxes," offering little insight into how predictions are generated [55,56]. In clinical contexts where transparency and accountability are paramount, this lack of interpretability may reduce clinician trust and hinder adoption [55,56]. Efforts to incorporate XAI are ongoing but not yet standardized in circadian applications.

From an ethical standpoint, privacy and consent are key considerations, particularly when continuous physiological monitoring is involved. Wearables, smartphone apps, and smart home devices collect sensitive temporal and behavioral data, raising concerns about data ownership, informed consent, and potential misuse [57,58]. There is also a risk of reinforcing health disparities, as access to these technologies is not evenly distributed across populations. Without careful design and policy safeguards, AI-based circadian tools may inadvertently widen the digital health divide [59].

Additionally, clinical validation remains a bottleneck. Despite promising results in research settings, relatively few AI models for circadian prediction have undergone rigorous prospective validation in diverse clinical populations. Regulatory approval, integration into electronic health systems, and reimbursement frameworks also present non-trivial barriers to widespread implementation [60,61].

To provide a structured overview, Table 6 below summarizes the key limitations and ethical concerns in the application of AI to circadian physiology:

Table 6: Limitations, Challenges, and Ethical Considerations in AI-Circadian Research [53-61]

Category	Specific Issues	Implications for Practice
Data limitations	Sparse, noisy, or poorly labeled time-series data	Reduces model accuracy and generalizability
Biological variability	Chronotype, genetics, age, disease, environmental factors	Requires large and diverse datasets for personalized models
Model interpretability	Deep models often function as black boxes	Limits clinical trust and hinders decision justification
Privacy & surveillance	Continuous monitoring via wearable and ambient devices	Raises data protection, ownership, and ethical consent issues
Health equity	Uneven access to digital health tools	Potential to reinforce healthcare disparities
Clinical validation	Lack of prospective trials and regulatory approval	Delays adoption in routine medical practice

Addressing these challenges requires interdisciplinary collaboration among clinicians, chronobiologists, data scientists, ethicists, and policy makers. It also calls for investment in open-access datasets, standardized protocols for circadian monitoring, and regulatory frameworks that ensure both innovation and patient safety. Ultimately, the ethical deployment of AI in circadian health must be grounded in transparency, inclusivity, and a commitment to evidence-based practice.

Future Directions

As AI continues to evolve, its integration into circadian physiology is poised to redefine our understanding and management of time-dependent biology. Future research must focus on enhancing the precision, accessibility, and clinical utility of AI-based models for circadian rhythm prediction. One promising direction lies in the development of multi-modal, chronobiology-aware AI systems that incorporate diverse data streams, such as transcriptomic profiles, wearable sensor outputs, environmental context, and behavioral patterns, to create holistic models of internal time. These systems could continuously adapt to individuals' changing physiology and lifestyle, enabling real-time feedback and dynamic health optimization.

The emergence of digital twins, personalized virtual representations of individuals that simulate physiological responses, offers another transformative opportunity. A circadian digital twin could integrate AI-predicted hormonal and metabolic rhythms with clinical parameters, allowing for proactive interventions, virtual clinical trials, and time-optimized treatment simulations [62]. Such models could help guide chronotherapy, forecast disease risk windows, or simulate the circadian effects of lifestyle changes and medications without direct exposure.

In parallel, explainable and transparent AI models will become increasingly important to gain trust and ensure safe implementation in clinical settings. By combining the interpretability of mechanistic circadian models with the predictive power of deep learning, hybrid frameworks may offer both performance and insight [63,64]. These models can help clinicians and patients understand the "why" behind predictions, supporting more informed decision-making.

Another critical future direction is the integration of AI with chronobiological biomarkers in precision medicine. Incorporating circadian timing into diagnostics and therapeutics, such as determining the optimal time for surgery, medication, or vaccination, requires predictive tools that are robust, personalized, and scalable [65,66]. AI will play a central role in stratifying patients not just by genotype or disease state, but by temporal phenotype, thereby introducing time as a new axis in individualized care.

At the population level, AI may support circadian public health monitoring, identifying community-level rhythm disruptions related to urban lighting, shift work, or social jet lag [67,68]. This could inform policy on school start times, work schedules, or urban planning, using predictive modeling to align environments with biological needs.

Finally, global collaboration and data sharing will be essential to advance the field. Open circadian datasets, common ontologies, and ethically governed data infrastructures will enable AI models to be trained and validated across diverse populations, ensuring equity and generalizability.

In summary, the future of AI in circadian physiology will depend not only on algorithmic advancement, but on its thoughtful integration with systems biology, clinical workflows, and ethical frameworks. As this convergence deepens, it promises to unlock a new era of time-informed medicine that aligns human health with our most fundamental biological rhythm.

Conclusion

The convergence of artificial intelligence and circadian physiology represents a pivotal advancement in modern biomedicine. As our understanding of biological time deepens, it becomes increasingly clear that circadian rhythms play a foundational role in regulating endocrine function, metabolic homeostasis, cognitive performance, and overall health. However, traditional methods for assessing these rhythms are often limited by invasiveness, temporal resolution, and scalability. AI technologies, particularly those designed for time-series prediction and multimodal data integration, offer powerful tools to overcome these challenges.

This review has highlighted how AI can accurately model and predict biochemical and hormonal rhythms, enabling new clinical applications in chronotherapeutics, diagnostics, metabolic monitoring, and precision medicine. From predicting melatonin and cortisol fluctuations to optimizing drug delivery based on circadian phase, AI has the potential to transform how we understand and intervene in time-dependent biological processes. Moreover, the ability to passively monitor and interpret circadian patterns through wearable sensors and personalized algorithms opens the door to truly dynamic and individualized healthcare.

Nonetheless, several barriers remain, including data limitations, inter-individual variability, model transparency, and ethical considerations related to privacy and access. Addressing these challenges will require interdisciplinary collaboration, regulatory innovation, and equitable deployment of AI-enabled technologies. As the field moves forward, integrating biological insight with computational power will be essential to translate circadian science into impactful, real-world medical practice.

In conclusion, the application of AI in circadian physiology marks a paradigm shift toward temporally-informed medicine, where when we diagnose, monitor, and treat becomes as important as what and how. Embracing this temporal dimension, powered by intelligent systems, holds immense promise for improving human health in ways both preventive and personalized.

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