

Deploying Artificial Intelligence to Better Understand Chronobiology: A Critical Review

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ABSTRACT

Use of artificial intelligence in discovering and understanding the chronobiology is a newer beginning in the field of computational science, biological rhythms and health informatics. This literature review aims at critical analysis of the available literature published within the past 3 years, which discusses the examples of applications of AI to the chronobiological phenomena, what difficulties and opportunities are still extant and what gaps in theoretical bases or methods still exist. The discussion follows a systematic structure in terms of (i) the background and context, (ii) methodological implementation of AI in chronobiology, (iii) critical evaluation of strengths and limitations, as well as (iv) future research directions. Through its ability to integrate evidence across disciplines, the review will not only provide both scholars in the fields of chronobiology as well as health informatics with current evidence on where the aspect of AI integration into chronobiological inquiry is headed. In addition to synthesising recent literature, this review develops a roadmap that is practically oriented and has specific requirements of experimental validation, interdisciplinary design principles, and step-by-step integration processes to implement AI-enabled chronobiology into a regular clinical decision-making process.

INTRODUCTION

Chronobiology as a discipline that studies biological rhythms (cycling, circadian and ultradian), has long been a target of deeper understanding of health and disease, and personalized medicine, but is subject to serious analytic difficulties due to its complexity and high dimensionality (Sadeghi et al., 2024). These time varying nature of molecular clocks, endocrine vocalization, and behaviour rhythms give rise to highly structured rich noisy data sets, which require technical computation methods. Simultaneously, AI, above all, machine learning, deep learning, and hybrid modelling have been experiencing a sudden maturation in the field of healthcare, where they have demonstrated the potential to classify patterns, objective models, and draw conclusions based on multimodal atypical inputs (Morid et al., 2023). The intersection of AI and chronobiology, therefore, presents an interesting paradigm to consider in further chrono medicine development, but at the same time, it introduces several methodology, interpretability, and reliability issues that deserve serious critical questioning (Teoh et al., 2024). Not to narrow the prospects of inclusiveness, the current work describes initially the theoretical and empirical bases of chronobiology and AI in health followed by evaluating the way AI has been utilized in those contexts, and an ultimate evaluation of the limitations, unsolved problems, and future working prospects (Dashti et al., 2025). Active developments in the field are needed that go beyond talk about conceptual promise by providing empirically based exemplars of how model interpretability, bias auditing, rhythm-sensitive protocols can directly alter clinical timing decisions and patient-reported outcomes in clinical practice.

BACKGROUND AND CONTEXT

The basic aspects of chronobiology focus on understanding how living things keep endogenous and synchronize them with external rhythms like the day and night light cycle with the suprachiasmatic nucleus (SCN) playing a central role (Tsuno et al., 2024). On the molecular level, the so-called clock gene networks have a roughly 24 hour periodicity and are regulated by feedback and post-translational mechanisms (Shen et al., 2023). The latest reviews focus on the interactions between these core oscillators with external zeitgebers, such as light exposure, feeding schedules, physical activity, and temperature, to decide on downstream physiology, metabolic flux, and behavioral outputs (Raji et al., 2024). An example is that exercise has potent circadian alignment modulating

effects and can mitigate rhythm disruption effects. In addition, the understanding of the role of meal timing in relation to biological clocks affecting cardiometabolic outcomes has been improved due to the study of chrononutrition, providing the health significance of the temporal organization of behavior (Gubin et al., 2025). With biology producing larger and increasingly temporally dense datasets (e.g. wearables and omics profiling), more challenging to analyze by traditional techniques with nonlinear interactions, time lags and intra-individual variability, are being modeled. Such complexity can be tackled with different artificial intelligence methods through the use of recurrent neural networks, temporal convolutional networks, reinforcement learning, and two-fold mechanistic-data models. AI is increasingly used in the healthcare context as a source of diagnostic aid, clinical decision support equipment, and predictive analytics but the particularity of chronobiological utilization has only lately begun to draw more scholarly focus.

In the context of health informatics, AI integration is not a controversial issue: the questions of data interpretation, biasness, transparency effectiveness, privacy and trustworthiness were foreshadowed in the discussion over the past years (Rosenbacke et al., 2024). Methods to interpret black box models to clinicians have developed in the field of explainable AI (XAI) but it remains problematic to balance model fidelity and explainability in temporal biomedical scenarios (Sedegu et al., 2024). The history of AI use in medicine over the past decades also indicates a path of adoption, rejection, and that governance structures need to be put in place to balance the protection of technology and the protection of the lives of patients and other groups (Wells et al., 2025). Accordingly, the challenge of task relating to the application of AI to chronobiology needs to be contextualized in this wider framework of potential methodological possibility with limitations imposed by the real world (Papagiannidis et al., 2025). Since circadian organisation coevolves both with behaviours and with environments, and with social determinants, a sufficient description of rhythm perturbation needs to encompass behavioural science terms, motivation and adherence and environment, and molecular and physiological oscillators to steer clear of not only biologically flawless but clinically fragile models.

Methodological Deployment of AI in Chronobiological Studies

One of the trendy features in the literature is the application of wearable sensors, actigraphy, and biomarker-based signals to input into AI models that see, identify, or forecast rhythmic states (Park et al., 2024). The gadgets measuring light exposure, movement, skin temperature, heartbeat, and various physiological overheats generate high-frequency time series that can be fed into AI models. As an illustration, one review that has been incorporated lordly corroborates how state-of-the-epoch neural-network designs have been used to analyze actigraphy information in the evaluation of rhythm amplitudes, phase stability and deviation linked to disease conditions (Lim et al., 2024). To provide a specific example, a rhythm-phase classifier would be prospectively tested on dim-light melatonin onset amongst a variety of shift-work groups and most importantly, predefined accuracy, calibration, and uncertainty limits, where a recommendation would indicate to the clinicians.

In studies of mood disorders, it was found the set of sleep-wake models trained only on smartphone and wearable devices data has the potential to predict an upcoming mood episode, illustrating how even the comparatively primitive aspect of temporal cue modeling with AI demonstrates the ability to forecast even the most complex psychiatric transitions. The other strand of research consists of programming rhythmical schemes directly into AI: a recent preprint suggests scaffolded LLMs, which predict the mechanisms of a simulated hormone cycle, (including menstrual and circadian) to adjust model responses over time (Weaver et al., 2024). The concept of second generation AI chronobiology has been proposed in infectious disease and pharmacology: algorithms can be used to maximize timing and dosing of antimicrobials in relation to circadian physiology with the aim of reducing cases of antimicrobial resistance and enhancing long term efficacy (El-Tanani et al., 2024). These models basically combine pharmacodynamic-pharmacokinetic constraints with time models in order to impose a variability consistent with a biological cycle. The methodological approaches include supervised classification (e.g. phase shift prediction), generative modeling (rhythmic trajectory prediction), reinforcement or adaptive schedule prediction, and hybrid mechanistic-data learning where AI models are biased by existing circadian differential equations or clock gene dynamics.

Most studies in training and validation use cross validation techniques, or a combination of a time series split, and a time segment hold out, or a time series split with a nesting hold out, to avoid leakage and prediction of time-varying autocorrelation (Morid et al., 2023). There are implementations that use attention usable across a

window in time in order to learn long range interactions and there are implementations that use periodic motifs delineation by use of learned temporal convolutional networks (Casolaro et al., 2023). Unfrequently, not a lot of literature combines longitudinal measurements based on omics (e.g. transcriptomics, metabolomics) as multimodal inputs into AI chronobiology paradigms, although this would have richer inferential ability (Mienye et al., 2024). In multi modal data, feature selection and dimensionality reduction (e.g. autoencoders) are frequently learned with the model (another example is augmenting with domain driven features, e.g., derived circadian amplitude or phase shift indices). The current methodological frameworks, therefore, represent an immature yet increasingly diversified array of AI application to chronobiological research, where the former option of predictions and the latter of time optimization can be used (Schouten et al., 2025).

Critical Appraisal of Strengths and Innovations

The ability to approximate nonlinear, multivariate, time lagged interaction that cannot be represented using traditional linear statistical models is one of the strengths of applying AI to chronobiology (Lim et al., 2024). AI could find latent temporal characteristics that might be relevant to physiologically significant rhythm aberrations to provide superior sensitivity to fine disruptions. This is a strength that has been depicted in mood disorder prediction studies with AI models differentiating between preclinical indicators of now clinically with relapse and baseline noise (Gubin et al., 2025). Moreover, scaffolded AI agents with rhythmic priors are a fascinating novelty: where endogenous oscillatory structure is given to the models, they can vary with timing circumstances biologically (Colonnello et al., 2025). When antimicrobial scheduling takes a second generation AI-based form of chronotherapy, further prescriptive induction of AI admits chronobiological mechanisms can be introduced, rather than just described. Moreover, the proliferation of wearable and consumer devices generating dense temporal data also reduces the cost of scaling the chronobiological AI models, further diversifying the sample and the possible use in the real world. The adoption of AI rhythmic algorithms into health informatics systems presents opportunities of individual monitoring interfaces, dynamic anomalies of patterns that are out of rhythm, and rhythm sensing supportive systems capable of identifying circadian disruption effect as a risk proposer (Aziz et al., 2025). It is the combination of these inventions that position AI as an enabling breakthrough in chronobiology to bring clinical effect to reality. Such deployments must regularly feature distributive checks of impartiality in terms of age, gender, chronotype, race, and socioeconomic standing, to avoid inequality in the error rates in the rhythm category or treatment regimen.

Limitations, Risks, and Methodological Challenges

Although AI is a promising device that can radically transform chronobiology, there are an array of limitations and critical drawbacks, yet to be addressed, along with technical limitations to adoption and effectiveness in practice in health domains (Cross et al., 2024). The opacification of many high-performing AI models, including deep neural networks and ensemble approaches, is one of the fundamental problems since they are typically non-transparent and non-interpretable (Sadeghi et al., 2024). In the absence of strong interpretability, medical professionals are likely to be opposed to the use of AI tools, especially where the models affect diagnostic-related decisions, medication time, and behavior intervention decisions. Specifically, it becomes intense in time-sensitive medical areas, as both the reasons and the manner of a prediction is understood have an ethical and clinical implication (Seoni et al., 2023). Despite the recent years having seen improvements with explainable AI frameworks, little has been done that has addressed the particular nuances of chronobiological data ratio like rhythmicity, periodicity, and interindividual variation. The other shortcoming is that AI models are susceptible to changes in the temporal patterns in relation to time, including when a patient falls out of circadian rhythm, because of hospitalization, illness, or irregular work shifts (Doherty et al., 2025). The rising complexity of such changes may invalidate all previous inferences, weakening the reliability of models and requiring recalibration or retraining that may be impractical within clinical periods. Other methodological risks are due to the biased training data, which can underrepresent the older adults, minor groups, or test subjects with abnormal circadian profiles. Unless such underrepresented groups are factored in training data, the generalizability and equity of AI outputs would be affected. Sensor noise, data drop out, and non-adherence to wearable devices by the user can also cause uncertainty and decrease model performance, although the majority of studies do not quantify uncertainty in AI-based rhythm prediction models. Although it would be more accurate when conducting such studies on an experimental scale, the translation to practice in the situation of continuous temporal monitoring

would be restricted by issues of privacy, consent, and data security. Besides, the regulation of AI in rhythm medicine remains reactive, and the challenges of how predictive models interacting with clinical care interventions should be validated, certified, and followed up after the implementation are doubtful. These issues demonstrate the necessity of multi-stakeholder models, which would combine technical rigor and ethical protection and adherence to regulations, in order to promote the responsible development of AI in the field of chronobiology.

Evaluation of Theoretical and Conceptual Gaps

The failure of previous studies on AI and chronobiology literature makes cognitive theoretical weaknesses due to the fragmented conceptualization of rhythm as a non-adaptive (as opposed to adaptive) biological attribute (Mortada et al., 2024). A variety of AI applications implied stable circadian dynamics, but there is empirical evidence that biological rhythms indeed exhibit a significant amount of plasticity as a result of environmental stress, life events, and determinants of health about the social environment (Lin et al., 2024). Those models that do not support such temporal plasticity tend to make false descriptions about rhythm disruption or over-responding to chronodisruption. The other conceptual gap involves the fact that most system-level chronobiology that can be implemented in AI modelling, including the interrelations of central and peripheral clocks in tissues, is underrepresented (Chawla et al., 2024). The vast majority of the models are rather somewhat restricted and single dimensions (e.g. actigraphy), without addressing multi-organ chronobiological dynamics, which can play the role of disease risk or therapeutic response. Moreover, there are minimal studies that present strong theoretical assumptions supporting the selection of the particular architecture of AI or learning components, which imposes underspecified methodological decisions as well (Young et al., 2023). Conceptual grounding is insufficient to promote coherence via cross-study and hamper cumulative growth of knowledge. In addition, a number of AI applications to chronobiology do not conform to the theory of behavioral sciences because they lack motivation, adherence, or change behavior models that would facilitate the execution of rhythm-informed interventions. Without an interdisciplinary conceptual framework, AI application to this domain will run the danger of being a success of disconnected technical illustrations as an alternative to a practical scientific program.

Emerging Directions and Recommendations for Future Research

The generation of hybrid AI models that combine both mechanistic biological knowledge and the use of data to make a prediction should be a priority in future research (Jia et al., 2025). As an example, biological plausible and generalizable predictions can be obtained by incorporating mathematical descriptions of circadian oscillators as priors into neural network structures. Such hybrid models will require interdisciplinary efforts between computational scientists, chronobiologists, and clinicians in co-designing them (Losada et al., 2024). The second direction is the introduction of adaptive artificial intelligence (AI) agents with the ability to learn and control feedback in real-time to aid in dynamically guided chronotherapy (Jayaraman et al., 2024). Continuous adjustments toward user context and response would be possible with reinforcement learning and online updating mechanisms capable of letting rhythm-aligned interventions react to their situations, regardless of whom they are interacting with. Simultaneously, the validation research is necessary to study the ability of AI-informed rhythm monitoring to enhance patient outcomes in the natural environment taking into account the questions of scalability, cost-effectiveness, and equity (Huang et al., 2024). Studies are also required on the ethical and social aspects of the temporal data collection, especially where vulnerable groups of people are involved or where such data sources are prevalent in the process of monitoring a patient or an individual. The processes of coming up with temporal data governance models and participatory consent models will be of paramount significance. Lastly, more needs to be done to implement AI-informed chronobiological knowledge into health information systems, patient portals, and clinician dashboards one to ensure it is accessible, user-friendly, and clinically relevant. These new directions indicate a paradigm shift in the stagnant rhythm-modelling to dynamic and personalized and do-not-resuscitation chronomedicine of artificial intelligence.

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