Wearable technology and systems modeling for personalized chronotherapy

Kim, Dae Wook; Zavala, Eder; Kim, Jae Kyoung

DOI:
10.1016/j.coisb.2020.07.007

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Kim, DW, Zavala, E & Kim, JK 2020, 'Wearable technology and systems modeling for personalized chronotherapy', *Current Opinion in Systems Biology*, vol. 21, pp. 9-15.
https://doi.org/10.1016/j.coisb.2020.07.007

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Systems Biology

Wearable technology and systems modeling for personalized chronotherapy

Dae Wook Kim[1], Eder Zavala[2] and Jae Kyoung Kim[1]

Abstract

Chronotherapy is a pharmaceutical intervention that considers the patient's internal circadian time to adjust dosing time. Although it can dramatically improve drug efficacy and reduce toxicity, the large variability in internal time across and within individuals has prevented chronotherapies from progressing beyond clinical trials. To translate chronotherapy developments into a real-world outpatient clinical scenario, a personalized characterization and analysis of a patient's internal time is essential. Here, we describe recent advances in wearable technology that enable real-time high-resolution tracking of circadian and ultradian rhythms. We discuss how integrating wearable data into analysis platforms including systems modeling and machine learning can pave the way toward personalized adaptive chronotherapy.

Addresses

[1] Department of Mathematical Sciences, Korea Advanced Institute of Science and Technology, Daejeon, 34141, Republic of Korea

[2] Centre for Systems Modelling and Quantitative Biomedicine, Institute of Metabolism and Systems Research, University of Birmingham, Edgbaston, B15 2TT, United Kingdom

Corresponding authors: Kim, Jae Kyoung (jaekkim@kaist.ac.kr); Zavala, Eder (e.zavala@bham.ac.uk)

Current Opinion in Systems Biology 2020, **21**:9–15

This review comes from a themed issue on **Mathematical Modelling (2020)**

Edited by **Daniel Forger** and **Olivia Walch**

For complete overview of the section, please refer the article collection - Mathematical Modelling 2020

Available online 25 July 2020

https://doi.org/10.1016/j.coisb.2020.07.007

Keywords

Chronotherapy, Wearables, Circadian rhythms, Ultradian rhythms, Mathematical model, Systems pharmacology model, Machine learning, Personalized medicine, Circadian medicine.

Introduction

The circadian (~24 h) clock is an innate timing system that coordinates diverse circadian rhythms seen in metabolic, physiological, and behavioral processes with external light–dark cycles [1]. The system is organized in a hierarchical manner, where the master clock in the suprachiasmatic nucleus (SCN) regulates downstream clocks in peripheral tissues by sending synchronization signals such as hormone rhythms (Figure 1) [2,3]. Around 50% of the protein-coding genome is transcribed rhythmically, and >80% of currently approved drug targets show rhythmic activity [4–6]. Furthermore, the mechanisms underpinning pharmacokinetics and pharmacodynamics, together with key processes such as the cell cycle and energy metabolism, display circadian rhythms (Figure 1) [2,7,8].

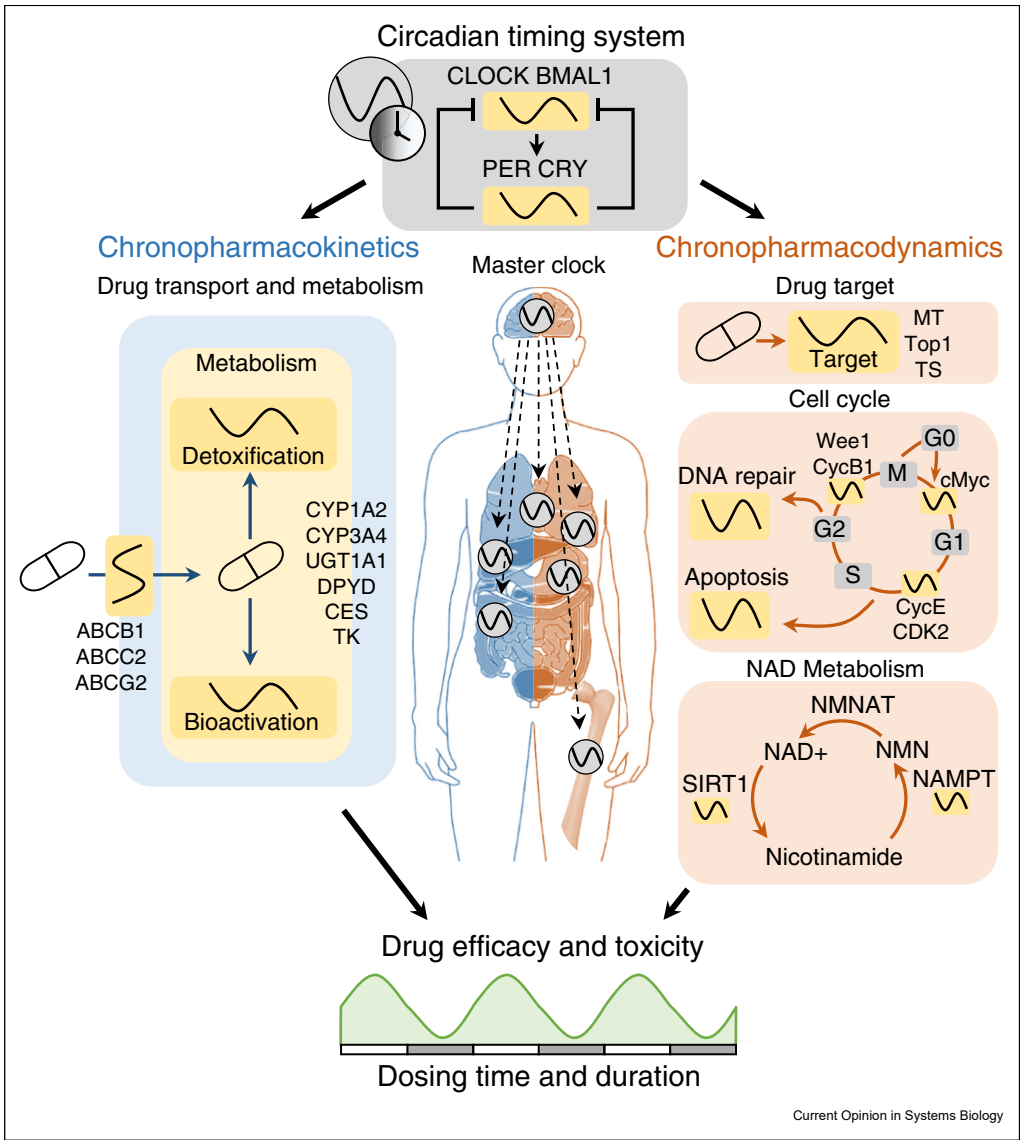
As a result, the efficacy and toxicity of diverse drugs can largely depend on dosing time (Figure 1). For example, melatonin, a clock modulator, can either delay or advance the circadian phase when administered in the morning or early evening, respectively [9]. Simvastatin, a cholesterol-lowering agent, works better at reducing levels of cholesterol when administered in the evening [1]. More than 50 anticancer drugs displayed chronotoxicity or chronoefficacy in mouse and human experiments [2,8], and ~75% of clinical trials investigating the impact of timing for 70 drugs found significant circadian variations of efficacy and toxicity [1].

Despite the potential benefits to patients from proper dose timing, most clinical trials and regulatory bodies have largely ignored it [1]. This might be due to the complexity of implementing chronotherapies in the clinic and the lack of dedicated technologies. The success of chronotherapy depends on precisely measuring internal circadian time, which has been difficult to do in real-time before recent advances in wearable technology. Here, we review how personalized chronotherapy can improve patients' quality of life by taking advantage of wearable data and its analysis through mathematical modeling and machine learning. Although previous reviews have addressed the overall benefits and challenges of adopting wearable systems in medicine [10–14], we focus on how these devices can be integrated into analysis platforms that enable personalized chronotherapies.

Challenges to chronotherapy: heterogeneity in patient circadian rhythms and response to chronotherapy

Historically, questionnaires have been used to assess the large inter-individual variability in chronotypes — the

Figure 1



The drug efficacy and toxicity depend on dosing time because of circadian rhythms in drug pharmacokinetics and pharmacodynamics. The circadian timing system, which comprises a hierarchy of oscillators in central and peripheral tissues, regulates key pharmacokinetic factors (e.g. drug transport and metabolism) and pharmacodynamic factors (e.g. drug targets, cell cycle, and energy metabolism). This leads to a strong dependency of drug efficacy and toxicity on dosing time. The human icon is adapted from Ballesta et al. [2].

most extreme being colloquially termed 'night owls' (evening types) or 'morning larks' (morning types) [15]. The chronotypes depend on factors such as age, gender, and genetic predisposition (e.g. clock gene polymorphisms) [16,17]. However, questionnaires only provide a static picture of the patient's circadian rhythms and may not contain the necessary information to personalize drug administration. The dim light melatonin onset (DLMO) has established itself as the most widely used biomarker of internal time [18]. This physiological measurement shows that even healthy individuals with the same sleep–wake cycle can have internal circadian times that differ by up to 5 h [19]. The natural intra-individual and inter-individual variability of internal time advocates against "one-size-fits-all" therapeutic strategies and highlights the need for a personalized approach to chronotherapy [1,20]. However, with resource-intensive DLMO measurement, it is difficult to track daily variations of circadian time in free-living conditions, which can be disrupted by external factors such as jetlag, artificial light exposure at night, mistiming of meals, or just one night of poor sleep [21,22]. Furthermore, it only provides information on one biomarker, whereas the circadian system relies on a

complex interplay between interrelated oscillators affecting drug responses (Figure 1).

Because of the variability of circadian rhythms, the effect of chronotherapy also shows large intra-individual and inter-individual variability. For instance, the effect of cancer chronotherapy shows a large variation across patients. A meta-analysis of three clinical trials for colorectal cancer found that chronomodulation of the anticancer drugs 5-fluorouracil, leucovorin, and oxaliplatin improves overall survival in men but not in women [23]. More recently, the chronotoxicity of irinotecan combined with 5-fluorouracil and oxaliplatin showed large sex-specific differences: the optimal dosing time was early morning for men but early afternoon for women [24]. Furthermore, using a systems pharmacological model, which accurately captures the intracellular action of a clock modulator inhibiting CK1ε/δ on the core clock molecules in the SCN, the modulator efficacy has been shown to change depending on exposure environment (e.g. a long/short day) when dosed even at the same external time as the exposure environment affects the phase of the SCN oscillation (i.e. the internal time) [25,26]. Furthermore, even under the same environment, as daily dosing of the modulator keeps altering the internal time, the modulator efficacy shows daily variations when kept dosed at the same external time [25,26]. Overall, these findings emphasize the need for patient-tailored chronotherapies.

Real-time individual monitoring of circadian and ultradian rhythms through wearables

To develop personalized chronotherapies, we need technologies that measure circadian rhythms of individual patients *quantitatively* and *continuously*. When combined with suitable computer analysis techniques, wearable devices are the most promising tool for tracking the internal time from real-time monitoring of physiological proxies such as rest–activity, heart rate, sleep, glucose, skin temperature and conductance, and even exposure to external cues such as light [20,27–31]. Indeed, with multiple wearable devices, daily variations in 62% of ~40 physiological and behavioral measures including blood pressure, heart rate, and dietary intake were uncovered [12]. Furthermore, circadian rhythm disruptions induced by cancer and anticancer drugs have been identified by measuring rest-activity rhythms with actimeters [2]. Recently, the PiCADo mobile eHealth platform identified significant sex- and age-related differences in circadian coordination during daily routine by combining skin temperature with rest–activity data, which was not detected from rest–activity data alone [32].

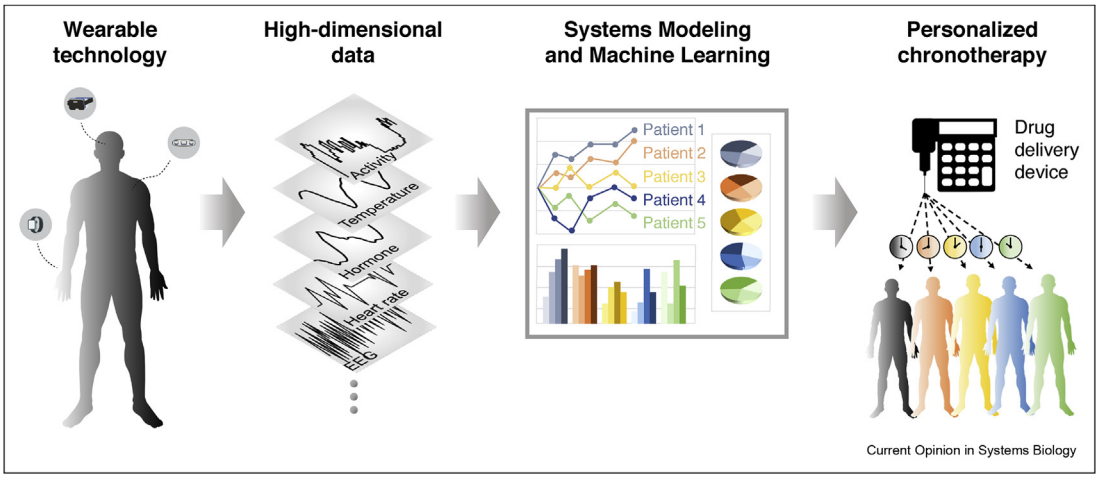
Wearables can also provide information about ultradian, monthly, and seasonal body rhythms not previously considered in chronotherapy. Because these rhythms overlap with circadian ones, we can expect that chronotherapeutic effects would also depend on these other rhythms. For instance, glucocorticoids are vital steroid hormones with ultradian, circadian, and seasonal rhythmicity that mediate stress response, metabolism, cognition, and inflammation [33]. However, the effect of ultradian and seasonal rhythms on the efficiency of drugs targeting the glucocorticoid receptor and on hormone replacement therapy has not been considered [34,35]. Furthermore, glucocorticoids also exert circadian and ultradian regulation of blood glucose, but the impact of these rhythms in the treatment of metabolic disorders such as diabetes remains unexplored [36]. In this direction, wearable continuous glucose monitoring devices have shown therapeutic potential as they have enabled the identification of glucotypes in a noninvasive manner [37], which could help develop chronotherapies in diabetics under the artificial pancreas [38]. Treatment of sleep disorders can also benefit from analyzing not only circadian but also intradaily variability of actigraphy data [39]. Lastly, wearable tracking of resting heart rate, an ultradian cardiovascular rhythm, as well as rest–activity rhythms and light exposure can also inform about the best course of action to fine tune chronotherapies in the face of susceptibility to seasonal ailments such as influenza and sleep disorders [40,41]. Taken together, this latest research suggests tracking changes in dynamics other than circadian rhythms via wearables can assist the development of novel chronotherapies.

Integration of high-dimensional data from wearables toward personalized chronotherapy

Systems pharmacology and machine learning to analyze wearable data

Another benefit of using wearables is that large high-dimensional data from various devices can be easily incorporated into a single platform via the Internet of Things and cloud computing (Figure 2) [14,28,31,32,42,43]. For instance, ~900 different apps based on smartphones and wearables are currently connected with the Apple HealthKit. To utilize the high-dimensional data from this platform to personalize chronotherapy, it is essential to identify key biomarkers and their complex nonlinear interactions determining therapeutic effects. The most promising tool to achieve this is systems pharmacology modeling and machine learning (Figure 2) [13,20]. For instance, a systems pharmacology model was used to analyze large variations in the efficacy of a clock modulator inhibiting CK1ε/δ depending on mutations of various clock genes and environmental light conditions [26]. Specifically, using the model, virtual patients having different genetic causes of circadian disruption were generated. Then, the source of their heterogeneous responses to the modulator was investigated. This revealed that the

Figure 2



Wearable-based systems medicine enables personalized chronotherapy. The real-time rest–activity rhythms, heart rate variability, sleep, glucose, skin temperature, and exposure to environmental light measured by wearable devices can be integrated into data processing platforms. The collected high-dimensional data are analyzed via systems pharmacology and machine learning models to estimate the status of key circadian biomarkers in patients that determine drug efficacy and toxicity. This predicts a proper personalized dosing time in real-time, thus enabling personalized adaptive chronotherapies coupled to smart drug delivery devices.

complex efficacy of the modulator is mainly determined by a single biomarker, the endogenous PER2 level. Similarly, by generating virtual subjects, another systems pharmacology model, which compared different dosing regimens of synthetic glucocorticoids, identified that gender, homeostatic variability, and chronic stress–induced regulatory adaptations in the hypothalamus–pituitary–adrenal axis are critical for the efficacy of hormone replacement therapy [44]. Furthermore, through a variance-based global sensitivity analysis using a systems pharmacology model, which accurately simulates the pharmacokinetics/dynamics of the anticancer drug irinotecan, the contribution of model parameters to the drug toxicity was dissected. This revealed that the chronotoxicity of irinotecan mainly stems from rhythmic *BMAL1* expression as it regulates the drug's bioactivation and detoxification [45]. Recently, the interpatient variability in pharmacokinetic parameters of irinotecan, oxaliplatin, and 5-fluorouracil was assessed using a nearly unbiased estimator of coefficient of variation on a physiologically based model, which accurately captures the delivery dynamics of the anticancer drugs to the patient blood and their pharmacokinetics. This revealed that the large interpatient pharmacokinetic variability of the drugs originated from differences in drug transport between organs rather than drug clearance [46].

Although systems pharmacology modeling requires data on the molecular mechanisms underlying dosing effects [26,45], machine learning is a more flexible alternative for modeling raw, unstructured wearable data and its links to internal time [14]. Although machine learning has not yet been directly applied to chronotherapy, it has already extracted insight from high-dimensional data collected with wearables. For example, a machine learning method based on balanced random forests successfully classified the activity mode from patterns of sleep and physical activity measured with wrist-worn accelerometers [42]. An analysis of acceleration and heart rate data from wearables with a neural net approach accurately differentiates wake, NREM sleep, and REM sleep [28]. Furthermore, a convolutional and recurrent neural network trained on ECG signals has successfully predicted hypoglycaemic events [30], and a similarity-based machine learning analysis using data from multisensor wearable devices has accurately predicted heart failure exacerbation and estimated the risk of rehospitalization [47]. Lastly, a linear regression model–based approach using long-term tracking of resting heart rate has also been investigated as a surveillance tool to monitor seasonal influenza-like illness [40].

Integrated platforms toward personalized chronotherapies

The integration of wearable devices and high-dimensional data platforms enables proactive supportive drug interventions and systematic real-time monitoring of their efficacy, which facilitates personalized chronotherapy (Figure 2). For instance, the inCASA telehealth project, which was named by the EU Commission, aimed to combine rest–activity recording with self-monitored body weight and self-rated symptoms in cancer patients receiving chronotherapy at home [43]. This domomedicine platform was further developed to

incorporate a new wearable that records activity, temperature, and position and now constitutes a unique tool for advancing safe home-based chemotherapy administration [32]. This platform is currently being used in the CIRCA DIEM study to evaluate the impact of shift work schedules on the circadian coordination and sleep of nurses [32].

The World Health Organization estimates that only about 50% of people with a chronic illness follow their prescribed treatment. Thus, keeping the right daily dosing time, which critically affects patient response [20], is expected to be challenging. This problem could be solved by wearable-assisted drug delivery systems (Figure 2). For example, a portable subcutaneous infusion pump has shown to improve the timing of hormone replacement therapy [35]. However, a more physiological dosing regimen will require dynamic control of hormone infusion that adapts to bodily needs in real-time. This can be addressed through practical, noninvasive wearable biosampling systems that feed information back to the infusion pump [48,49]. Furthermore, by integrating smart wearable drug delivery systems with systems pharmacology models [26], individual differences in efficacy of time-varying dosing regimens could be analyzed systematically. This would provide a unique opportunity to investigate inter-individual and intra-individual variability in drug efficacy. This approach constitutes an important step toward personalized adaptive chronotherapies that dynamically adjust dosing time to achieve the desired effect [9,26,50].

Identification of new chronotherapy with wearables

Wearables can also be used to identify unknown dependencies of drug effects on dosing time. Because considering circadian timing adds complexity in clinical trials, only 1% of all clinical trials incorporate circadian timing, and it is, therefore, nearly excluded from drug development [1,5]. On the other hand, unlike in typical clinical trials, the timing of treatment has been tracked when wearables have been used to monitor the effect of various therapies. For instance, the smart inhaler for asthma developed by Propeller Health has tracked dosing time and patient response [51]. Dexcom's continuous glucose monitor and SleepOn's Go2Sleep also have recorded the timing of treatment and responses in diabetics and sleep apnea patients, respectively [52]. These data will provide a valuable opportunity to test whether the therapeutic effect depends on the timing of treatment and to initiate new clinical trials for chronotherapy. Furthermore, compared with traditional clinical trials, those that involve wearables have better patient recruitment rates and automated data collection and monitoring. For instance, Apple ResearchKit—powered apps such as MyHeart Counts successfully recruited ~10 000 patients in just a day and have monitored their daily activity, fitness, and cardiovascular risk [53].

Conclusion

Real-time data collection with wearables and analysis with mathematical modeling and machine learning can facilitate personalized chronotherapy. However, various technical challenges remain (see Perez-Pozuelo et al. [14] for details). Although circadian rhythms are markedly diverse among tissues because of organ-specific regulation of circadian function, current wearable devices can only measure system-level rhythms rather than tissue-specific rhythms [54] that can be altered by disease (e.g. tumors and inflammation) [2,55]. Thus, to truly personalize chronotherapy, it will be important for analysis platforms to account for tissue-specific internal time. This can be achieved by tailoring machine learning—based algorithms such as TimeTeller [56], Body Time [57], and CYCLOPS [58] to the target tissue sample. The personalized adaptive chronotherapies supported by these platforms promise to improve current clinical interventions by taking advantage of a dimension previously unaccounted for: 'time.'

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank Annabelle Ballesta for valuable comments. This work was supported by the Human Frontiers Science Program Organization (RGY0063/2017) (to JKK), a National Research Foundation of Korea Grant funded by the Korean Government [NRF-2016 RICIB 3008468 (to JKK)], a NRF-2017-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program (to DWK), and an Engineering and Physical Sciences Research Council grant (EP/N014391/1) and a Medical Research Council Fellowship (MR/P014747/1) (to EZ).

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. ** Ruben MD, Smith DF, FitzGerald GA, Hogenesch JB: **Dosing time matters**. *Science* 2019, **365**:547–549.
Excellent review for circadian precision medicine. In particular, the effect of time-of-administration of drugs is analyzed for more than 100 human clinical trials

2. Ballesta A, Innominato PF, Dallmann R, Rand DA, Levi FA: **Systems chronotherapeutics**. *Pharmacol Rev* 2017, **69**: 161–199.

3. Zavala E, Wedgwood KCA, Voliotis M, Tabak J, Spiga F, Lightman SL, Tsaneva-Atanasova K: **Mathematical modelling of endocrine systems**. *Trends Endocrinol Metabol* 2019, **30**: 244–257.

4. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB: **A circadian gene expression atlas in mammals: implications for biology and medicine**. *Proc Natl Acad Sci USA* 2014, **111**: 16219–16224.

5. Panda S: **The arrival of circadian medicine**. *Nat Rev Endocrinol* 2019, **15**:67–69.

6. Mure LS, Le HD, Benegiamo G, Chang MW, Rios L, Jillani N, Ngotho M, Kariuki T, Dkhissi-Benyahya O, Cooper HM, *et al.*: **Diurnal transcriptome atlas of a primate across major neural and peripheral tissues**. *Science* 2018, **359**.

7. Selfridge JM, Gotoh T, Schiffhauer S, Liu J, Stauffer PE, Li A, Capelluto DG, Finkielstein CV: **Chronotherapy: intuitive, sound, founded...But not broadly applied**. *Drugs* 2016, **76**:1507–1521.

8. Levi F, Okyar A, Dulong S, Innominato PF, Clairambault J: **Circadian timing in cancer treatments**. *Annu Rev Pharmacol Toxicol* 2010, **50**:377–421.

9. Nesbitt AD: **Delayed sleep-wake phase disorder**. *J Thorac Dis* 2018, **10**:S103–S111.

10. Chan M, Esteve D, Fourniols JY, Escriba C, Campo E: **Smart wearable systems: current status and future challenges**. *Artif Intell Med* 2012, **56**:137–156.

11. Depner CM, Cheng PC, Devine JK, Khosla S, de Zambotti M, Robillard R, Vakulin A, Drummond SPA: **Wearable technologies for developing sleep and circadian biomarkers: a summary of workshop discussions**. *Sleep* 2020, **43**.

12. Skarke C, Lahens NF, Rhoades SD, Campbell A, Bittinger K, Bailey A, Hoffmann C, Olson RS, Chen L, Yang G, *et al.*: **A pilot characterization of the human chronobiome**. *Sci Rep* 2017, **7**: 17141.

13. Topol EJ: **High-performance medicine: the convergence of human and artificial intelligence**. *Nat Med* 2019, **25**:44–56.

14. * Perez-Pozuelo I, Zhai B, Palotti J, Mall R, Aupetit M, Garcia-Gomez JM, Taheri S, Guan Y, Fernandez-Luque L: **The future of sleep health: a data-driven revolution in sleep science and medicine**. *NPJ Digit Med* 2020, **3**:42.
Review of the state-of-the-art in technologies for the digitization of sleep and current technical challenges. This provides detailed descriptions for a digital sleep framework and a data-driven sleep application

15. Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, Merrow M: **Epidemiology of the human circadian clock**. *Sleep Med Rev* 2007, **11**:429–438.

16. Kalmbach DA, Schneider LD, Cheung J, Bertrand SJ, Kariharan T, Pack AI, Gehrman PR: **Genetic basis of chronotype in humans: insights from three landmark GWAS**. *Sleep* 2017, **40**.

17. Fischer D, Lombardi DA, Marucci-Wellman H, Roenneberg T: **Chronotypes in the US - influence of age and sex**. *PloS One* 2017, **12**.

18. Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, Kayumov L: **Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders**. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2007, **31**:1–11.

19. Wright Jr KP, Gronfier C, Duffy JF, Czeisler CA: **Intrinsic period and light intensity determine the phase relationship between melatonin and sleep in humans**. *J Biol Rhythm* 2005, **20**: 168–177.

20. ** Klerman EB, Rahman SA, Hilaire MA St: **What time is it? A tale of three clocks, with implications for personalized medicine**. *J Pineal Res* 2020, e12646.
Clear description of three different types of time which are critical for circadian precision medicine: solar, social and circadian times.

21. LeGates TA, Fernandez DC, Hattar S: **Light as a central modulator of circadian rhythms, sleep and affect**. *Nat Rev Neurosci* 2014, **15**:443–454.

22. Lewis P, Oster H, Korf HW, Foster RG, Erren TC: **Food as a circadian time cue - evidence from human studies**. *Nat Rev Endocrinol* 2020, **16**:213–223 (Issue Data April 2020).

23. Giacchetti S, Dugue PA, Innominato PF, Bjarnason GA, Focan C, Garufi C, Tumolo S, Coudert B, Iacobelli S, Smaaland R, *et al.*: **Sex moderates circadian chemotherapy effects on survival of patients with metastatic colorectal cancer: a meta-analysis**. *Ann Oncol* 2012, **23**:3110–3116.

24. Levi F, Ballesta A, Karaboué A, Huang Q, Focan C, Chollet P, Bouchahda M, Adam R, Garufi C, Innominato P: **Optimizing FOLFIRINOX tolerability in patients with colorectal cancer through dosing irinotecan in the morning for men and in the afternoon for women**. *J Clin Oncol* 2020, **38**:120.

25. Kim JK, Forger DB, Marconi M, Wood D, Doran A, Wager T, Chang C, Walton KM: **Modeling and validating chronic pharmacological manipulation of circadian rhythms**. *CPT Pharmacometrics Syst Pharmacol* 2013, **2**:e57.

26. ** Kim DW, Chang C, Chen X, Doran AC, Gaudreault F, Wager T, DeMarco GJ, Kim JK: **Systems approach reveals photosensitivity and PER2 level as determinants of clock-modulator efficacy**. *Mol Syst Biol* 2019, **15**, e8838.
An analysis of pharmacokinetic and behavioral experiments for the efficacy of a clock modulator inhibiting CK1ε/δ with a systems pharmacology model, which accurately captures the intracellular reactions among core clock molecules and their interaction with external stimuli, light and the clock modulator, using ordinary differential equations based on mass action kinetics. This reveals a major determinant for the modulator efficacy, the endogenous PER2 level, and enables a patient-tailored adaptive chronotherapy

27. Hasselberg MJ, McMahon J, Parker K: **The validity, reliability, and utility of the iButton(R) for measurement of body temperature circadian rhythms in sleep/wake research**. *Sleep Med* 2013, **14**:5–11.

28. ** Walch O, Huang Y, Forger D, Goldstein C: **Sleep stage prediction with raw acceleration and photoplethysmography heart rate data derived from a consumer wearable device**. *Sleep* 2019, **42**.
Application of machine learning to raw acceleration data and heart rate collected with a ubiquitous wearable device. A neural net is trained and tested using both Monte Carlo cross validation and leave-one-out cross validation to classify sleep/wake and sleep stages. The neural net classifier differentiates sleep/wake and sleep stages with approximately 90% and 72% accuracy, respectively, which is higher than that of other machine learning-based classification algorithms such as a random forest classifier

29. * Smets E, Rios Velazquez E, Schiavone G, Chakroun I, D'Hondt E, De Raedt W, Cornelis J, Janssens O, Van Hoecke S, Claes S, *et al.*: **Large-scale wearable data reveal digital phenotypes for daily-life stress detection**. *NPJ Digit Med* 2018, **1**: 67.
Identification of digital phenotypes for daily-life stress detection from large-scale wearable data. This study is a step toward building personalized stress models for precision medicine

30. ** Porumb M, Stranges S, Pescape A, Pecchia L: **Precision medicine and artificial intelligence: a pilot study on deep learning for hypoglycemic events detection based on ECG**. *Sci Rep* 2020, **10**:170.
An analysis of ECG signals using artificial intelligence techniques enabled the identification of hypoglycemic events validated through CGM devices. This study is a step toward the use of non-invasive techniques to assist adaptive chronotherapies.

31. Roberts DM, Schade MM, Mathew GM, Gartenberg D, Buxton OM: **Detecting sleep using heart rate and motion data from multisensor consumer-grade wearables, relative to wrist actigraphy and polysomnography**. *Sleep* 2020, **43**. zsaa045.

32. ** Komarzynski S, Huang Q, Innominato PF, Maurice M, Arbaud A, Beau J, Bouchahda M, Ulusakarya A, Beaumatin N, Breda G, *et al.*: **Relevance of a mobile Internet platform for capturing inter- and intrasubject variabilities in circadian coordination during daily routine: pilot study**. *J Med Internet Res* 2018, **20**, e204.
Monitoring of both rest-activity and chest temperature of healthy subjects and cancer patients with a new mobile electronic health platform (PiCADo). This reveals striking inter-subject differences in circadian time during daily routines

33. Oster H, Challet E, Ott V, Arvat E, de Kloet ER, Dijk DJ, Lightman S, Vgontzas A, Van Cauter E: **The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids**. *Endocr Rev* 2017, **38**:3–45.

34. Lightman S, Terry JR: **The importance of dynamic signalling for endocrine regulation and drug development: relevance for glucocorticoid hormones**. *Lancet Diabet Endocrinol* 2014, **2**: 593–599.

35. Russell GM, Durant C, Ataya A, Papastathi C, Bhake R, Woltersdorf W, Lightman S: **Subcutaneous pulsatile glucocorticoid replacement therapy**. *Clin Endocrinol* 2014, **81**:289–293.

36. Zavala E, Gil-Gómez CA, Wedgwood KC, Burgess R, Tsaneva-Atanasova K, Herrera-Valdez MA: **Dynamic modulation of glucose utilisation by glucocorticoid rhythms in health and disease**. *bioRxiv* 2020, https://doi.org/10.1101/2020.02.27.968354.

37. ** Hall H, Perelman D, Breschi A, Limcaoco P, Kellogg R, McLaughlin T, Snyder M: **Glucotypes reveal new patterns of glucose dysregulation**. *PLoS Biol* 2018, **16**, e2005143.
A machine learning analysis of high-resolution glucose levels sampled through CGM devices identified specific patterns of glycemic responses denominated "glucotypes." These heterogeneous dynamic responses have important implications for the interpretation of diagnostic tests and personalized chronotherapy.

38. Peyser T, Dassau E, Breton M, Skyler JS: **The artificial pancreas: current status and future prospects in the management of diabetes**. *Ann NY Acad Sci* 2014, **1311**:102–123.

39. Fossion R, Rivera AL, Toledo-Roy JC, Ellis J, Angelova M: **Multiscale adaptive analysis of circadian rhythms and intradaily variability: application to actigraphy time series in acute insomnia subjects**. *PloS One* 2017, **12**, e0181762.

40. * Radin JM, Wineinger NE, Topol EJ, Steinhubl SR: **Harnessing wearable device data to improve state-level real-time surveillance of influenza-like illness in the USA: a population-based study**. *Lancet Digi Health* 2020, **2**:E85–E93.
A two-year study of sleep and resting heart rate data from commercial wearables identified seasonal respiratory infections such as influenza, suggesting it is possible to plan seasonal pharmacological and non-pharmacological interventions from wearable data analysis.

41. Shochat T, Santhi N, Herer P, Flavell SA, Skeldon AC, Dijk DJ: **Sleep timing in late autumn and late spring associates with light exposure rather than sun time in college students**. *Front Neurosci* 2019, **13**:882.

42. * Willetts M, Hollowell S, Aslett L, Holmes C, Doherty A: **Statistical machine learning of sleep and physical activity phenotypes from sensor data in 96,220 UK Biobank participants**. *Sci Rep* 2018, **8**:7961.
An analysis of large-scale health sensor datasets with machine learning methods. This identifies sex-specific differences in behavioral patterns and provides an opportunity to investigate the health consequences of behavioral variation.

43. Innominato P, Komarzynski S, Karaboue A, Ulusakarya A, Bouchahda M, Haydar M, Bossevot-Desmaris R, Mocquery M, Plessis V, Levi F: **Home-based e-health platform for multidimensional telemonitoring of symptoms, body weight, sleep, and circadian activity: relevance for chronomodulated administration of irinotecan, fluorouracil-leucovorin, and oxaliplatin at home-results from a pilot study**. *JCO Clin Cancer Inform* 2018, **2**:1–15.

44. * Scherholz ML, Rao RT, Androulakis IP: **Modeling inter-sex and inter-individual variability in response to chronopharmacological administration of synthetic glucocorticoids**. *Chronobiol Int* 2020, **37**:281–296.
Identification of the key determinants of the variability in the response of chronopharmacological glucocorticoid treatment with a systems pharmacology model, which accurately accounts for the reactions among the primary mediators of the hypothalamus–pituitary-adrenal axis and their interaction with external stimuli, synthetic glucocorticoids and light, using ordinary differential equations based on Michaelis-Menten kinetics. This reveals that sensitivity to endogenous glucocorticoid suppression under the treatment varies mainly due to the intersex and interindividual differences in adrenal sensitivity and chronic stress-induced regulatory adaptations in the hypothalamus–pituitary-adrenal axis.

45. Dulong S, Ballesta A, Okyar A, Levi F: **Identification of circadian determinants of cancer chronotherapy through in vitro chronopharmacology and mathematical modeling**. *Mol Canc Therapeut* 2015, **14**:2154–2164.

46. * Hill RJW, Innominato PF, Levi F, Ballesta A: **Optimizing circadian drug infusion schedules towards personalized cancer chronotherapy**. *PLoS Comput Biol* 2020, **16**, e1007218.
An analysis of PK data of the OPTILIV trial of a cancer chronotherapy with a systems pharmacology model, which accurately captures the transport dynamics of anticancer drugs, including irinotecan, from the drug infusion pump to the patient blood, and their pharmacokinetics in colorectal cancer patients using reaction-diffusion partial differential equations. This identifies the major source of inter-patient PK variability, which is critical for personalized cancer chronotherapy.

47. * Stehlik J, Schmalfuss C, Bozkurt B, Nativi-Nicolau J, Wohlfahrt P, Wegerich S, Rose K, Ray R, Schofield R, Deswal A, *et al.*: **Continuous wearable monitoring analytics predict heart failure hospitalization: the LINK-HF multicenter study**. *Circ Heart Fail* 2020, **13**, e006513.
Multivariate physiological telemetry from a wearable sensor and machine learning analytics using the telemetric data provided an accurate early detection of precursors of hospitalization for heart failure exacerbation. Similarity-based model, which is configured to handle the telemetric data including 1-min trim-mean heart rate and respiratory rate, predicts the expected physiological signals of patients. Then, they are compared with the observed remote monitoring data in a cloud platform to identify precursors of heart failure exacerbation hospitalization.

48. Torrente-Rodríguez RM, Tu J, Yang Y, Min J, Wang M, Song Y, Yu Y, Xu C, Ye C, IsHak WW: **Investigation of cortisol dynamics in human sweat using a graphene-based wireless mhealth system**. *Matter* 2020, **2**:921–937.

49. Zhao Y, Wang B, Hojaiji H, Wang Z, Lin S, Yeung C, Lin H, Nguyen P, Chiu K, Salahi K: **A wearable freestanding electrochemical sensing system**. *Science Advances* 2020, **6**, eaaz0007.

50. Peng HT, Bouak F, Vartanian O, Cheung B: **A physiologically based pharmacokinetics model for melatonin–effects of light and routes of administration**. *Int J Pharm* 2013, **458**:156–168.

51. Merchant RK, Inamdar R, Quade RC: **Effectiveness of population health management using the propeller health asthma platform: a randomized clinical trial**. *J Allergy Clin Immunol Pract* 2016, **4**:455–463.

52. Guk K, Han G, Lim J, Jeong K, Kang T, Lim EK, Jung J: **Evolution of wearable devices with real-time disease monitoring for personalized healthcare**. *Nanomaterials* 2019, **9**.

53. McConnell MV, Shcherbina A, Pavlovic A, Homburger JR, Goldfeder RL, Waggot D, Cho MK, Rosenberger ME, Haskell WL, Myers J, *et al.*: **Feasibility of obtaining measures of lifestyle from a smartphone app: the MyHeart Counts cardiovascular health study**. *JAMA Cardiol* 2017, **2**:67–76.

54. Qu M, Duffy T, Hirota T, Kay SA: **Nuclear receptor HNF4A transrepresses CLOCK:BMAL1 and modulates tissue-specific circadian networks**. *Proc Natl Acad Sci USA* 2018, **115**: E12305–E12312.

55. Altman BJ: **Cancer clocks out for lunch: disruption of circadian rhythm and metabolic oscillation in cancer**. *Front Cell Dev Biol* 2016, **4**:62.

56. Vlachou D, Bjarnason GA, Giacchetti S, Levi F, Rand DA: **TimeTeller: a new tool for precision circadian medicine and cancer prognosis**. *bioRxiv* 2019:622050.

57. Wittenbrink N, Ananthasubramaniam B, Munch M, Koller B, Maier B, Weschke C, Bes F, de Zeeuw J, Nowozin C, Wahnschaffe A, *et al.*: **High-accuracy determination of internal circadian time from a single blood sample**. *J Clin Invest* 2018, **128**:3826–3839.

58. Anafi RC, Francey LJ, Hogenesch JB, Kim J: **CYCLOPS reveals human transcriptional rhythms in health and disease**. *Proc Natl Acad Sci USA* 2017, **114**:5312–5317.