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What time is it? A tale of three clocks, with implications for personalized medicine

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The circadian system regulates the timing of physiologic processes ranging from gene expression to drug metabolism. Even when healthy individuals maintain the same sleep-wake and rest-activity schedules, their endogenous circadian time can be up to 5 hours apart, suggesting that the same drug administered at the same local clock time in two patients may be metabolized differently solely due to different time of administration relative to endogenous circadian clocks (i.e., circadian time). Therefore, for better clinical outcomes, we may need to consider the circadian time of the patient. In this commentary, we aim to summarize the commonly used definitions of time as they relate to human chronobiology, highlight their caveats, underscore the importance of using standardized definitions based on biomarkers, and consider how this knowledge may be used for personalized medicine.

In this context, time can be derived in at least three ways:

- Solar: This refers to timing derived from the geophysical light/dark schedule set by the sun.
- Social: This refers to local time, as on a watch or computer. It is derived from a combination of the solar time and societal considerations.
- Circadian: This refers to the time of the endogenous central circadian clock.

We describe differences among these three derivations of time and question the validity of using the derivations interchangeably; for example, when social time is used to approximate circadian time.

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Social time does not equal solar time:

The terms “midday” and “midnight” are associated with solar time; midday is defined as the time at which the sun is at its apex and midnight is defined as the midpoint between sunset and sunrise. Due to how time zones are defined, however, solar time and social time do not always align for at least three reasons [1]: (i) each time zone spans one hour, so only the locations in the center of the time zone are expected to have this alignment and only during Standard Time; (ii) during (Daylight) Saving Time, the difference between social and solar time is increased by one hour; and (iii) a country may choose to be in a different time zone (e.g., Spain, Iceland, parts of China) than what would be expected based solely on geophysical location (i.e., longitude). Thus, waking up at 7am, for example, will result in different light/dark exposure patterns at different times of year in different latitude and longitude locations within a time zone, and in Standard vs. Savings Time.

Social time does not equal circadian time:

Even among individuals living in the same social time zone and maintaining the same sleep-wake rest-activity schedules, there are wide ranges in circadian time (~5 hours in healthy young individuals [2], ~ 8 hours in people with insomnia [3], and even more dramatic differences in patient populations, including patients with circadian rhythm sleep disorders (e.g., some individuals with delayed sleep phase syndrome [4]and free-running or abnormally entrained blind individuals [5]). There may be several reasons for this wide range in circadian time relative to social time, including individual differences in behavior [e.g., self-selected light exposure patterns from both natural (including different seasons) and artificial sources [6, 7]] and genetic factors [8] related to sleep and circadian regulation. These differences may be expressed as morningness/eveningness preference [9] or chronotype [10].

Solar time does not equal circadian time

Artificial lighting allows individuals to change the timing, duration, and intensity of their light exposure to differ from solar time, and therefore affects the relationship between solar time and circadian time (e.g., [11]), since light exposure modulates circadian time.)

Consequences of misaligned time

There are negative consequences to the misalignment of solar, social, and circadian time. The one hour change between Standard and Saving Time is associated with adverse acute and chronic health and safety outcomes [1]. Even less than one hour of circadian misalignment to social time may have adverse consequences: there are health disparities associated with living in the western vs. eastern side of a time zone [12, 13]. Eating later relative to circadian time rather than social time is also related to lean vs non-lean body composition in one study of college students [14] and weight gain in rodents [15]. Finally, the many adverse consequences of misaligned social and circadian times from shift- or night-work or jet lag are reviewed in [16] and elsewhere.

Moving to applications

As principles of chronobiology are applied in medicine, it is important to note that descriptive statistics (e.g., the relationship between X and Y, which are frequently expressed as the mean and SD) do not describe what happens at an individual level. Medical practice (including personalized medicine) requires predictions, which require different statistical methods than used for descriptive statistics. We can try to improve predictions by including known stable individual-level factors that affect biological variability (such as sex and age) as well as additional variable individual-level factors (e.g., one night of poor sleep because of pain or a sick child). In addition to circadian predictors such as phase, phase angle of entrainment, and amplitude, other relevant covariates related to circadian physiology that may be important for personalized medicine may include self-reported preferences (e.g., chronotype) and core clock gene polymorphisms [8]. Many more clinical studies investigating the effects of these circadian and other relevant covariates on medical outcomes (e.g., length of stay, rate of readmission, medication use, side effects) are needed to examine whether there is a "target" circadian phase for interventions for each medical condition.

Another issue in applying circadian timing to personalized medicine is deciding the "allowed" variability in circadian time estimates. The necessary precision may depend on the application. For example, for an overnight flight from Boston to Paris, the light exposure upon arrival could phase advance (as desired) or phase delay (undesired) the traveler because the transition between light exposure causing phase advances or delays occurs during the biological nighttime. Therefore, mistiming light exposure by only 1 to 2 hours may cause a circadian shift in the wrong direction. For other treatments (e.g., light therapy for Seasonal Affective Disorder or non-motor symptoms of Parkinson's, melatonin for hypertension, chemotherapy timed by the circadian clock, small model pharmaceuticals to shift circadian phase), there are not enough data yet to determine how precise the timing needs to be effective beyond the current prescriptions of "morning" or "evening" [17] or over a hours-wide range [18]. The precision needed for interventions can and should be tested. It will be critical, however, to continue to conduct experiments that precisely define circadian phase (even when real-world data currently are not precise); we may have precise estimates of circadian phase and amplitude even in patients available soon.

In addition, the "allowed" variability may depend on the population: in a relatively healthy person, a large variation in estimate of circadian time may not be important for timing an intervention (e.g., medication to lower lipid levels) but in a sick individual there may be a narrower time window of effectiveness. Or, hospitalized patients may have no central (e.g., from hypothalamic) or peripheral (e.g., liver or cardiac clocks) circadian rhythmicity, or altered relationships among central and peripheral clocks, due to side effects of medication or the abnormal pathology associated with their illness(es). Furthermore, the relationships between circadian time and social or solar time may differ in healthy and patient groups and among patient groups, especially those in whom circadian abnormalities may be involved. Therefore, we need to define "normal" before we can define "abnormal" and under what conditions the timing of the circadian system is changed (e.g., in some disease states or in a hospital environment). We need data from populations besides healthy young individuals

studied under controlled conditions. Understanding the cause for extreme points or statistical outliers in a given dataset may reveal useful information about normal and abnormal physiology. For example, genetic variants in sleep timing were identified in patients with Advanced Sleep Wake Phase Disorder (ASWPD) and Delayed Sleep Wake Phase Disorder (DSWPD), in which there can be large differences between social and circadian time [19, 20].

Finally, patient behavior may limit translation to real-world applications, since a patient may not always take a medication at a specific time. Alternatives may need to be designed; one option may be timed release medications.

Assessing circadian time

We need better ways to define and assess circadian time, preferably in real time or close-to-real time and at home and other environments (e.g., schools, health care facilities, work), keeping in mind that all these assessments are markers of circadian time and have their own variability [21]. We need to define which are the best biomarkers of circadian time for prevention, for diagnostic tests, and/or for medications/other interventions since the biomarkers for these three may not be the same.

One major consideration is the use of bedtime or waketime as proxies for circadian time. Researchers may assume that (i) bed time corresponds with darkness and wake time with the onset of light exposure, and (ii) bedtime/sleep time may reflect circadian phase since light and dark timing affect circadian phase. However, a person’s reported bedtime and wake time (e.g., via questionnaire or actigraphy) may be significantly different from the lights-off and lights-on time, respectively, due to in-bed behaviors (e.g., reading before trying to sleep and/or not immediately turning on lights after awakening); Most questionnaires do not differentiate among these different behaviors, and actigraphy cannot distinguish between sleep and quiet wake. Therefore investigators should be careful not to use light/dark, activity/rest, and wake/sleep information interchangeably. In addition, although the sleep/wake cycle is an output of the circadian system, sleep timing is modulated by additional factors, including homeostatic sleep pressure [22]. Chronotype, light levels when awake, age, genetics, behavioral, early vs. late sleep times [23], whether the person is in free-running or entrained conditions [24], also affect the relationship between bed time and circadian time [2, 23, 25, 26].

Current methods for calculating the circadian biomarker Dim Light Melatonin Onset use multiple samples from home under specific conditions or inpatient collections that require later assay. There are two problems: (i) this is resource intensive and (ii) dim light exposure changes the physiology such that melatonin levels may be higher for several hours earlier and longer during the data collection than what the individual experiences under their habitual lives. The same caveat may apply to other measures that require special conditions during data collection. Several methods for assessing circadian time are currently in use or under development that explore the use of data that are less resource intensive to collect, and can be combined novel analytic approaches. These methods include those that use (i) sleep, activity, and/or light levels analyzed with Bayesian statistics, regression/correlation,

prediction, and/or machine learning; (ii) omics-based approaches using one or two samples from invasive (e.g., blood) or non-invasive (e.g., breath, saliva, urine) techniques; (iii) data from wearables (e.g., heart rate, blood pressure, skin temperature); (iv) mobile phone on/off/use statistics or movement monitoring, or questionnaires on mobile apps; and (v) mathematical modeling approaches, including the application of control theory [27]. One issue to resolve for wearables is whether cross-device and/or software versions need to be harmonized. Another factor to consider is the individual's willingness or ability to collect data for a specific time window (e.g., 1 vs 7 days) and whether the data collection is passive (e.g., wearables) or active (e.g., diary, questionnaire). Both nature (e.g., genetics) and nurture (e.g., individual choice of behaviors such as light exposure and sleep timing) affect circadian time and should be included in circadian time estimation procedures. In our opinion, a combination of physiologically-based mathematical models combined with relatively concurrent data from multiple biometric sources, including wearables, will produce the most sensitive and specific circadian phase assessment for an individual.

There are opportunities in many areas for appropriately incorporating circadian time into personalized medicine; these areas include medical/pharmaceutical (e.g., hospital medical record/order entry, pharmacy, and safety/quality offices; insurers), environmental (e.g., lighting conditions at work, institution/hospital, or home), and educational intervention). Important to this endeavor will be a concerted effort from the entire chronobiology community. The considerations discussed above also can be applied to cellular- and animal-model based research to translate the fundamental mechanisms of chronobiology, learned using model systems, to personalized "medicine" for humans and other species.

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