A Wearable Sensor System with Circadian Rhythm Stability Estimation for Prototyping Biomedical Studies

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Abstract—Despite recent growth in the field of wearable devices, persistent collection of data with clear biomedical relevance remains elusive. The majority of products focus on short-term personal fitness metrics instead of long-term biomedical monitoring. The ideal wearable platform for researchers would include flexibility to test different biometric sensors. We present an open-source, modifiable, and user-reconfigurable wearable sensor system capable of enabling biomedical investigations not feasible with currently-available devices. Our armband device has been configured to measure skin temperature, light, and activity across days to detect internal circadian rhythms. Instability of circadian rhythms is linked to risk of many diseases, including mental illness such as depression, and has predictive power for personal affective state, yet its clinical use is slow in adoption in part because of the difficulty in acquiring relevant data. We provide evidence that such measurements are attainable at high resolution, low cost, and with minimal subject burden. Our device was tested with a variety of other sensors, and results indicate that daily circadian stability and hourly ultradian rhythms in core body temperature and hormone concentrations can be predicted from armband data. Future devices will be self-powered and perform automatic data collection to improve data continuity.

Index Terms—Biomedical transducers, wearable sensors, body sensor networks

1 Introduction

Medicine is in the first stages of transforming from a reactive, intervention-heavy model to a future of preventive medicine based on predictive algorithms running on large volumes of individuals' data. The wearable device market is blooming rapidly, with ever-increasing diversity of "smart" devices incorporating a variety of personal and environmental sensors such as heart rate, GPS position, or steps taken. So far however, most of this market is dedicated to personal fitness. For personal data gathered from wearable devices to be of direct clinical use, two criteria must be met. First, the data must capture variables of known medical value, and second, the algorithms parsing these data must be informed by biomedical theory. Failure of the first results in engineers misdirecting time designing components that clinicians and researchers cannot or will not use, and failure of the second results in inefficient use of the data, as random or brute-force pattern detection blindly strives to generate predictive value where solid biological theory could instead light a path.

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Biological rhythms—on the scale of a day (circadian), hours (ultradian), a year (circannual), or a menstrual cycle—guide more than half of human gene expression [1], [2], manifest in every organ system [3] and, due to their cyclic nature, reduce the variance of a state variable (e.g., core body temperature or CBT) by placing it in a known temporal context (e.g., high CBT at noon is healthy, but the same CBT at midnight will cause sleep disturbance). A great deal of research has made clear that people with less day-to-day stability in their circadian biology are at higher risk for a host of diseases, including cancer, heart disease, obesity, addiction, cognitive impairment, and depression [4], [5], [6], [7], [8], [9]. Though the impact of such circadian instability is clear epidemiologically, studies are usually limited to large, invasive equipment or stays in lab or hospital settings. In both cases research focuses on large-scale effects, such as rotating night work shifts, and so any predictive value from more subtle, persistent life-style choices are missed. The cost and effort necessary for these studies limit the populations that can be examined, and their inconvenience upsets the results. Although this is sometimes addressed by journaling, errors in subjective recall may still add sufficient noise to drown out subtle effects.

Biomedically-inspired instrumentation drives the design of all clinical tools and the benefits of reconfigurable engineering systems are well-documented [10], but few published works have combined the two fields to offer the flexibility necessary to support early hypothesis testing when a dedicated device is nonexistant. For some work, "reconfigurability" comes in the form of taking advantage of modern rapid-prototyping tools to iterate design ideas [11]. Closer to our goal, the pulse oximeter in [12] offers a

high degree of reconfigurability and its form factor enables it to be used for a variety of biomedical studies. Finally, the commercial product SHIMMER [13] offers a wide variety of wearable sensing options but its price point and lack of complete open-source documentation are boundaries for researchers who wish to conduct large-scale studies with new and different sensors.

We present an open-source, modifiable, and user-reconfigurable wearable sensor system capable of enabling biomedical investigations that are impossible with currently-available devices. Realized as an armband, the device has been used to test hypotheses in the field of circadian biology research with significant results, including circadian and ultradian patterns currently unreported in the literature.

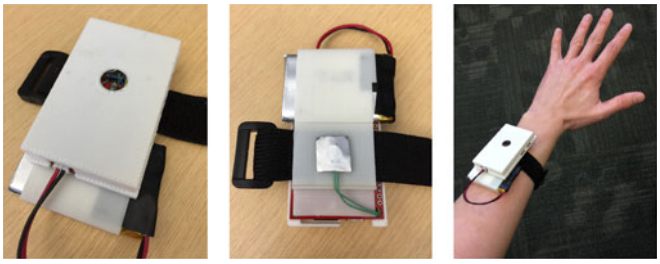
The outline of this paper is as follows: in Section 2 we detail why the human circadian rhythm is worthy of study for its predictive value in affect and disease states thereof, the current state-of-the-art in studying it in humans, and the direction human study should take to enable personal, predictive value for clinicians. The device we have created to enable biomedical researchers to non-invasively study free-living individuals is described in Section 3. This device was used in a biomedical experiment, described in Section 4; the circadian rhythm data it produced along with ground-truth measurements to validate those data are presented in Section 5. Discussion of these results is given in Section 6. In Section 7 we outline our plans for a more advanced device to enable collection of massive volumes of better-quality biomedical data, eventually creating a personalized medicine feedback system to optimize individual health. We summarize and conclude with Section 8.

2 Biomedical Motivation

Because the sun has effectively arced through the sky at the same pace for all of evolution, single cells evolved circadian time-keeping mechanisms that persist in our cells today [3], [14], [15], [16]. Thus humans are complex symphonies of rhythmic cells, which, when playing in time, allow efficient coordination of function across organ systems. Due to the historic stability of the light:dark cycle, mammalian brains use light to daily realign internal oscillators [17], [18] and as a cue for time of year (summer may or may not be hot but, except for right on the equator, the duration of daylight always increases as summer approaches) [19], [20]. The invention of artificial lights have thus introduced cues to which humans are not well adapted. Light at night or sudden changes in the light:dark cycle (as in jet lag or shift work) will cause internal desynchronization [21], [22], [23], [24], [25], [26], as some oscillating tissues adjust more quickly to the change than others. Acute desynchronization impairs learning and memory, sleep quality, and emotional well-being, whereas repeated or persistent internal desynchronization increases the risk for disease across tissues—including cognitive disruption and mental disease [8], [24], [25], [27]. Therefore, interpreting biomedical data within the framework of biological rhythms not only allows more precise detection of a given measure's deviance from expected values, but also allows interpretation in the context of internal synchrony, the maintenance of which will help with disease prevention. As a specific example, depressive illnesses (e.g., major, bipolar, seasonal affective, etc.) feature circadian comorbidities [28], [29], [30], [31], [32], [33]; though the direction of causality is only sometimes from disruption to disease state, the detection of the disruption could provide an early alert for onset of a depressive or manic episode.

The role of chronic internal desynchrony in the etiology of disease is well documented, but the adoption of circadian maintenance by the medical community has not been rapid, in part because of the difficulty in acquiring high temporal-resolution samples with clear biomedical relevance. For example, the hormone cortisol is a central component of the body's arousal and stress response, and disruptions to cortisol impact affective state directly [31], [34], [35], [36], [37], [38], [39]. Cortisol normally follows a circadian rhythm, with a wake-promoting peak in the early morning, followed by diminishing ultradian pulses through the day, then an evening, sleep-promoting trough [31]. Cortisol regulation is disrupted by circadian instability [40], [41], likely playing a role in the etiology of mental illness that also increases with circadian disruption. If clinicians have insight into one's cortisol rhythm, the detection of disruptions before they result in clinical affective disturbance could be permitted. Although, cortisol can be measured in blood, saliva, or feces, few if any patients will suffer to have samples collected frequently throughout the day, or as part of an ongoing medical maintenance process. On top of the very real increased inconvenience and risk such repeated samples would impose on the patient, the clinician would also have to process the samples for analysis, making such an arrangement financially unfeasible as well.

We see a solution to this problem with the incorporation of wearable devices designed to persistently and noninvasively capture data at high temporal resolution, in variables proven to allow inference of circadian state and internal, circadian-modulated systems. To this end, we recently demonstrated the design and implementation of a reconfigurable, wearable device capable of measuring skin temperature, light exposure, and locomotor activity continuously across several days on a free-living individual, with only 1 min of user time required per day to swap batteries [42]. These variables have been shown to allow prediction of internal circadian state [43], [44], but had not previously been shown to do so from a single, non-invasive device. Here we show an improved version of the device, capable of higher temporal resolution and increased precision without cost to battery life. In addition, we show one week's continuous data collection, with important detectable differences between one subject with an early circadian phase, showing signs of stable circadian entrainment (alignment to and prediction of the environment's light:dark cycle), and another with a later phase, showing signs of minor but persistent circadian disruption. Finally, we collected salivary samples and CBT measures across two days of constant routine from the first subject. These measures allowed comparison of CBT (a standard measure of circadian rhythmicity) and salivary cortisol to the output of our wearable device. These comparisons enabled the generation of an algorithm to predict CBT and cortisol rhythms in a free-living individual instrumented only with our wearable device.



(a) Top (b) Bottom (c) Worn

Fig. 1. Photos of current device showing light port (a), skin temperature plate (b), and device in use (c).

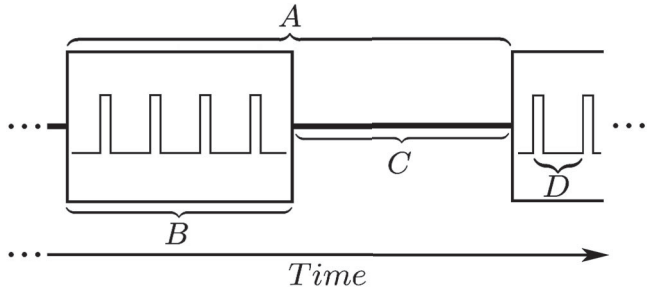


Fig. 2. Data collection timing diagram. Each pulse represents all three sensors sampled and logged. Time A is the time between the start of each sampling window. Time B is the duration of each sampling window. Time C is the time spent outside of a sampling window, when the device is in sleep mode to conserve power. Time D is the time between samples. Times A, B, and D are user-defined via an interactive Python script, and Time C results from the combination of A, B, and D.

3 Device Description

Our wearable device is realized in an armband form factor and designed to be reconfigurable; at the start of the project, there were several possible approaches to collecting relevant circadian biology data and the device needed to be easily modified to test each one. While circadian biology was the intended application, the device's open-source nature now allows it to be easily modified for other biomedical or ecological investigations requiring persistent, non-invasive on-body sensing. Interested investigators can find complete designs of the device at http://www.eecs.berkeley.edu/~db/taffc2016.

3.1 Hardware

The core of the device is an NXP LPC2148 ARM7-based PCB (Logomatic V2, SparkFun, Niwot, CO, USA). Starting with an off-the-shelf board kept initial costs and build time low and allowed quick replacement when damaged during testing. The board was enhanced to include sensors to measure the three aforementioned analytes relevant to detecting circadian state: distal body temperature (DBT), activity, and light exposure. To support I2C communication with the activity sensor, the STAT1 LED current-limiting resistor, R5, was desoldered to free up that pin for use with I2C SCL signals. I2C SDA signals were available via pin breakout labeled "BSL." Sensors and their interface circuits were chosen to be as simple as possible to maximize the potential for low-cost, large-population monitoring with similar devices. Sensors were verified to function as expected before experimental data collection.

The PCB and sensors were combined with a 3D-printed enclosure, fastening strap, 2 GB SD card, and rechargable 3.3 V 1,000 mAh lithium-ion battery to form the complete device capable of logging several months of data (Fig. 1) and requiring battery changes between 1 and many days, depending on logging frequency settings. Its dimensions are approximately $7 \times 4 \times 2$ cm and it weighs 52 g with battery (31 g without), making it appropriate for comfortable wrist wear (Fig. 1c). Since [42], an elastic fastening strap has made long-duration wear more comfortable, and the 3D-printed enclosure has been improved to add resilience against day-to-day activities.

3.2 Operation

Users set sampling frequency, duration of sampling window, and length of low-power sleep mode before beginning another sample window with a config file on the SD card. These settings, illustrated in Fig. 2, are contained in a binary configuration file generated by answering questions posed by a custom Python script. For each sample, ADC values for temperature and light are taken and the current accelerometer reading is requested over the I2C bus. While the device is in sleep mode, temperature and light are ignored but any activity that generates an acceleration greater than 0.1 g-force sends an interrupt to the microcontroller to increment a counter. Comma-separated sensor values with appropriate headers are written to an ASCII text file on the SD card, with a new log file created each time the device is powered on. The log files are parsed with a second custom Python script, which are readable by a Matlab script to convert reported digital values into real-world data. Conversion is performed as per sensor datasheets and analog-to-digital converter interface circuit scaling factors, after which the data is available for analysis.

3.3 Firmware

Rudimentary open-source firmware was provided with the off-the-shelf board which further shortened engineering time, though this work represents a significantly more advanced use requiring extensive firmware modifications. The firmware included with the ARM7 board was augmented to include I2C communication, sleep mode, interrupts, custom data logging formats, and adjustable sampling periods, as well as disabling extraneous features like LEDs to conserve power. Digitally-controlled power gating of sensors was written into the firmware, but using it proved unnecessary to meet the 24 h battery life target. These features were deemed necessary for wearable sensor sampling, and future biomedical studies in fields besides circadian biology may also benefit from their inclusion.

3.4 Sensors

3.4.1 Temperature

A negative temperature coefficient thermistor (NTCG163JF-103F, TDK Corporation of America, Lincolnshire, IL, USA), was attached to a thin 1.5×1.5 cm aluminum plate with non-conductive thermal epoxy (Arctic Silver Thermal Adhesive, Arctic Silver, Visalia, CA, USA) and affixed with foam tape to the inside of the band such that the aluminum plate would make skin contact when worn (Fig. 1b). This

configuration maximized thermal conductance between the thermistor and the wearer's skin while minimizing thermal loss to the rest of the device and ambient environment.

The temperature sensor was initially designed to provide accuracy greater than clinical thermometers in use today [45], but our initial model suffered from an offset (more offset at the start of a window, exponentially approaching no offset after about 15 minutes of 10 Hz sampling, then resetting to the initial offset value after the microcontroller entered and exited low-power sleep mode) that caused smearing of temperature readings within a given sampling window [42]. According to [46], assuming a size 0603 thermistor affixed to metal in contact with a thermal reservoir such as a human arm is analogous to a a thermistor mounted to a PCB, and knowing the thermistor nominally dissipates 0.5 mW of power, we can expect about $0.032\,^{\circ}\mathrm{C}$ of temperature increase due to self-heating. The thermistor dissipates a fixed amount of power for at a given temperature, so we also expect this offset to be constant after power-up. However, we observed the time-dependent offset in each window even after hours of device use. Later testing showed that the time-dependent offset's size was ameliorated by reducing the ADC sampling rate from 10 to 1 Hz.

The interface circuit was also improved with $3\times$ gain plus voltage offset to focus on a specific temperature range, $21\,^{\circ}\mathrm{C}$ to $51\,^{\circ}\mathrm{C}$, with a resolution of about $0.03\,^{\circ}\mathrm{C}$ resolution when connected to a 10-bit ADC. This well-surpasses the thermistor's own claimed accuracy of $0.1\,^{\circ}\mathrm{C}$, which further improved measurements compared to [42]. These enhancements have made the temperature sensing of the device sensitive enough not only for detection of daily circadian rhythms, but also hourly ultradian rhythms as described in Section 5.

3.4.2 Activity

Activity was recorded by a triaxial digital accelerometer (MMA8452, Freescale Semiconductor, Tempe, Arizona). It was determined that any one of the three axes were sufficient to infer activity level; the axis horizontally perpendicular to the arm was chosen for analysis and acceleration along other axes was ignored. Communication to the microcontroller took place over I2C when awake to measure instantaneous acceleration, or via interrupt signal during low-power sleep mode to count all instances the device experienced acceleration beyond 0.1 g-force.

The accelerometer installed in this device is capable of capturing both greater temporal resolution and greater dimension depth than was deemed necessary for the application of the device to discerning circadian phase. Circadian studies traditionally rely on gross measures of locomotor activity, such as 10 min bins of acceleration counts across the day. Initially the device revealed foot steps and hand motions, but this extraneous information was eliminated when accelerometer's output was pared down to mere 1-dimensional counts. This generated savings of storage space and power while not impacting the biological application. This choice is an example of the kinds of optimization possible when device development is coupled to a specific biological framework.

3.4.3 Light Exposure

A photoconductor (CL9P5L, Clairex Technologies, Plano, Texas) was used to determine light exposure. It was attached to the surface of the device on the hypothesis that visible light reaching the wrist is a good approximation of the blue light entering the wearer's eye and stimulating the melanopsin ganglion cells that contribute to circadian rhythm maintenance [18]. The data from this sensor needed only be qualitative to be useful, so the logarithmic response of the photoconductor didn't need to be linearized. A resistive divider was built to roughly divide the range of the ADC into five brightness regions, which can be subjectively described as dark, dim, indoor night (artificial light only), indoor day (artificial light augmented by diffuse sunlight, and direct sun light.

Early tests with the light sensor confirmed our ability to see consistent logarithmic changes in resistance with light intensity as expected. Repeated measures outside under noon-time sun, inside under fluorescent laboratory lighting with and without daylight nearby, inside under low light, and concealed in a dark box allowed for the designation of consistent resistance ranges to different common lighting conditions. Although quality (e.g., wavelength decomposition) of light is not a feature of this device, the greater intensity of daylight than office lighting, and regressions against known sunrise-sunset times allow confident disambiguation of most light sources (i.e., the light intensity at all but sunrise and sunset may be enough to infer the source of light as artificial or natural in most circumstances; the presence of smooth transition curves under natural light at sunrise and sunset further help differentiate the source of light at those times, when intensity alone is insufficient—see [42]).

4 Experimental Methods

The armband device described in the previous section was designed generally to enable new biomedical studies through simple, reconfigurable, cost-effective wearable instrumentation. It was also designed to be specifically configured with sensors to study human circadian rhythms using a single, non-invasive wearable device. In this section, we describe the experimental methods used to determine the effectiveness of this non-invasive armband-based approach to measuring human circadian stability.

4.1 Constant Routine

To unmask underlying circadian rhythms without disruption from exogenous factors, Subject A spent 2 consecutive days in a lab room under the following controls: Subject A had iButton thermal loggers (Thermochron iButton, Embedded Data Systems, Lawrenceburg, Kentucky) taped to left and right armpits, wrists, ankles, and inner thighs. These were set to collect data at 1 min intervals continuously from 05:30 on the first day. The subject also began their seven-day collection with our armband device, which was set to collect data from each sensor once per s for 10 min every 30 min as illustrated in Fig. 2. Every 30 min from 05:30 to 22:30, timed to just before the armband recording window onset, a saliva sample was collected from the subject, after which the subject then ate a snack (50-100 calories) and drank 100 ml of water. Subject A had ~400 lux light exposure (overhead office lights) from 05:30 until 17:30; for collection and feeding after lights-out at 17:30 dim (~5 lux) light was provided. Subject A stayed in a comfortable sitting or reclining

position from 05:30 to 22:30, after which the subject lay flat for 7 h of sleep in total darkness. The subject was allowed to use the restroom only during the light phase each day, and only immediately after the armband collection window had closed, so as to provide maximum time for physical recovery from any deviations movement might have caused to the subject, thus minimizing artifacts in the collection either before or after restroom use. The subject opted to do this twice each day. The subject was allowed to bring materials to help pass the time, but nothing that, in their judgment, would be too stimulating, so as to avoid causing a cortisol reaction. No such deviations appear in the data.

Subject B was unable to submit to constant routine observation, and so this subject's CBT were taken at home. IButtons were taped into both armpits, and the subject was advised to stay seated or reclining, to eat small, light meals, and to avoid anything too stimulating, although saliva was not collected. Light was not controlled, but this is unlikely to impact the CBT recorded, as light exposure adjusts future predicted daily phase, meaning the rhythm of the following day could be affected, but not the rhythm being currently recorded. The subject indicated compliance with these conditions.

The purpose of this experiment was only to demonstrate the investigative possibilities using a device with sensor capabilities as described in section 3. As only one subject was run in each constant routine, all findings are tentative until larger sample populations can be investigated.

4.2 Salivary Cortisol Assay

The concentration of cortisol was determined by ELISA (salivary cortisol ELISA kit, Rocky Mountain Diagnostics, Inc., Colorado Springs, Colorado). All samples from both days were run in the same assay, with a control curve of known cortisol concentrations run at the beginning and end of the assay to account for any drift in results caused by the time taken to pipette all samples at all steps. Standard curves were sensitive from 0.001 to 30 ng/ml, and the intra-assay variability across the two control curves was 9 percent, with the second curve consistently higher than the first. Sample concentrations were therefore back-calculated by comparison to a best-fit curve of the mean of the control curves. No samples were outside of the sensitive range of the assay, and so no corrections or omissions occurred.

4.3 Armband Recordings and Analysis

Subjects were advised to wear the armband at all times except when showering. Batteries were swapped after the end of a recording window, and recording was restarted on the new battery exactly 30 min after the previous recording window's onset time. Subjects successfully executed this and no loss of data is apparent across seven days for Subject A and five days for Subject B. At the end of the recording sessions, the armband data were collected, concatenated, and processed in Python and Matlab to generate a single activity, temperature, and light log for each subject. To generate predictions of daily CBT and cort from daily DBT, the median DBT was generated. This curve had the median subtracted, and was then fit by the sum of sines function in Matlab. This same fitting process was applied to constant routine CBT and cort, as well as for each daily DBT. The coefficient ratios from constant routine to median DBT were then applied to the coefficients of the daily DBT to generate coefficients for that days CBT and cort fit functions. The median value was then added back in to generate the final prediction for each day. These sum-of-sines fits also allowed comparison across the different sampling frequencies used for each measure in constant routine (e.g., 1 per 30 min for cortisol, 10 min per 30 min with the armband, 1 per min with iButtons), as shown in Figs. 3 and 4. Correlations were run using the Curve Fitting Matlab 2015 app, and predictive algorithm generation was done in Matlab 2015. Plots were made in Matlab 2015 and arranged in Adobe Photoshop.

5 Biomedical Results

The high temporal resolution of the sampling allowed for clear detection of days in all variables (Fig. 3a). The days in constant routine resulted in stable daily waveforms of DBT and CBT (Fig. 3b), as well as typical salivary cortisol curves (Fig. 3c). The subsequent five-day recording also revealed ultradian patterns in distal body temperature (Fig. 3d) which did not correlate with peaks in locomotor activity ($R^2 < 0.05$), as would be expected if these transient peaks resulted from heat generated by muscle use. The existence of human ultradian DBT rhythms has received passing mention in the literature [47], but the data presented here appear to be one of the most complete descriptions of a single subject's free-living rhythms yet published. This finding turns out to be critical to the generation of predictive models, as alignment of ultradian peaks across days more accurately reveals the similarity of an individual's internal state than does locomotor activity or time of light exposure, both of which are more easily masked by artificial (exogenous) schedule constraints. In Subject A, the alignment of these daily ultradian DBT waves was strikingly high, as revealed both by the closeness of fit of the median daily DBT to the median of the daily DBT fits (Fig. 3e) and by the phase-alignment of the daily DBT fits to the same clock time (Fig. 3f). These stable daily DBT fits reveal a clear phase relationship from this free-living rhythm to the CBT and cortisol rhythms taken under constant routine (Fig. 3f).

Although an investigator could apparently infer cortisol or CBT phase by "eye" in Subject A, a more algorithmic approach is needed for the predictive inference to scale across days and subjects. The ratio of the coefficients of two sum-of-sines fits can be used to algebraically transform one fit into the other, described in detail in the methods. Briefly, to automate the prediction process of daily CBT and cortisol concentration from daily DBT measures, the ratio of coefficients of the median daily DBT fit and the median CBT or cortisol fit were applied to each daily DBT rhythm along with a linear corrective factor. This generated CBT and cortisol curves for each free-living day based on that day's DBT data, but influenced by the subject's CBT and cortisol rhythms uncovered during constant routine measurement (e.g., Fig. 4a). The output of the predictions falls into the expected range and circadian and ultradian wave form of CBT and cortisol, but shows daily variance.

Subject B showed signs of persistent circadian disruption in light and activity records, allowing a comparison of the clean waveforms found with Subject A to see if

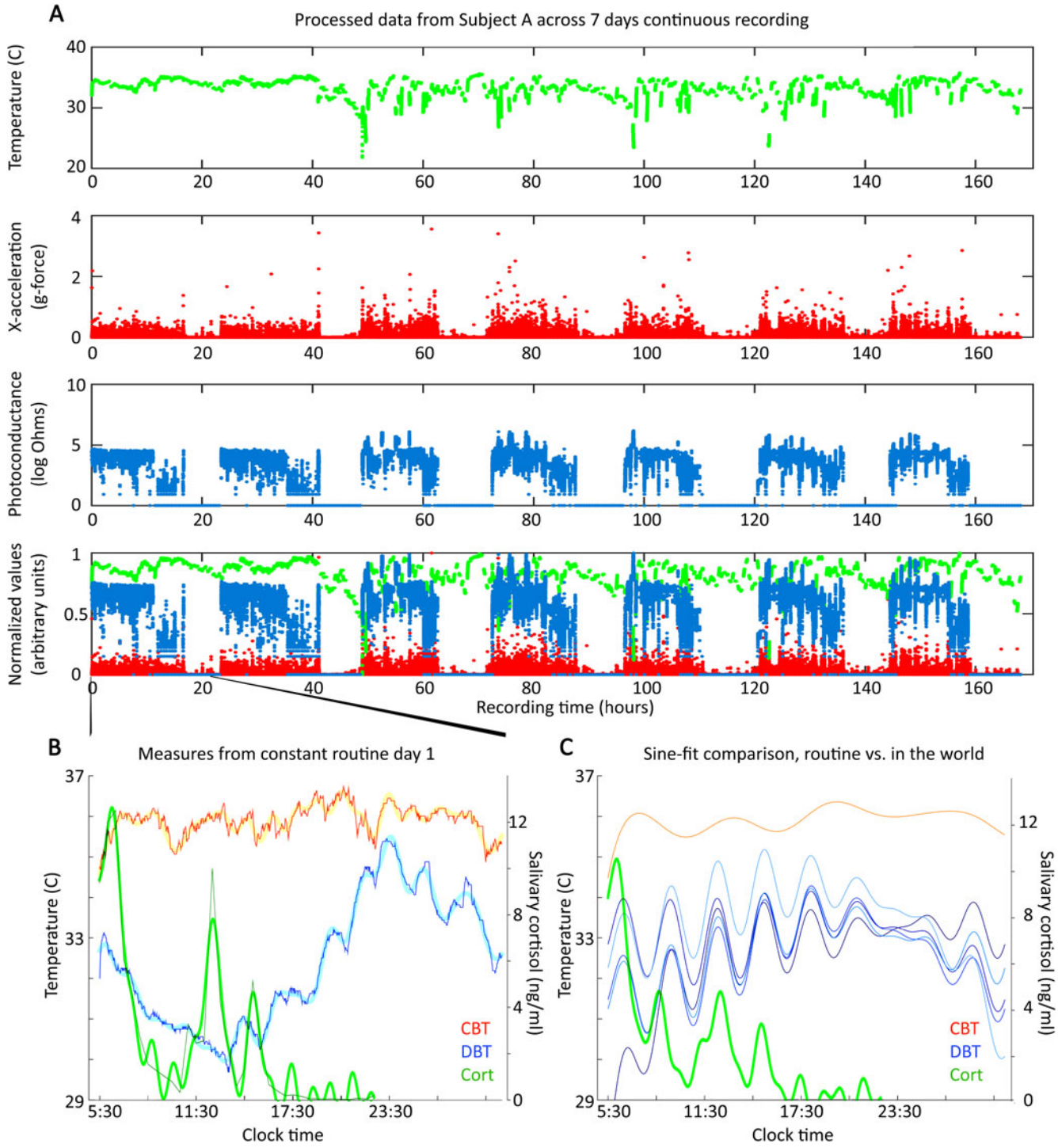


Fig. 3. High temporal resolution recording of Subject A across seven days allows comparison of constant routine to free-living measures of circadian and ultradian rhythms. (a) Unfiltered, continuous recording by our armband across two days of constant routine and five subsequent days of free-living (temperature in green, acceleration in red, photoconductance in blue; overlay below to show relative temporal alignment). (b) Raw recordings (thin lines) and fit curves (sum of sines - thick lines) from one day of constant routine (core body temperature in red, distal body temperature or DBT in blue, cortisol in green). (c) Average fit lines from constant routine (CBT in red, cort in green) compared to armband temperature fit lines of all five free-living days, revealing phase-alignment of ultradian DBT rhythms as measured from our armband to ultradian rhythms of CBT and cort rhythms uncovered in constant routine.

perturbations would arise in Subject B. Though both an N of 1, we find these comparisons valuable as a first validation of expectations and of the data being produced by our device. These comparisons are also important as hypothesis generators for identifying differences to validate in larger sample groups in the future using future generations of circadian logging tools. As expected, though a circadian pattern emerges in the daily DBT rhythms of Subject B, the alignment of ultradian peaks is far less precise (Fig. 4c), suggesting a lack of internal circadian synchrony. Subject B's CBT also shows a 24 h oscillation, but has more high-frequency variance than Subject A (Fig. 4c). Using the same predictive approach as with Subject A, Subject B's daily CBT was predicted and shows a clear circadian pattern

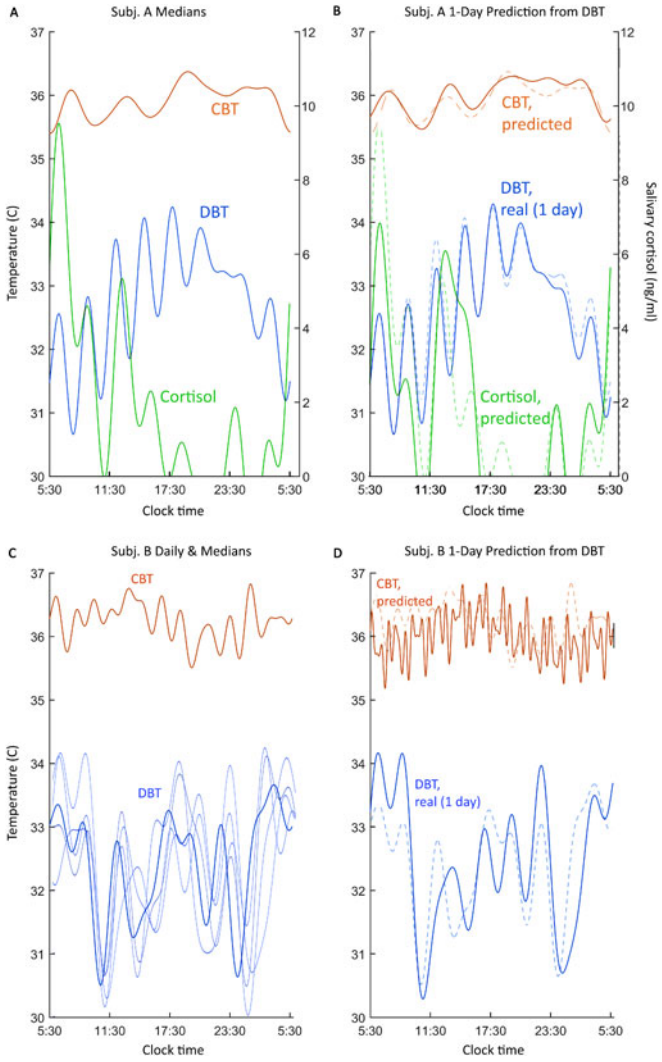


Fig. 4. Algorithmic predictions of core body temperature from distal body temperature and salivary cortisol fall within expected range. Top: Median CBT (red) and cort (green) sum-of-sines fits from two days of isolated, constant routine shown with median of five days of normal, free-living DBT from armband for Subject A (A). Medians from (A) shown as dotted lines at (B) for comparison to predicted values for one specific day of free-living, based on transformations of that day's DBT recording. Note the close fit. Bottom: Median CBT (red) and DBT (blue) for Subject B (Subject B did not record cort) (C). Light blue lines are each of five free-living days' DBTs recorded by the armband; dark blue line is the mean those five days. Note the lack of ultradian rhythm alignment as compared to Subject A in Fig. 3c. Predicted CBT of one specific day of free-living calculated from that day's DBT (D). Dotted blue line is the mean line from (C). Note that while the range and circadian rhythm are appropriate, a high-frequency component arises as an indication of the lack of daily DBT alignment.

with temperature estimates in the expected range and phase, but with a high-frequency component that is not likely to reflect the true biological state (Fig. 4d). Thus, although circadian phase and amplitude appear to be extracted from DBT, artifacts appear to arise from the higher variance of daily DBTs, making the prediction less precise moment-to-moment. Obviously a smoothing algorithm could be run to eliminate such high-frequency features, but we share them here because such artifacts might arise systematically as heuristics of internal instability. The validation of features that identify individuals at risk for internal circadian desynchrony is a tantalizing possibility.

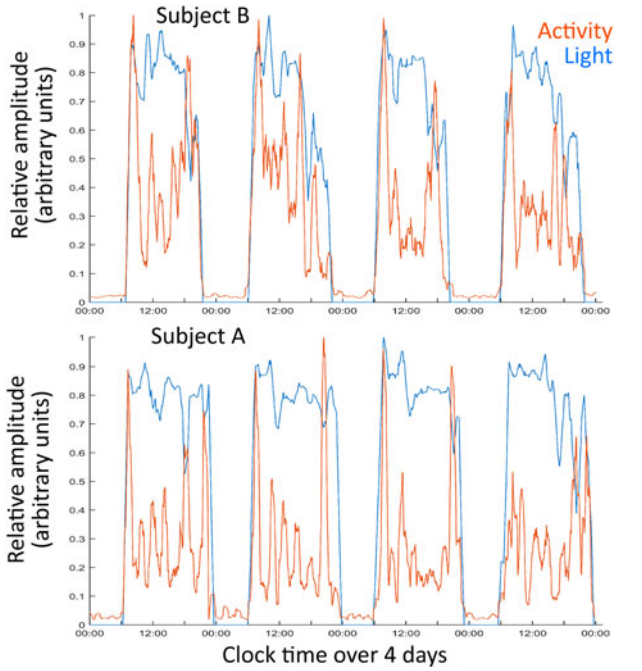


Fig. 5. Armband measures of activity and light exposure show less stable ultradian structure than temperature measures, but reveal probable sleep windows, individual manifestation of chronotype, and could indicate severity of circadian disruption. Both subjects' light (blue) and activity (orange) records over four free-living days are given. Both records begin at midnight and end at midnight 96 h later. Note the persistent lag of light and activity offset of Subject B relative to Subject A, likely identifying both subjects as different chronotypes.

Although DBT waves proved adequate for predictions of CBT and cortisol, light and activity records also provide insight of value to description and prediction of adverse affective events. Fig. 5 shows four days of free-living record for Subject A (top) and Subject B (bottom). Both show clear daily rhythms, but personal phase differences are captured. First, it should be clear from these data that measures such as "steps per day" given by commercial pedometers do not capture the structure or variance of each subject's routine. Second, both subjects show tight coupling of lights-off and lights-on with the onset and offset of the consolidated bout of daily activity. This allows for the identification of "probable sleep windows," (PSWs) defined as times during which activity and light are both at trough values. These PSWs provide a simple measure of sleep duration, sleep duration variance, and daily activity-phase stability. For instance, Subject A appears to sleep for 7 h 25 min per night, +/− 34 min, while Subject B sleeps for 6 h 12 min per night +/− 15 min. Subject A is also defined as an early chronotype, or "lark", because Subject A leaves PSW around 05:15 each morning, and enters the PSW at 21:37 on average each night. By contrast, Subject B is identifiable as a late chronotype, or "owl", because the PSW begins at 23:39 and though it ends at 05:54 (Fig. 5), the subject reports that this is from an alarm.

The comparison of light and activity records also corroborate the temperature finding that Subject A has less internal desynchrony than Subject B. Subject A's activity onset consistently precedes light onset, by an average of 26 min each day, whereas Subject B's activity onset is the same as light onset to within 1 min each day, again, due to the use of an alarm. This suggests that Subject A has stable circadian

entrainment to the environment, and is woken by an internal clock (the subject reports not using an alarm clock, which further substantiates this observation). This is in contrast to Subject B's activity and light onset, which are constrained by work obligations, so that sleep duration is shortened and the subject's internal clocks are daily having to adjust to light input before that input is expected (before the subject's natural circadian wake time).

6 Discussion

Our imputation of reasonable CBT and cortisol rhythms, and our demonstration of the ability to infer chronotype, PSWs, and daily stability across individuals open many potential avenues of exploration with specific regard to affect. For instance, manic depression carries a comorbidity of circadian and sleep disruptions, with manias typically characterized by increased activity and lack of sleep, and depressions characterized by decreased activity and either a lack of sleep or an overabundance of sleep [28], [48]. Why sleep manifests differently in some depressive episodes is not clear, and while some bipolar patients show a rhythm in their affective states, many do not. Once broadly validated, a device like the one we present could be used to explore the possibility that individuals with different manifestations (rhythmic or not, high or low amplitude episodes, etc.) might be identifiable and separable by qualities of their daily rhythms, with implications for targeting medications or treatments. In addition, descriptions of circadian and sleep disruptions could be traced across episodes to explore the relationship of causal and resultant disruptions, enabling a more clear understanding of the relationship between circadian stability and affective well-being. For example, here we found evidence that Subject A had a more stable entrainment of the circadian system, and so woke in anticipation of the start of the day (activity onset preceded light onset), whereas we found a lack of light-anticipatory activity in Subject B, suggesting this subject's internal clocks were in a more reactionary state upon wake. While chronic circadian insult is often framed in terms of large-scale daily changes, (e.g., rotating night shifts, transatlantic jet lag, etc.), there is no reason to think that small but persistent circadian shifts, as Subject B appears to be experiencing daily, do not also become risk factors for mental illness or loss of subjective well-being.

Similarly, sleep and circadian rhythms tend to lose coherence with advanced aging. Given the impact circadian disruption has on healthy individuals, it is not surprising that geriatric populations are more at risk of emotional and cognitive damage as their internal timing systems degenerate [49], [50], [51]. A device such as ours could be used in the short run to identify individuals with less stability, and try to identify environmental factors—such as light at night, inactivity, or insufficient day light exposure—that might contribute to a downward spiral of circadian stability. In the long run, working with aging populations may help develop predictors of the onset of biorhythmic decline, or even help to identify at-risk populations before decline manifests; the device could then aid in studying the effects of efforts to exogenously bolster an individual's circadian stability, for instance by enabling precise measures of compliance with light:dark schedules or timed activity regimens to reinforce internal clock coherence through regular external feedback.

As previously noted, experiments capturing small circadian shifts over long periods are impossible with traditional methods. By using a device designed with circadian biology and minimal-invasiveness in mind, these questions become straightforward analyses once deeper validation and a user base exists, and provide hope for more subtle, more predictive patterns being discovered to aid long-term stability of affective health.

7 Future Directions

For broader use (years of recording across a wide population and/or accessibility to young children or the technically disinclined) cost and user burden still need to be reduced to near zero. Therefore the device presented here is also the starting point for future generations of devices able to gather circadian data over long periods without user input, maintenance, power and data management, or obstruction of the user's day-to-day life.

In the short term future, we plan to use a moderately smaller and more capable second-generation device to validate networking capability, user compliance and ease-of-use (for instance, how tightly the device must be worn to gain consistent and usable temperature readings), and accuracy of predictive algorithms across more subjects, covering different demographics, such as age, sex, body-mass index, etc.

A later-generation version of the wearable presented here is being concurrently developed as a fully-integrated wireless sensor system in the spirit of the Smart Dust mote concept [52]. Such a device is intended to be small enough to be worn unobtrusively, use thermal gradient, kinetic, and/or solar scavengers to obtain power, and sense data relevant to circadian biology as described in this work. It may also sense other health-relevant biomedical and environmental analytes benefiting from reliable, periodic sensing such as pulse oximetry and air pollutants. It is also intended to utilize existing work in wireless body-area networks [53], [54], and low-power mesh networks [55] to minimize power budget by communicating only with nearby network nodes.

In the long term, we hope to contribute to systems in which user data would be aggregated and analyzed by a doctor-in-the-loop feedback system to provide patient advice based on individual and aggregate data, and allowing the device's sampling rate, etc. to be tuned to maximize health feedback benefits for the individual. A conceptual network layout is given in Fig. 6. These features would allow continuous monitoring without depending on the user for maintenance, and the fully-integrated form factor may reduce the likelihood of the user removing the device and breaking continuity of data. Enabling continuous data gathering from each user will maximize the potential to identify patterns that can be used to optimize long term health and affective well-being across a lifetime of exposure to the modern, disrupted circadian environment.

8 Conclusion

For the entire history of life, availability of sunlight has shaped the evolution of behavioral "temporal niches"

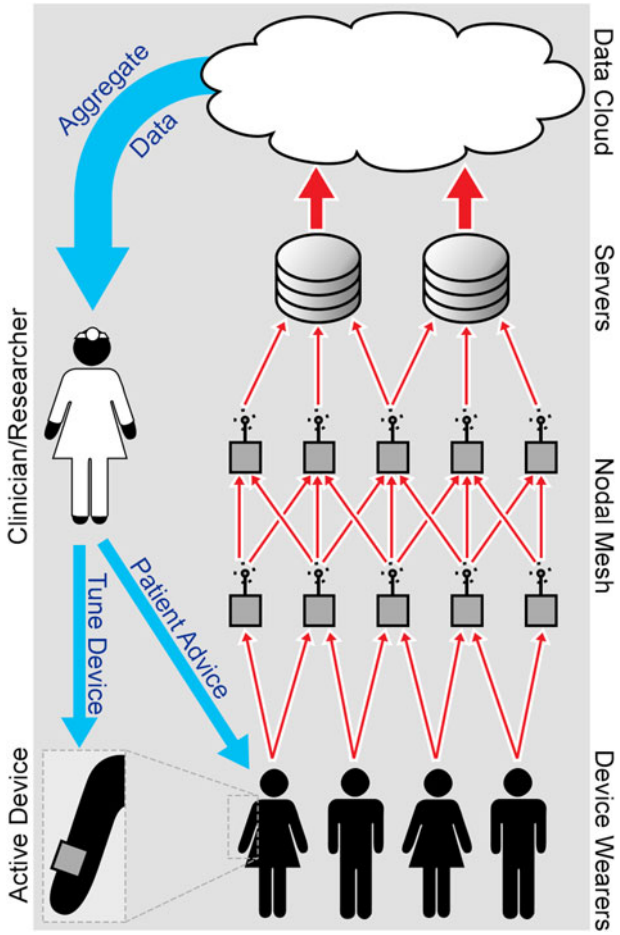


Fig. 6. Conceptualized ambient network to collect and process wearable health monitor data, including unattended collection and aggregation of data through nodal networks, and cloud processing of data to minimize user and clinician/researcher burden. The network also includes a doctor-in-the-loop capability to enable medical professionals to advise patients based on patterns found in individual and aggregate data, and tune device configuration as application areas or patient needs change.

(e.g., diurnality in humans) and been the most reliable marker of seasonal change. Therefore, biological visual systems evolved to enable both image formation (i.e., seeing) and correctly timed daily and seasonal biological changes (e.g., sleep timing and increasing fat mass in shortening days, respectively). The integration of electric lights into modern life therefore disrupt biological timekeeping mechanisms. For this reason, the current urban environment presents a number of challenges to human health, such as shift work or light exposure at night, discussed in the introduction. Over a lifetime, such disruptions increase the likelihood of disease in every organ system, from cancer to arthritis to depression. However, the manifestation of circadian rhythms and the impact of artificial circadian disruptions are different in different people. Though the reality of negative health impacts from circadian disruption is now clear, studies in modern populations to identify best practices for different demographics (or individuals) are blocked by a lack of available data. Wearables provide a non-invasive mechanism of gathering such data, but are most useful only if researchers can iteratively experiment with the kinds of data acquired: starting from their knowledge of biological systems and developing with successive experiments. As the result of several trials, the armband we present here exhibits a useful configuration for those interested in studying circadian disruptions in people living freely in their environments.

Our device is capable of measuring distal body temperature, light exposure, and activity, and we present evidence that it can be used to track users' sleep and predict the circadian phase of a user's core body temperature and cortisol rhythms, as well as estimate their internal circadian synchrony relative to others. Normally such measures would require frequent, invasive measurements and/or considerable subject burden, whereas our device requires only 1 min per day to change the battery and upload data. More validations are clearly needed to assess accuracy of this specific device across users, changes by demographic, compliance issues, and so forth. Nevertheless, our findings are positive indicators that such a device leads to more precise and higher resolution measurements at less expense and with minimal disturbance of the subject. Though these findings cover just two individuals—one early "lark" chronotype and one late "owl" chronotype—they also provide support for the hypothesis that our device can recognize individual daily rhythms, and that statistical analysis of these rhythms can be used to monitor a patient's circadian stability, with application for predicting short-term onset likelihood and long-term future risk management of mental health episodes or mental degeneration.

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