Wearables Database and Analysis Platform (WDAP) to study sleep, circadian rhythms and mood

Platform: We have developed a database and app to collect wearable data globally and anonymously (see Figure 1). An individual's phone or wearable can contain an enormous amount of physiological data. Our first goal was to create a way in which users would be motivated to send this data to us securely and receive benefits to them. The first version of this is the "Social Rhythms" app available for free for Apple devices. The app also works with a variety of wearables, including the Apple Watch, Fitbit, and MiBand. When users download the app, they answer several basic demographic questions including age, gender, and race. For this specific app, we also asked them when they began social distancing.

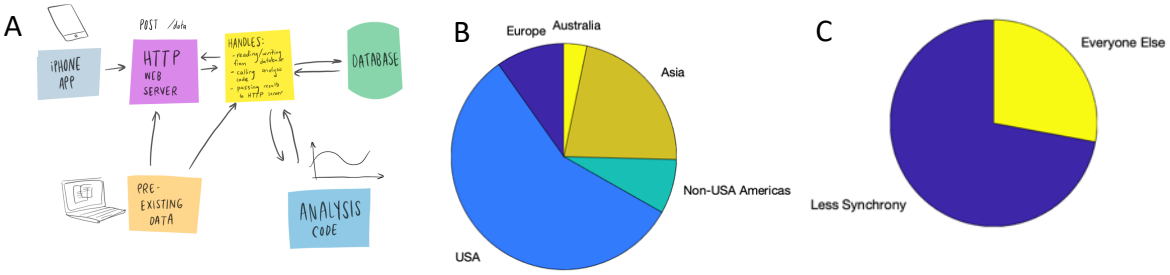


Figure 1: Wearables Data and Analysis Platform: (A) Computing infrastructure. (B) Pie chart showing geographic distribution of participants who submitted wearable data. (C) Comparison of the regularity of circadian rhythms of users before and after they began social distancing. Social distancing dramatically increased circadian desynchrony in most users.

Users can then send us back data; our default is the past two years of activity, heart rate, and sleep data, but users can choose which and how much data they would like to share with us, and can remove their data from our servers at any time. We have developed this platform so that the information is sent anonymously. Once on our servers, data is analyzed with the latest tools we have created (see Analysis section below). After this is completed, users receive a push notification saying that a report is ready and they can view the information. The data in the report is sent anonymously. As noted, users can remove their data from our servers at any time with the app. If they leave their data, new reports will be sent to them when available. They can also be contacted through the app to see if they would like to participate in more detailed studies at other labs, which are identified. We currently have data from over > 1,000,000 days of measurement.

Analysis: Our modeling work has developed tools to extract critical information from heart rate about activity, sleep, and circadian timekeeping (see Figure 2) (*4*). A similar research effort could be applied to breathing rate, temperature, and neurocognition as data on those systems become available through wearables (*5*). Activity, sleep, and circadian timekeeping are the largest factors affecting heart rate and most other wearable signals, although their prominence may vary in exceptional cases, for example, during disease. Accounting for these three factors first will allow better prediction of infection from the residual signals (*5*). Among the foundations of our work are advances in signal processing and mathematical modeling of physiological systems. To highlight one method, published in *Science Advances (6)*, we developed a new modeling framework for studying coupled oscillators, and in a paper published in the *Journal of Biological Rhythms*, we used this new method to create a model of the human circadian clock (*7*).

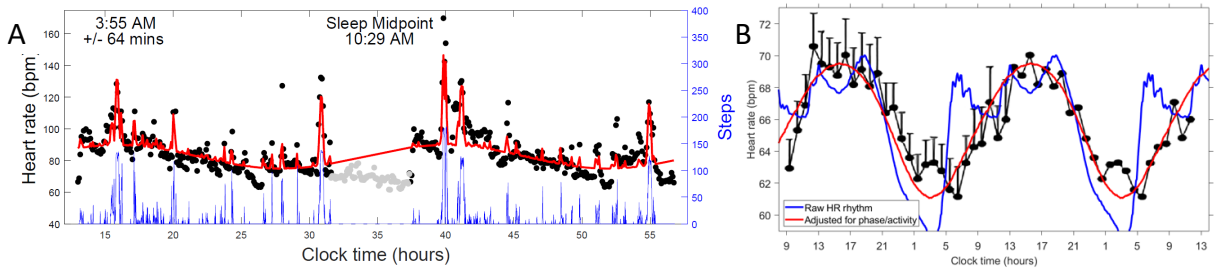


Figure 2: Method of extracting circadian phase from ambient heart-rate measurements: (A) Sample heart-rate (hr) measurements from a medical intern (black dots) along with minute-by-minute step counts as measured by a Fitbit. Heart-rate measurements during sleep are plotted in grey since they are not used in our analysis. HR adjusted for sleep, and activity is shown in red. The timing of midsleep and the timing of the trough of the adjusted hr rhythm with estimated error is also shown. (B) Average daily hr rhythm while awake using over 100,000 days of hr data from medical interns (blue). The average adjusted HR rhythm (red) is shown in (A) and compared with the hr rhythm measured in a carefully controlled laboratory setting (*8*).

However, societal effects such as changing work schedules can lead to racial disparities, stress, and comorbidities, and might even be the triggers for disease (*9*). They are part of the fundamental basic science of disease. We have begun understanding how this sleep and circadian misalignment affects mental health in a population of > 1,000 patients at Michigan Psychiatry we track.

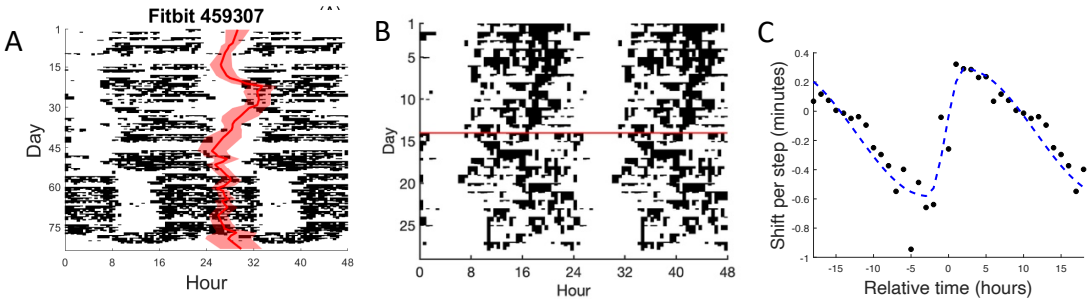


Figure 3: Dynamics of circadian rhythms in the real world: (A) HR rhythm and actogram for a medical intern. Daily steps are plotted for every 48 hours. Each day's data is double plotted. The subject begins a shift around day 55. Our estimate of the phase of the hr circadian rhythm is also shown in red +- 1 SD. Interestingly, this intern's hr circadian clock does not adjust to the new schedule, while the hr circadian clock of other interns does (data not shown). (B) Actogram of an individual who submitted data to WDAP and reported being COVID-symptomatic. The red line indicates the beginning of their isolation. Isolation is followed by significant circadian disruption, as shown by the timing of the start of daily activity. (C) We characterize the circadian pacemaker of users who submit > 50 days' worth of data. Here, we plot a phase response curve showing the resulting phase shift in circadian timekeeping for steps taken at different times of day with respect to their hr circadian pacemaker.

Additionally, the markers that are measured by wearables are different from those typically used in clinical studies. While they usually are noisier, they can have the advantage of being more relevant. The effects of activity on heart rate have previously been well characterized. Other factors that can be studied in relation to the data from wearables include the following.

1) Circadian: Wearables also can collect data much more efficiently than laboratory studies. To illustrate this, we consider the human circadian clock. Heroic human-subject studies have characterized properties of the human circadian clock, for example, its average rhythm in heart rate (*10*), period, and phase response to exercise (*11*). We were able to reproduce all these studies using existing wearable data in our database with our analytical tools (see Figures 2 and 3, which contain figures we recently generated in response to reviewers' comments on the included manuscript (*8*)). Additionally, we found significant variation in the timekeeping in different individuals. Our algorithms were able to personalize these predictions and indicate how other individuals would respond to shift work. Additionally, in two companion papers in collaboration with the Henry Ford Health System, (*12*), we found that permanent night shift workers may have a fundamentally altered circadian timekeeping system. However, models were able to correctly predict circadian phase based on wearable data in individuals with typical daytime schedules (Figure 4).

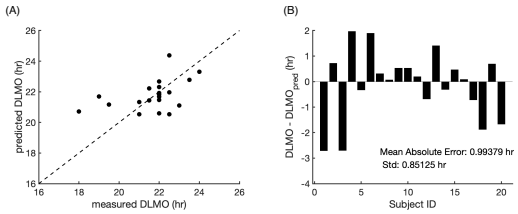


Figure 4: Testing circadian phase prediction in shift workers: Here, we predict the circadian phase based on ordinary differential equation models we have built of the human circadian clock. The individual wore an Apple Watch for one week before a laboratory measurement of circadian phase using dim-light Melatonin onset (DLMO). Our models used data from the Apple Watch to predict DLMO within an error of about 1 hr. Measured vs. predicted DLMO is shown in (A) along with the difference in DLMO prediction (B).

2) Sleep: We showed how societal effects on sleep could be measured through wearables (see included paper (*13*) and Figure 5). This was based on data we collected from an app (Entrain) that we developed to help travelers overcome jetlag. Entrain was installed in > 200,000 devices. We also have developed and validated algorithms to score sleep from the Apple Watch. Our algorithms were released open-source; we suspect they played a significant role in Apple's proprietary algorithms that score sleep in the latest Apple Watch release.

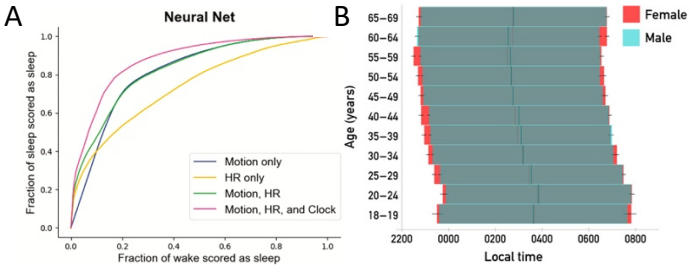


Figure 5: Predicting real-world sleep: (A) Receiver operating characteristic curve showing the accuracy of our ML algorithm to predict sleep from Apple Watch data (*4*). We score 90% of epochs correctly, with 60% of actual wake epochs and 93% of actual sleep epochs. This open-access algorithm compares well with the accuracy of proprietary algorithms used in the wearable industry. (B) Timing of sleep and wake by age as self-reported by users of our Entrain app (*13*). We found that women schedule more sleep than men, a finding that was subsequently validated by other studies.

3) Mood Dynamics: We showed how the mood dynamics of individuals suffering from bipolar disorder could be classified into three categories (*14*). The equations for our model are:

$$dD_t$$

$$= a_D(b_D - D_t)dt$$

$$+\sqrt{2a_D\sigma_D D_t}\left(\sqrt{1-\rho^2}dV_t + \rho dW_t\right)$$

$$dM_t = a_M(b_M - M_t)dt + \sqrt{2a_M\sigma_M M_t}dW_t$$

and are further described in Figure 6. Testing these categories, we found that one of them had a much higher rate of suicide attempt than the others. We are currently looking into the circadian rhythms and sleep of these individuals, believing these factors are essential for the etiology of bipolar disorder. Preliminary work we published in *Nature Communications* suggests that it is GSK3β, a target of lithium, that controls

the circadian rhythm of the electrical activity of neurons (*15*). This gives a molecular target to follow up on.

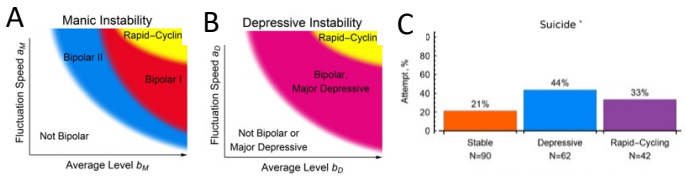


Figure 6: Characterization of mood dynamics through mathematical models: Each individual's weekly mood scores were fitted to a mathematical model (equation 1) of mood characterized by depressive (variable D_t) and manic (variable M_t). Fitted parameters of the model were used to phenotype individuals with bipolar disorder based on the parameters related to (A) mania and (B) depression (*16*). (C) Using a Markov-chain model for mood dynamics, we were able to classify bipolar subjects into three categories. Testing these categories, we found that the depressive category has over twice the rate of a suicide attempt as the stable category (*16*).

We are currently monitoring how medical interns use our circadian predictions (*17*).

Future applications include correcting circadian phase and sleep for those suffering from addiction, and studying racial disparities in sleep and circadian timekeeping, for example, with Michigan's Poverty Center. The University of Michigan Health System is also giving free Apple Watches to thousands of its patients. We have access to this dataset and the patient's medical records.

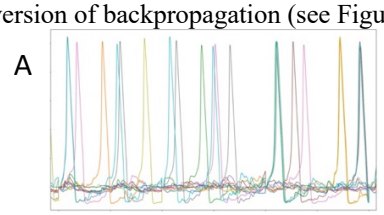
Large Scale Neuronal Simulation

Background and Results: Machine Learning (ML) is impacting many areas of neuroscience. One fundamental limitation of this computational technique is that it is built on elements that only vaguely represent actual neurons. To address this, we have created HHANN, a new kind of ML that is based on mathematical models of the ionic currents that generate action potentials in neurons as pioneered in the work of Hodgkin and Huxley (HH).

HHANN is based on large-scale models of networks of neurons as used in many areas of computational neuroscience. The model that is used for each neuron can vary based on the ionic content of the neurons under study. So, for example, we use models of cortical neurons when studying cortex (*18*), and models of suprachiasmatic nucleus (SCN) neurons when researching biological timekeeping (*19*). Their link to ML is that we use ML techniques, such as modified backpropagation, to train the models and determine the connectivity of the neurons. Aspects of ML are required since neuroscience is far from resolving the connectivity of thousands of neurons rapidly in the laboratory.

The benefit of this new approach is that models can give accurate predictions of the underlying neural networks that generate many of the functions of the brain. So while traditional ML approaches could learn a simple task, our framework not only already knows this task, but also shows how it is changed when different ionic currents or neuronal types are used in the model, when various neurotransmitters or neuropeptides are present, or when a drug is administered.

The reason previous researchers have not tried this approach is the much higher computation cost of HH models when compared with the elements of ML. We have addressed this with new computational methods that can simulate millions of HH model neurons on desktop computers rapidly on GPUs. Additionally, we have built strategies to train these models using stochastic search algorithms (see included paper (*20*)) or a new unpublished version of backpropagation (see Figure 7).



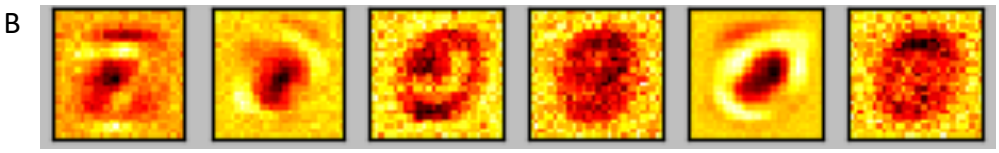


Figure 7: Hodgkin–Huxley Artificial Neural Networks (HHANN): We develop a new form of artificial neural networks based on mathematical models for neurons characterizing their ionic currents as done initially by Hodgkin and Huxley. (A) A sample plot of the voltage of several neurons in an HHANN. Spikes are shown as well as lateral inhibition. Different mixtures of ionic currents can be used. We trained the model on the MNIST dataset, which consisted of handwritten digits. Basis functions (B) show how five hidden neurons respond to different parts of the visual field. Darker colors indicate excitation.

As ANNs have provided excellent models for static visual signals, HHANN naturally extends these models to spatiotemporal patterns since HH models naturally include temporal dynamics. We have built such models for subconscious vision, which lead to the intriguing hypothesis that the SCN, the center of mammalian circadian timekeeping, also is an important center for subconscious vision, particularly gaze control (*20*).

Future Work: Our goals for this platform include continuing to incorporate neurophysiology, particularly the structure of the human brain. Using Hiroki Ueda's CUBIC database (*21*), we have included data on the position of every neuron in the mammalian brain into an HHANN. We have also added paracrine signaling to HHANN through new methods to solve the diffusion equation on GPUs quickly. This gives a "whole brain" HHANN, which can be used to study complex phenomena like sleep (See Figure 8). In preliminary work, we have seen that the dynamics of paracrine signaling (e.g., through VIP) can significantly affect the waves which travel across the brain. How to optimize such a network remains a key challenge because of its computational cost, and so we will continue to maximize the performance of our simulation methods.

One way to address the sizeable computational cost is to blur individual neurons into a population density where we study the probability that any neuron is in a particular state. We published a symmetric particle method to accomplish this (*22*) and have new, more accurate asymmetric particle methods and level-set methods. Thus, each region of the brain is treated as a population density, and these regions can be connected through data from fMRI (see Figure 8). But most importantly, these kinds of models can be directly fitted to fMRI data. Very impactful work has recently addressed the fitting of a neuronal model to fMRI observations (cite Murray), but this work used simplified neuron models that did not account for the ionic currents within neurons.

Another application of HHANNs is in mammalian sleep. We are currently training an HHANN with cortical model neurons to reproduce slow-wave sleep. Once this is completed, we will simulate how changes in ionic currents affect sleep. This will be compared with data from Hiroki Ueda's and Steven Brown's group on how slow-wave sleep is changed in animals with mutations affecting key ion channels that play roles in sleep regulation.

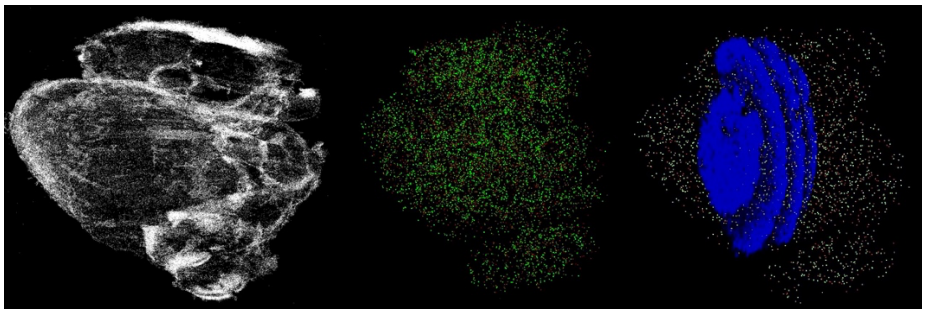


Figure 8: Whole-brain simulation with HHANNs: We incorporated the spatial position of neurons in the mouse brain from the Ueda lab, as shown on the left plot. The Allen Brain Atlas gives coarse connectivity between different brain regions. One timepoint from a sample simulation is shown in the middle plot. Green dots indicate the peak of an action potential. Neuropeptides and neurotransmitters can also be incorporated into this framework. The plot on the right shows a simulation, similar to that in the middle, with the neuropeptide concentration shown in blue. Traveling waves, as seen in slow-wave sleep, are seen.

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