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Recent trends & applications of big data science in chronobiology

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Abstract

With the advent of sequencing technologies, now we have observed rapid advancements in biological research. Avenue of big data science steered the development of many new areas of interests with life science researchers. Approaches using big data mining and machine learning (ML) along with other well-established methods of genomics, molecular biology and biotechnology may be implemented with researches in chronobiology. Methodologies demonstrating usage of these techniques with “omics” studies have shown a noteworthy impact on the results of the same. On the other hand, data science unaided will not reject the need for a considerate understanding of the field of research, nor can such approaches substitute the need for researchers and analysts. Hence, so far understanding with this region of investigation is significantly important. It is obvious that the familiarity which has been generated via chronobiology and the applications of various tools resulting from big data science has backed up the acknowledgement of the various patterns and immense biological rhythms reported in organisms. The present text goals to create novel and vital applications in the coming future through chronobiology research orchestrating with big data science.

Keywords: Chronobiology, bioinformatics, artificial intelligence, machine learning, big data

Introduction

Chronobiology is encapsulating beautiful sciences of bodily rhythms; these rhythms controls the biological maintenance of many living organisms. Also referring to biological clocks, these cycles are always seen in certain pattern of recurring and regularly occurring events with specified intervals. Further, not only these rhythms provide organisms with the challenge of survival but also guides their evolutionary developments [1]. Such cyclical variations are seen in a varied range of time periods, which may vary by day to week to months or even a year. Constant evolution over the time has incorporated organism-specific biological rhythms adequately supporting various phases of development in a lifetime. Many researchers reported these clocks in wide assortment of forms such as, biochemical, physical or even behavioural [2, 3].

Physiologists have classified their domain pertaining to frequency of event happening i.e., ultradian, circadian, and infradian rhythms [4]. These are classified as per duration, circa viz. once a day (*Latin*), circadian rhythms it refers, by definition to rhythms with periods between 20 and 28 hours. Therefore, infradian refers to refers to rhythms of >28h. In fact, all denominations (circaseptan, circannual, etc.) always refer to a nominal period (e.g., 1 week or rather 168 hours) and a range (in that case, +/- 2 days or rather 48h). Same for ultradian, these are those biological rhythms (e.g. feeding cycles) with a period much shorter (i.e., frequency much higher) than that of a circadian rhythm. Ultradian rhythms include wide diversity of short-range events such as firing or neurons which happens over milliseconds or heart beats happening over minutes' period [5]. Yet, another kind of biological rhythms are diurnal rhythms, a circadian rhythm that is synchronized with the day/night cycle.

Circadian rhythms – the most studied one and why?

Chronobiology encompasses a big question of theoretical interest i.e., how various alterations in the body of organisms (like as physiological, biochemical, psychological, behavioural or physical) are controlled endogenously.

This has been remaining a major motive of chronobiology researches so far. Among the discussed three kinds, circadian rhythms remain to be favourite of many biologists studying this domain. One of the most dramatic features of the world in which we live is the cycle of day and night. Correspondingly, almost all species exhibit daily changes in their behaviour and physiology. These circadian rhythms are not simply a response to the 24-hour changes in the physical environment imposed by the earth turning on its axis but, instead, arise from a timekeeping system within the organism. This timekeeping system or biological clock, allows the organism to anticipate and prepare for the changes in the physical environment that are associated with day and night, thereby ensuring that the organism will “do the right thing” at the right time of the day. The biological clock also provides internal temporal organization and ensures that internal changes take place in coordination with one another. Hence, these are the one of most well suited rhythms for experimental studies. Also, these rhythms establish minimum requirements for data sampling and intervals of sampling around the clock or during the daytime or other intervals of relevance for harvesting information from time series to enable usable BIG data. For example, it may be comprising of an oscillatory set-up, together with a central pacemaker, the SCN nuclei present in the hypothalamus, and many peripheral oscillators located in many tissues and cells, such as cardio-myocytes, fibroblasts, smooth muscle cells, and vascular cells [6], abdominal adipose tissue [7], and skeletal tissue [8]. The steadiness and synchronization of this mechanism supports the body to foresee events and behaviours required to sustain homeostasis.

Chronobiology is not specific to humans or animals

Studies involving rhythms are not limited to animals or humans, many reports for such studies are available in the plant kingdom. Plant experiments including *Arabidopsis thaliana* and *Populus trichocarpa* indicates that most of the transcriptomic profile is subjected to circadian control [9]. The concept of the certainty for such kind of regulation, which further led to the development of chronobiology was given by Jean-Jacques D’Ortous, who showed that the daily rhythm of the closing and opening of plant leaves was happening even in complete absence of light. After this finding, many showed that biological rhythms are mere replications of external environmental variabilities.

What chronobiology entitles today?

Modern-day chronobiology research covers areas related to biological functions, health and disease along with the rhythms associated with them. All these forms the major cluster in bio-medical researches giving upsurge to the branch of chronobiology in a broader term. Day to day researches and experimental studies are giving birth to multidisciplinary researches in the area of chronobiology i.e., chronomedicine, chronopharmacology, chronotherapy, chronopharmakinetik, chronoenergy, chronoanaesthesia and so on.

Emergence of Chronomics studies

Concept of chronomics came after researchers started realizing the existence of phenomenon such as desynchronization i.e., disturbances in circadian rhythms of various living organism. One prominent example for the same is phenomenon of “Jetlag”. Such desynchronization is proved scientifically to cause serious damage to sleep cycle, normal

physiological disruption, diabetes and other metabolic diseases including development of various forms of cancers and tumours. The overall mechanisms (both endogenous and exogenous) controlling these phenomena of desynchronization and synchronization are fundamental to understanding and development of chronomics [10-12]

Prediction of chronomics

Earlier and even today there is not much highlight in the mathematical prediction of chronomics, but by the conventional methods of hormonal assay and like of those comes into play. Nonetheless, the latest advances in sequencing technologies and use of genomics information have directed the creation of many sorts of biological models and genetic framework towards cracking anonymities of chronobiology. Use of ‘omics’ sciences along with more and more complex biometrical methods are giving huge impetus to big data sciences in chronobiology and fastening up the emergence of chronomics. Wide usage of how big data methodologies of genomics, machine learning (ML) and artificial intelligence (AI) must be incorporated with chronobiology are discussed in forthcoming text.

What pertains BIG data?

Big Data is collection of data which you cannot store or process using the traditional database system within the given time frame. There is a lot of misconception while referring the term big data, we use the term big data to refer to the data that is either in gigabytes or terabytes or petabytes or anything that is larger in size. But this does not define the term big data completely. Big data can be of many types, concerning to biological research here, it’s important that how we define it. As far as our interests are concerned, Genomics is now well-thought-out a legitimate big data field – just one whole “human genome sequence” produces approximately 200 gigabytes of raw data. If we manage to sequence 100M genomes by 2025, we will have collected over 20B gigabytes of raw data. Now the question arises, what are the opportunities for using such a brilliant and insightful resource in chronobiology research. Also, what tools and methods can enable this? This is exactly what we offer to our readers in forth coming text.

Big data science and chronomics

The big data in a literal sense dictates the genomics information of any living organism in expressions of sequences, more like a mathematical code of that organism. Transparency and the huge potential of big data is not realised completely yet in the understanding of many living organisms. Knowledge about big data science is extremely needful for the management and sustainable utilization of animal genetic resources [13]. In quest of enhanced understanding of various rhythmicity associated metabolic disorders, the “omics” science approaches can be implemented. “omics” terms define the integrated use of genomics and its adjacent arms like transcriptomics, proteomics and metabolics [14]. The temporal i.e., time structural mapping of ever increasing biological diversity has steered creation of another ‘omics’ science i.e., Chronomics, firstly mentioned by Sir Halberg *et al.* Halberg also recommended the joint practice of both experimental technique and bioinformatics to identify and map expectation of experiences [15]. Thus, hereafter the methods of chronomics could beautifully quantify any biological phenomenon in

terms of a biological watch and its occurrence as rhythm. This also makes possible the replication of said events to better comprehend any complicated natural or pathological phenomenon [16]. This can be wrapped up like a beautiful orchestra of experimental and biometrical methods (bioinformatics, omics etc.) together producing music out of complicated biological occurrences.

Bioinformatics and chronomics:

Traditionally many studies in medicine had been piloted using methodologies of chronomics. Such as in the case of measurement of blood pressure – a classic example yet subtle in understanding [17]. Chronomics here allows the tracking of changes in blood pressure and associated dynamics over a comprehensive circadian cycle and thus facilitates the accurate diagnosis of various blood pressure related disorders. This diagnosis can prime effective treatment and prevent other heart related diseases. Bioinformatics and chronomics may offer a way of predicting or understanding the communication among the components involved in any biological system. This can further be used to boost predictions over a wide scale and to relate a specific component with the various frequencies of biological rhythms and modulations [18]. The diagnosis here may also be linked to specific limits of rhythms of any undertaken biological

system. Bioinformatics tools which can be provided in a cost-effective manner to assist in different aspects is not yet explored in cattle breeding programmes. High density single nucleotide polymorphism (SNP) chips now act as significant bioinformatics tools for improving and developing dozens of species of domesticated animals [19]. In our study, we have attempted to describe methods of reducing the number of SNPs in order to develop a panel specific to the breed. Considering chronomics, the major tools applied to analyse, understand, and categorise the rhythmic events are taken from bioinformatics. Using these methodologies various chromosomes are mapped and grouped together [20]. This resulting in the accurate prediction of correlation among the rhythmic frequency and changes in biological rhythms. Chronomics needs to be improved with many latest bio-informatics technologies, including the creation of specific instrumental functionality suited to this modern area of study.

The assistances of information technologies are unquestionable, particularly biotechnology and bioinformatics for the management, treatment, storage, analysis, and picturing of very large quantities of data assembled from the databanks within the pursuit of “omics” sciences. Following table (Table 1) illustrates the various recent and past studies undertaken with bioinformatics to study rhythmic events.

Table 1: Recent and past studies undertaken with bioinformatics to study rhythmic events

<i>Team & Year</i>	<i>Work</i>
Johnston <i>et al.</i> 2012	They analyzed the transcriptomic profile of mice for the period of 24 hours and identified the occurrence of circadian rhythms in fat cells i.e., adipocytes
Lockinger <i>et al.</i> 2004	Using the approaches of proteomics they aimed at evaluating the circadian time structure of various circulating peptides that are usually secreted by peripheral neuronal cells
Passos <i>et al.</i> 2012	They noted that during the progression of adaptation to physical exercise, the body is reorganized and subsequently returned to cycling rhythms of sleep very similar to its state before the onset of physical exercise using methods of ‘omics’
D. Hadrich, 2006	Novel tools in bioinformatics have been developed by them, like as EUCLIS (EUCLOCK Information System), so that many new kinds of circadian models can be studied and explored
Roenneberg, 2011	They developed the advanced architecture of the databank-database that was used in pioneering liver cell studies, called as the HepatoSys

Artificial intelligence and Chronobiology

Big data sciences with chronobiology are subjected to interdisciplinary study and cannot emerge as a viable area to work without artificial intelligence influences. Big data science's main goal in chronobiology is to solve problems emerging within biological sciences using IT (Information Technology) based techniques such as artificial intelligence (AI), data mining, artificial neural networks (ANN), Bayesian statistical models and complex evolutionary algorithms. Intelligence can be described as a primarily human capacity to accomplish tasks that computers and animals typically consider difficult. Artificial Intelligence (AI) is a discipline that aims to perform certain tasks with computers. As are reports of its association with Biological Intelligence, AI is becoming increasingly common. Such arguments are also made to suggest better odds of success for a given technology, based under the premise that AI systems that imitate Biological Intelligence processes will be more successful.

A case study with AI in hands

Bioinformatics also conducts research on human health. Through this research, it is important to explain how each mechanism of a natural cycle functions under rest conditions or in various circumstances, such as through physical tension or in a pathological disorder. Thus, each compound and its

associated interactions can be depicted on a metabolic map (known as integrated representation of standard human body metabolism), which also offers a full map of the metabolome we usually consider a ‘sportomic’. The physiological and metabolic reactions to exercise are complex and briefly conditioned. Because of the wide volume of data extracted from this research, the bioinformatics tools i.e., MarkerLynx (Waters Corporation, USA) and ChromaLynx (Waters Corporation, USA) were used to classify and quantify the related metabolomic compounds in compliance with a National Institute of Standards and Technology (NIST) library database [21, 22]. The latest techniques used in molecular biology for high-throughput analyses, such as microarray and RT-PCR, provide a tremendous deal of results. With such massive datasets, the focus was on shifting from conventional statistical research to modern data mining methods [23, 24] that derive their origins from analytics, artificial intelligence, and machine learning [25].

Machine Learning and Chronobiology

Machine Learning (ML), as the name implies, is in essence, an AI division through which the computers know how to solve a problem themselves, as opposed to a series of specific guidelines about how to solve the problem. Typically, this is accomplished through studying new rules by multiple

attempts for the said task, and through the feedback of input on the level of progress. It is the first underlying link between modern AI and Biological Intelligence developments [26]. We weren't born with the ability to recognize the things that surround us, nor (mostly) were we given laws that enabled us to recognise certain items. We saw a very large amount of items often labelled (think parents pointing out objects to a child) and benefited from the experience. Same is the analogy used for the development of machine learning methods.

Machine Learning works in a very same mode. Computers are taught and shown billions of pictures highlighting many kinds of objects unless they slowly learn how dogs, cats, hats etc. look like. While this similarity may seem trivial and superficial, it is by far the most important concept which drives AI's current success. While the correlation between artificial and biological intelligence goes far deeper, there remain significant distinctions. The mechanism that has permitted computers to acquire these powerful skills i.e., Artificial Neural Network is straight away stimulated by neural networks in brains (biological) [27, 28].

Case study with machine learning in chronobiology:

Several laboratories have established "clock genes" in the last two decades that communicate to produce underlying molecular oscillations. Though, many characteristics of circadian molecular functioning remain unsolved. Here, researchers used a basic "machine learning" method to classify new clock genes by scanning the genome for candidate genes that share clock-like features such as rotation, broad-based RNA expression of tissue, in vitro circadian behaviour, genetic associations and species-wide homology. Genes were classified by their similarities to recognized components of the clock, and candidates were tested and checked in vitro for proof of clock activity. One candidate gene, called *CHRONO* (Gm129) associated with the clock's master regulator, *BMALI*, which interrupted its transcriptional function. They also reported that Chrono-knockout-mice was showing extended locomotor commotion rhythms and it was getting up gradually late and late every next day. This study has shown that *CHRONO* interferes with *BMALI*'s capacity to recruit CBP, a bonafide histone acetylase and the circadian clock's primary transcriptional coactivator [29].

Big data mining and chronobiology

Data mining is focused on the automation of knowledge discovery, which is not easily perceptible but included in a database. The usage of data mining in a database is considered the central phase in a larger cycle named Knowledge Discovery Databases (KDD), which involves many other phases that can be separated into pre- and post-processing measures [30]. KDD pre-processing phase involves many steps, like as incorporation, filtering, data curation, and the assortment of pertinent attributes for the job of data mining. Post-processing phase via KDD modifies and improves the collective understanding of the results which will be obtained from data mining. Data mining further can also be applied in problems of gene expression rhythmic activities [31]. Chronobiological experiments used data mining or, more precisely, task-clustering to derive suitable trends from the given data about gene expression in humans, rodents and plants [32]. To discuss few, Filichkin *et al.* demonstrated that enquiry of the rhythmic transcriptomic profile of plants could assist simplify the resemblances and modifications, along with the shared points of regulation in both

monocotyledonous and dicotyledonous plants [33]. For this goal, the researchers applied a combination of various oligonucleotide micro-arrays and data mining methods to inspect the daily biological rhythms in the pattern of gene expression with rice variety i.e., *Oryza sativa* ssp. japonica and one more plant, poplar (*Populus trichocarpa*). The transcriptomic profile and data associated with rhythm were witnessed in diverse periods and under variable temperature set-ups. Other studies have identified circadian gene expression control in the rat's skeletal muscle, white adipose tissue, and lung tissue. In another study by Almon and co-workers, expression of micro RNA was studied in the gastrocnemius muscles in a uniform yet diverse series of 54 animals that were sacrificed at different time period within the designated 18 cycle comprising of 24 hours [34]. Data mining of this data led to the identification of a total of 109 genes those were expressing with rhythmicity and further got grouped into eight different categories in respect to corresponding 11 functions in the framework of time-based expression. Several research in the area of wellbeing and health have been carried out using data processing techniques to explain pathological processes. A research by Wood *et al.* used data from OncoPrint, an electronic microarray platform that provides a collection of data on gene expression from various human cancers coupled with standard tissue controls. Such results were studied to assess the rates of PERIOD gene expression in colon cancer and rectal and intestinal adenomas (Per1, Per2, and Per3). The findings revealed that the function of these genes in circadian desynchronization may be used as a justification for nocturnal light exposure in cancer therapy [35].

Genome-wide association studies (GWAS) and chronobiology

A genome-wide association analysis (GWAS) is a technique that is used in genetic science to relate particular genetic variants to specific diseases. The SNP markers arose as valuable services for conducting studies of genetic linkage and association. Both scientific and corporate groups are trying to develop large numbers of SNP datasets across their genomes [36]. The approach includes analysing the genomes of several different non-related people and searching for genetic variants that can be used to determine the existence of a disease. Dataset repositories are used for many systemic as well as functional genomics research. Several reports, viz. The mapping of admixtures, the recognition of population structures and the quantification of genetic diversity require a small information panel of relatively evenly spaced markers across genomes [37]. Here we describe a case study research wherein researcher used principles of GWAS in understanding chronomics problem.

Being a morning person is a behavioural predictor of the circadian rhythm underlying an individual. Using the genome-wide data available from a repository of 697,828 United Kingdom Biobank along with 23 and me member nominees this team upsurge the total genetic loci related with being an early morning person from 24 to 351. Using data from 85,760 people with activity-monitor dependent sleep-time measurements they noticed that the chrono-type loci is correlated with sleep-time: The normal cycle period for the 5% of people bearing the most morning alleles is 25 minutes shorter than the 5% with the fewest. The loci are enriched for genes that are active in the signalling pathways of circadian modulation, base, glutamate and insulin and those found in

retina, hindbrain, hypothalamus, and pituitary. Using Mendelian Randomisation, we prove that becoming a morning person is causally correlated with improved mental wellbeing but does not impact BMI or type 2 diabetes incidence. This research gives insights into the circadian physiology and its relation to human disease [38].

MicroRNAs: a potential interface between the circadian clock and health

A 24 hour (circadian) clock forms the metabolic behaviour of a remarkable variety of cell types and organ systems. This rhythmicity push to most of the transcriptome (up to 15 percent of all coding genes) imparting circadian regulation through a wide range of physiological and behavioural processes (from cell division to cognition). Epigenetic studies also help to assess many factors inclusive of the age, diet, stress, drugs, lifestyle, and disease state of the subject, pollution and the immediate environment [39]. In fact, clock dysregulation became implicated in the pathogenesis of a broad variety of diseases such as obesity, cancer, and depression. Indeed, the possibility of using therapeutic approaches a target physiology of the clock (i.e. chronotherapy) has gained broad interest. Nonetheless, to truly appreciate the potential of chronotherapies would need a greater understanding of the fundamental molecular processes that modulate the clock, which give rise to organ-specific clock transcriptomes. MicroRNAs have recently emerged as major players in circadian clock timing, thus increasing the likelihood that clock-controlled microRNAs may lead to human circadian timing disorders [40]. The primary corner of utilizing RNA systems is that mandatory genome change can be avoided and is therefore actually better to the DNA-based system.

ANN & Chronobiology

In addition to data mining, other artificial intelligence methods have led to the study of chronobiology, such as artificial neural networks [41, 42] and rule-based (RBS) systems [43]. An artificial neural network is a parallel computing device whose key characteristic is non-algorithmic computation, which is reminiscent of the nature of the functions of the human brain neurons [44]. The model initially goes through a learning process in troubleshooting mode, this strategy, in which a limited range of examples are introduced to the network. The network then immediately learns the features required to reflect the details given and therefore identifies some current specification that can be used to define similar data in an unfamiliar data set later.

In recent years, Artificial Neural Networks has gained significant attention in many fields as a computational device, including the learning judgment process, statistical issues, pattern similarity detection, data extraction, automated knowledge acquisition, tracking and rapid diagnosis, and incomplete information processing.

Artificial neural networks have been used, in chronobiological experiments, to classify variations of human circadian rhythms. Kolodyazhnyi *et al.* study introduced an overview of a nonlinear regression model focused on artificial neural networks in order to understand variations in the circadian cycles of 25 young humans. The results were collected during everyday activities over a week utilizing an ambulatory multichannel tracking program. The sensors collected vast volumes of data linked to physiological, behavioural, and environmental variables like body temperature, cardiovascular

and respiratory processes, breathing, orientation, ambient temperature, eye-perceived light strength, and sleep [45]. An intelligent method for detecting and forecasting myocardial diseases by evaluating the electrocardiogram curve was established in 2009 [46].

Conclusion

The observation and recording of endogenous and exogenous biological rhythmicity is the primary focus of chronomics in collaboration with big data science and associated methods. This approach will contribute to wide improvements in the diagnosis of disease and understanding the patho-physiology and treatment of many diseases, as well as identifying the temporal variables of such diseases, based on quantitative and qualitative interpretations of various disorders. The fields of chronomics with big data are applicable not only in diagnosis but also in understanding the chronomes according to an individual's rhythm. It is evident that our knowledge has already increased in the field of chronobiology, and the use of tools derived from data science, bioinformatics, AI, ML can contribute to the recognition and understanding of the patterns in the biological rhythms of living organisms. Novel and many important applications for chronobiology will be developed in the near future taking these discussed considerations.

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