Inter-subject differences in circadian coordination captured in real time in healthy and cancerous individual persons during their daily routine using a mobile internet platform

AUTHORS

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Short title : Inter-subject differences in circadian coordination

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ABSTRACT:

Background: Experimental and epidemiologic studies have shown that circadian clocks disruption can play an important role in the development of cancer and metabolic diseases. The cellular clocks outside the brain are effectively coordinated by the body temperature rhythm. We hypothesized that concurrent measurements of body temperature and rest-activity rhythms would assess circadian clocks coordination in individual patients, thus enabling the integration of biological rhythms into precision medicine.
Methods: Non-invasive real-time measurements of rest-activity and chest temperature rhythms were recorded during the subject's daily life, using a dedicated new mobile e-health platform (PiCADo). It involved a chest sensor that jointly measured accelerations, 3D-orientation and skin surface temperature every 1-5 min, and relayed them out to a mobile gateway via Bluetooth-Low-Energy. The gateway tele-transmitted all stored data to a server via GPRS every 24 h. The technical capabilities of PiCADo were validated in 55 healthy subjects and 12 cancer patients, whose rhythms were e-monitored during their daily routine for 3-30 days. Spectral analyses enabled to compute rhythm parameters values, with their 90% confidence limits, and their dynamics in each subject.
Results: All the individuals displayed a dominant circadian rhythm in activity with maxima occurring from 12:09 to 20:25. This was not the case for the dominant temperature period, which clustered around 24 h for 51 out of 67 subjects (76%), and around 12 h for 13 others (19%). Statistically significant sex- and age-related differences in circadian coordination were identified in the non-cancerous subjects, based upon the range of variations in temperature rhythm amplitudes, maxima (acrophases), and phase relations with rest-activity. The circadian acrophase of chest temperature was located at night for the majority of people, but it occurred at daytime for 26% (14/55) of the non-cancerous people and 33% (4/12) of the cancer patients, hence supporting important inter-subject differences in circadian coordination. Sex, age and cancer significantly impacted on the circadian coordination of both rhythms, based on their phase relationships.
Conclusions Complementing rest-activity with chest temperature circadian e-monitoring revealed striking inter-subject differences regarding human circadian clocks coordination and timing during daily routine. To further delineate the clinical importance of such finding, the PiCADo platform is currently applied for both the assessment of health effects resulting from atypical work schedules, and the identification of the key determinants of circadian disruption in cancer patients.

KEY WORDS :

Circadian clock, e-Health, temperature rhythm, rest-activity rhythm, time series analyses, domomedicine, biomarkers, time series analyses.

Highlights

- Circadian biomarkers were measured and tele-transmitted in real time for up to a month using a mobile e-Health platform
- Three classes of circadian coordination were disclosed among healthy and cancerous people during their daily routine
- Sex, age and cancer moderated circadian coordination, robustness and timing.

INTRODUCTION

Circadian (about-24-hour) rhythms regulate mammalian physiology, as well as cell metabolism, proliferation and survival over the 24 hours. These rhythms play an important role in disease processes and treatment effects, which has been largely overlooked in medicine [1-3]. They are generated at single cell level by molecular clocks consisting of interwoven feedback loops involving transcription/translation of 15 known specific “clock” genes including Bmal1, Clock, Per2 and Rev-erbα [4]. The molecular clocks are coordinated at whole organism level by the suprachiasmatic nuclei (SCN), a hypothalamic pacemaker, which also helps circadian rhythms adjust to light-dark and other environmental 24-h cycles through the rhythmic control of rest-activity, body temperature, feeding, as well as cortisol and melatonin secretions [1-4]. Thus both, glucocorticoids and body temperature rhythms, reset molecular clocks and cellular circadian rhythms *in vitro* and *in vivo* [5-8].

Rhythm studies in humans have assumed similar circadian synchronization among subjects, thus inferring the reliability of transverse sampling of different subjects at different time points over 24 hours, and using average values for describing circadian patterns in the group or the population [9]. Treatment effects could also differ according to circadian timing or chronomodulated scheduling of medications in a

consistent fashion across individual subjects with a similar circadian entrainment [1, 10-12]. Such standardized approaches to chronotherapy proved valid in experimental rodents of same sex, strain and age which were synchronized with the same alternation of 12-h of light and darkness, especially for anticancer drugs [1, 13]. This was also true for healthy subjects maintained in human physiology laboratories under controlled environmental conditions [14]. However, little is known regarding circadian rhythms in individual healthy humans or patients during their daily routine.

Inter-subject variability in circadian phase has been suggested, based on chronotype questionnaires administered to large populations of presumably healthy subjects [15]. Inter-subject differences in both daily timing and 24-h pattern have also been shown in individual patients collecting up to 5 daily samples of salivary cortisol and/or melatonin determinations for up to 2 days [16-18]. The limitations resulting from such low sampling frequency were overcome through rest-activity monitoring, using a wrist watch accelerometer for a few days to a few weeks [19-21]. The rest-activity time series led to identify the dichotomy index I<O, the relative amount of activity in bed that was below the median activity out of bed, as an independent predictor of progression-free survival and overall survival among 436 patients with metastatic colorectal cancer [22]. Most importantly, the patients whose I<O was below the median value of 97.5% had a median survival of 11.9 months, as compared to 21.6 months for those with an I<O index over 97.5% [22]. The I<O was also negatively associated with fatigue and appetite loss, and positively with health-related quality of life as assessed by both the EORTC QLQ-C30 and the M.D. Anderson Symptom Inventory (MDASI) questionnaires in cancer patients with locally advanced or metastatic disease [23, 24]. Furthermore, circadian rest-activity disruption, as measured with an I<O of 97.5% or less, in patients receiving cancer chemotherapy could indeed represent an early warning signal of deterioration and emergency hospitalisation [25, 26]. However, I<O values did not correlate with sex, both in healthy subjects or in cancer patients or with efficacy of a standardized chronomodulated

chemotherapy protocol in cancer patients [19, 20, 27], whilst the latter profoundly differed between men and women [28]. These clinical data stressed the need for the combination of rest-activity with circadian temperature biomarker in order to gather more reliable estimates of the circadian phase, and to personalize the timing of chronotherapy.

Indeed, despite their consistent and reproducible clinical relevance, the rest-activity time series provide imprecise estimates regarding circadian phase, due to both its square-wave 24-h pattern and the strong masking effect of the societal routine on the endogenous activity rhythm. Predominant low values of activity suggest prolonged periods of rest during nighttime, while frequent high intensity activity occur during the day, with substantial within day and day-to-day variability [29]. Nevertheless, a first fixed e-health internet platform was developed within the inCASA European project combining telemetric activity monitoring with self-rated symptoms and self-measured body weight. Testing of the platform in 31 cancer patients on chronotherapy at home demonstrated a per protocol compliance rate of ~85% over one month, and enabled prediction of emergency hospitalization due to treatment toxicity three days in advance [26].

Precise information regarding circadian phase and circadian coordination is also critical for the appropriate timing of treatment delivery in order to reduce adverse events and/or enhance efficacy [1, 10-13, 30]. Moreover, both diseases such as cancer and treatments can disrupt the circadian timing system (CTS), and result in associated symptoms and reduced survival, especially in cancer patients [31]. To address these issues, we have designed an upper chest e-sensor that records and teletransmits both activity, temperature and tri-axial orientation. This sensor is integrated into a novel e-health platform (PiCADo). The circadian rhythms in core and skin surface temperature of men are usually 8-12 h out of phase, with respective maxima occurring near 16:00 at day time, and near 2:00 at night [32]. The early night drop in core body temperature, results from the vasodilatation of the skin vessels and associated

rise in skin surface temperature [33]. Such temperature changes are critical for triggering the onset of sleep [34]. The site of temperature measurements for achieving continuous and non-invasive yet reliable assessment of human body temperature rhythms in real life has been a challenge over the past decades. The use of a rectal probe has been discouraged as a result of the risk of rectal perforation [35]. Axillary and wrist skin surface temperature records were shown to be largely contaminated by changes in environmental temperature [36-39]. The recent availability of an oral temperature pill has enabled the continuous recording of internal body temperature, yet only for durations that match the gastro-intestinal transit time, i.e. ~24-48 h [40, 41]. Previous work by others highlighted the reduced influence of environmental temperature changes on skin surface temperature measurements taken at the upper-anterior chest wall [42, 43]. We confirmed these findings through combining infrared technology with continuous recording of patched temperature sensors [44, 45]. We further developed dedicated statistical methods to compute dynamic changes in rhythm parameters by combining the inference methods for obtaining interval estimates based on spectral bootstrap with time varying spectral estimation [46, 47].

Here, we assessed for the first time the performance and relevance of the PiCADo platform for capturing inter-and intra-subject variabilities in the circadian timing system both during daily routine and in real time. We hypothesized that the combination of rest-activity and temperature monitoring would identify large inter-individual differences in circadian coordination. The latter would notably support the personalized adaptation of the optimal timing of medications in order to jointly minimize treatment morbidities and enhance efficacy.

METHODS

Study Design

The main objective was to determine whether any inter- and intra-subject differences in human circadian coordination could be captured in real time through remote and non-invasive real-time monitoring during the subjects' usual routine. Such goal represented a critical step toward the personalization of treatment timing according to individual circadian rhythms, especially for cancer therapies. A new mobile e-Health platform (PiCADo) was designed on purpose. The PiCADo specifications were defined within several multidisciplinary and multiuser focus groups involving nurses, medical oncologists, general practicioners, biomedical and informatics engineers, socio-anthropologists, and chronobiologists, and through analyzing elderly people's responses in living labs. Three parameters – activity, temperature and position – are measured using a single CE-marked chest sensor-emitter (Movisens, Karlsruhe, Germany) and a pocket-size CE-marked gateway (Eeleo, Montrouge, France), which could gather further information from other Bluetooth (BT) and Bluetooth Low Energy (BLE)-connected devices, and send them to a server via the General Packet Radio Service (GPRS) at the required frequency, which may be tuned down as low as every h, in case of measurements of preset emergency values (**Fig. 1**). This latter function was not activated here. Thus, the PiCADo platform consisted of a chest sensor that measured skin surface temperature every 5 min, the number of accelerations and the orientation in 3 dimensions every min. All data were teletransmitted via BLE to a pocket size gateway, which also could gather data measured by other connected Bluetooth and BLE devices, such as a weight scale. The gateway sent all data to a server every 24 h. Three cohorts of people were involved, each with different specifications regarding observation span (4 days vs 7-30 days), sensor-carrying method (patch vs dedicated vest or bra), and health condition (healthy vs cancer). Subjects in cohorts 1 and 2 had to be 21 years or more,

display no active disease, and not work at night. The study was planned without any intervention. Subjects were advised to remove the sensor for around 20 minutes once per day to avoid contact with water during showering. The study was conducted according to the Helsinki Declaration [48]. All the subjects enthusiastically volunteered and provided informed consent for carrying and testing the platform system.

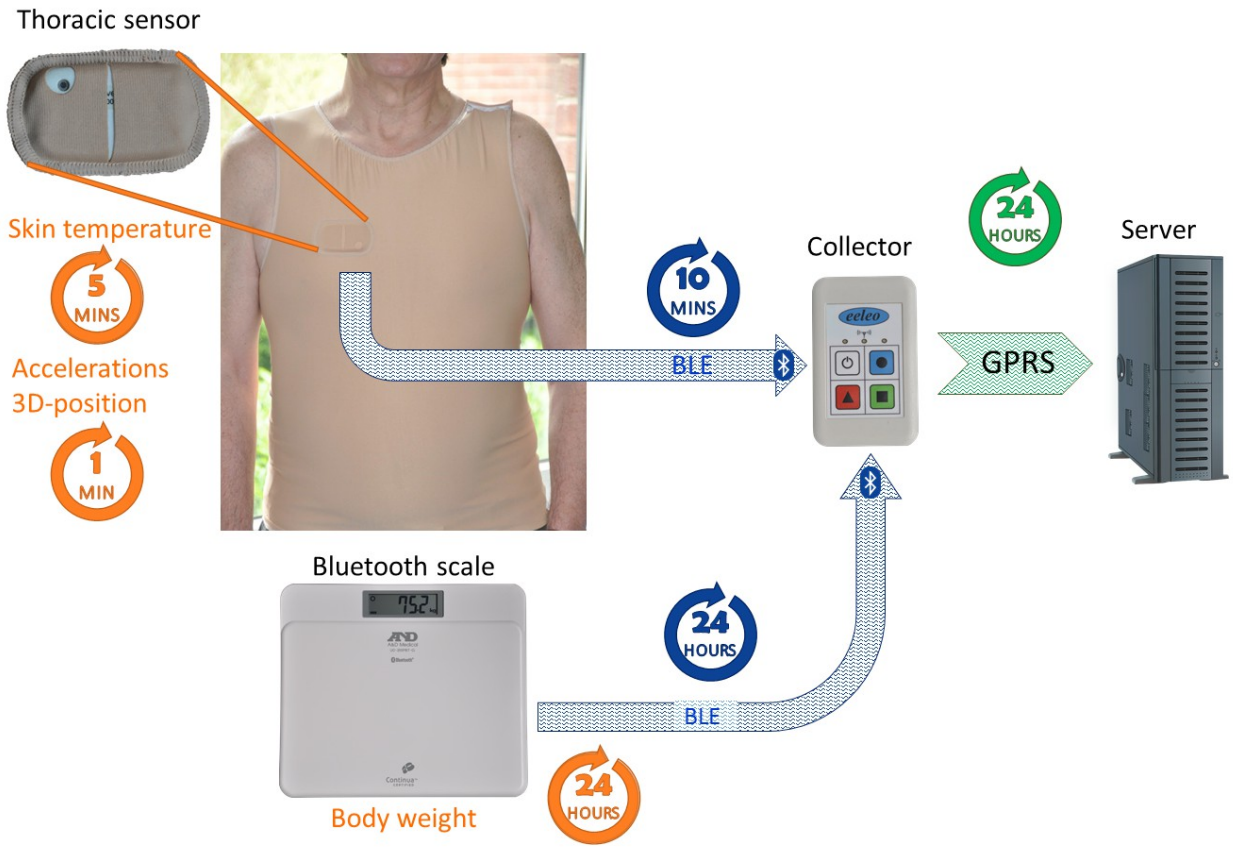

Fig. 1: E-health domomedicine platform technology. The chest sensor embedded into the vest shirt with an open area for infrared temperature measurements is shown in the upper left corner. The epoch length of the data points as well as length of time intervals between teletransmission events are indicated within each circle for each variable. Teletransmissions involve Bluetooth Low Energy from sensor to gateway and GPRS from gateway to server, from which data can be retrieved continuously.

Data management

All anonymous electronic data were transferred from the gateway at home to the server according to the GPRS communication protocol. Once on the server, the data were stored based on HL7 standards (international standards for transfer of clinical and administrative data). Data were downloaded from the server to the computer of our biomedical engineer, who was the only person having access to the server. Data were saved on a secure storage server according to the national Data Protection and Freedom of Information Acts guidance. Data transmission was inspected at least twice per week during the monitoring sessions to insure the proper functioning. Data were retrieved and processed at the end of the monitoring.

Statistical Methods

Treatment of Missing Data and Data Pre-processing

Times at which subjects removed the sensor were identified retrospectively by noting a string of zero Position and Activity counts, jointly with corresponding temperature measurements decreasing towards room temperature values. These intervals were marked as missing values. To perform spectral analysis the raw activity and temperature data were aggregated over hourly intervals, and corresponding median values were computed. The hourly interval length provided a good resolution of the periodogram at frequencies of interest, especially those corresponding to the circadian range. The endpoints of the hourly aggregated data were connected using linear interpolation in case of recording gaps ≤ 7 h. For gaps > 7 h, as it did occur for 7 subjects, the recordings of the whole corresponding 24-hours were ignored for purposes of the analyses.

Estimation of circadian parameters

The Spectrum-Resampling (SR) algorithm [46] was applied to estimate the circadian parameters of

interest, namely period, amplitude and phase of the first and second largest peaks in the spectra for both rest-activity and temperature time series. This method first identified the most important frequencies and their corresponding periods from the estimated spectrum, then fitted a Fourier type regression model to the data, in order to obtain the corresponding amplitudes and phases. The SR method provided a bootstrap framework, where all circadian parameters were estimated as the median of the bootstrap samples, and their 90% central confidence intervals were approximated by the corresponding percentiles of the bootstrap samples. In order to analyze the intra-subject variability over time the same methodology of spectral analysis was performed over moving windows of 3 days each, with a 1 h shift per spectral estimate [49]. We note that the window length should be at least 2-3 days as at least 2 full cycles are needed to estimate the period length.

Regression analysis

Multivariate regression analysis was applied to test for the effects of covariates such as sex, age, weight, and cohort. As response variable Y, we considered a selection of estimated circadian parameters that summarized the behavior of the biomarkers for each subject, including (i) the amplitude of the main period of temperature, that was obtained from spectral estimation; (ii) the amplitude of activity, during prolonged (usually daily) activity spans, as approximated by the inter-quartile-range (IQR) or amplitude of 50% central values of observed values; (iii) the spectral gravity center (or mean period) of temperature; and (iv) the spectral gravity center (or mean period) of rest-activity. Possible explanatory variables were sex, age, weight, amplitude of daily activity as given by the IQR of daily activity counts, cohort, and the following interaction terms: sex*age, sex*weight, sex*IQR of daily activity. Model selection was performed stepwise (as implemented in R function and based on Akaike's information criterion [50]. Significance of explanatory variables was tested by t-tests of the corresponding coefficients where a significant effect was concluded for p-values smaller than 0.05. As 0 and 1, respectively, encoded for females and males, a sex-specific effect was computed in a straightforward way

in that a sex-specific influence of a covariate was concluded, if the coefficient corresponding to the interaction term sex*covariate was significant in the regression.

RESULTS

Subject characteristics and study conduct.

The PiCADo Domomedicine platform was tested by 69 people. Assessable time series of the three variables were obtained for 67 of 69 subjects (97%) over a median duration of 6 days (1^{st}-3^{rd} quartiles, IQ, 4.0 to 12.1), ranging from 3 to 29.7 days. Thirty males and 37 females, aged 21 to 83 years participated in one of three cohorts of subjects (**Fig. 2**, **Table 1**).

All subjects were asked to keep their usual daily routines, besides carrying the sensor day and night for the whole monitoring duration, and keeping the gateway within a distance of 2 m. The sensor was initially patched onto the upper left anterior thorax of 28 healthy subjects in Cohort 1, using Tegaderm™ (10x12 cm, 1626W, 3M™, Diegem, Belgium) for a median duration of 4 days. To avoid the use of the potentially irritating patches for longer durations, a dedicated vest and bra were designed which could properly lodge the sensor (Thuasne Medical, Saint Etienne, France). This system was tested by 27 healthy subjects in two countries for durations ranging from 3.6 to 28.3 days (Cohort 2). The platform was used by 18 subjects in the UK for a median duration of 7 days (Cohort 2.1), and by 9 subjects in France, jointly with a BLE weight scale, for a median duration of 19 days (Cohort 2.2) **(Table 1)**. In order to probe the platform for a prolonged use in patients with cancer, the sensor/cloth/gateway system was further assessed in 12 patients with advanced or metastatic cancer for a median duration of 18.5 days (Cohort 3, see characteristics in Multimedia Appendix 4).

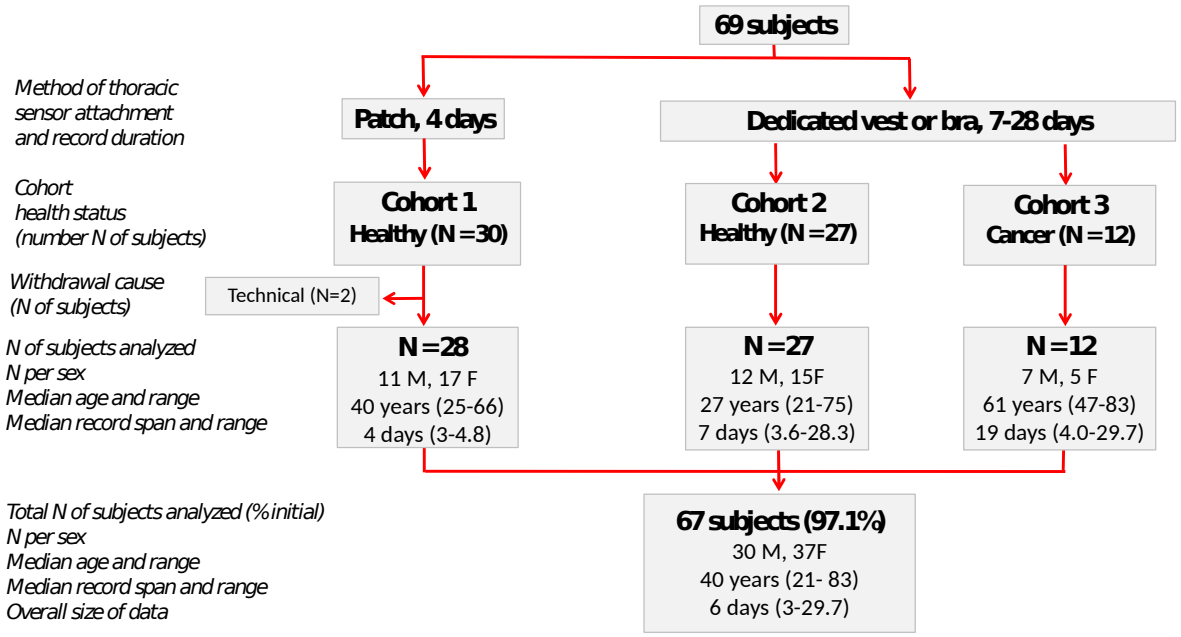

Fig. 2. Consort diagram. The 69 subjects were enrolled in one of three cohorts, that differed according to method of sensor attachment and record duration (first row), health status (second row), and number of subject per group, including sex, age (median and range, and record duration (median and range).

Table 1. Subjects and records characteristics. Median and distribution of data for all quantitative variables.

Cohort	Total N (M/F)	Age, years (range) [25-75% IQR]	Weight, kg (range) [25-75% IQR]	Height, cm (range) [25-75% IQR]	BMI, kg/m^2 (range) [25-75% IQR]	N of subjects with partial record (cause)	Valid time series duration, days (range) [25-75% IQR]	Missing data, % (range) [25-75% IQR]
1	28 (11/17)	40 (25 to 66) [32.7 - 49.5]	73 (44 to 93) [61 – 77.5]	--	--	0	4.0 (3.0 to 4.8) [3.9 – 4.0]	0.8 (0 to 6.8) [0.3 – 2.6]
2.1	18 (8/10)	26 (21 to 75) [24 – 32.3]	73 (46 to 93) [66.7 – 78]	172 (156 to 183) [168.5 – 175.5]	24 (19 to 28) [22.2 – 26.1]	1 (charger dysfunction)	7.0 (3.6 to 12.4) [7.0 – 7.4]	1.5 (0.3 to 4.3) [1.0 – 2.0]
2.2	9 (4/5)	34 (25 to 57) [27 – 38]	71 (54 to 83) [65 – 72]	169 (155 to 195) [162 – 171]	24 (18 to 31) [23.3 – 26]	3 (subject-related) * 1 (unsticking of electronic circuit)	19.0 (4.9 to 28.3) [17.0 – 21.7]	7.7 (5.0 to 24.6) [5.9 – 13.1]
2	27 (12/15)	27 (21 to 75) [24.5 - 37.5]	70 (46 to 93) [65 – 77]	171 (155 to 195) [165 – 174]	24.3 (17.9 to 31.2) [22.3 – 26.2]	3 subject-related 2 technical failures	7.4 (3.6 to 28.3) [7.0 – 15.3]	2.0 (0.3 to 24.6) [1.3 – 5.7]
3	12 (7/5)	61 (47 to 83) [54 – 66.5]	66 (45 to 80) [60 – 72]	170 (152 to 185) [164 -176]	22.8 (18.5 to 26.1) [21.4 – 23.9]	5 (subject-related) **	20.3 (4.7 to 29.7) [16.5 – 27.2]	5.0 (0 to 49.1) [3.5 – 9.3]

*Forgetfulness after charging (N=1), travel abroad starting before end of recording span (N=1), wrong charging procedure applied (N=1)
** Wrong charging procedure applied (N=2); poor tolerability of adjusted sensor-dedicated cloth due to no current use of bra (N=1), or treatment-related itching (N=1); need for more feedback and support (N=1).

Inter- and intra-subject differences captured by time series analyses

Time series were pre-processed to account for missing data (see Material and Methods). Using the spectrum resampling method, period, amplitude and acrophase corresponding to the largest (fundamental) and, if significant, second-largest peak in the spectrum were estimated, along with their respective 90% Confidence Limits (CL), for each subject over the whole time span [46]. Time-varying

features of the spectrum were also estimated, through the application of the same method to 3-day windows, which were moved along each time series with 1-h shifts. The clinically-relevant Dichotomy Index I<O was further computed, over consecutive 3 day-spans, with 24-h shifts [26, 51]. Strikingly different circadian patterns, rhythm parameters, and I<O values were identified among the 55 healthy subjects (**Fig. 3-4**). Although the rest-activity pattern remained consistent from one day to the next in the 55 healthy subjects, the temperature pattern varied from day to day in 16 of them, as revealed by changes over time in the dominant periods and the amplitude-acrophase vectors (**Fig. 4**, subjects 3 and 4). Thus, our methodology revealed and quantified day-to-day changes in circadian parameters, thereby enabling the determination of circadian variability both within- and between subjects during real life conditions.

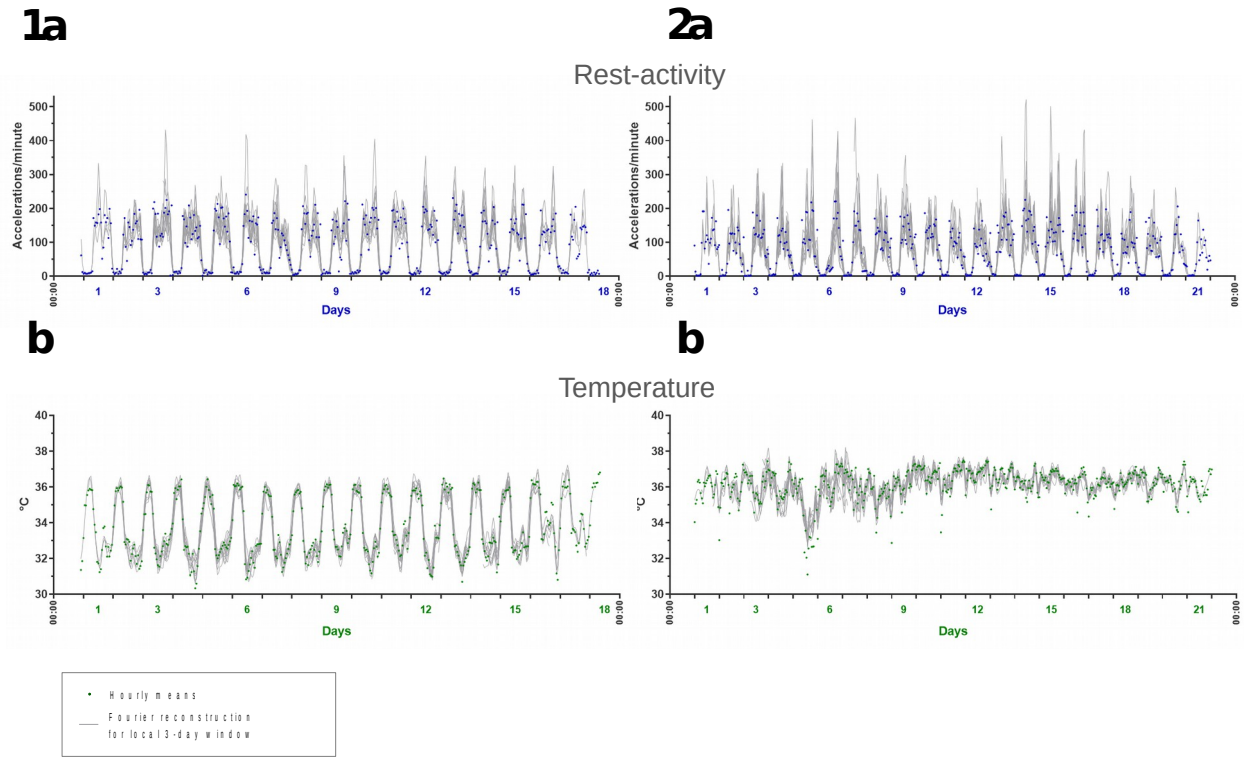

Fig. 3: Inter- and intra-subject variability in circadian patterns illustrated by chronograms of rest-activity (a) and thoracic skin surface temperature (b) of two healthy subjects. *Panel 1 (left):* time series from a 57 y-o. female researcher, with usual respective times of awakening and retiring at 8:30 and 22:30; mean rest-activity I<O of 99.7%, with intrasubject coefficient of variation of 0.2%.

Panel 2 (right): time series from a 27 y-o female student, usually awakening at 8:40 and retiring at 01:00; mean I<O of 99.2%, with a coefficient of variation of 1.2%.

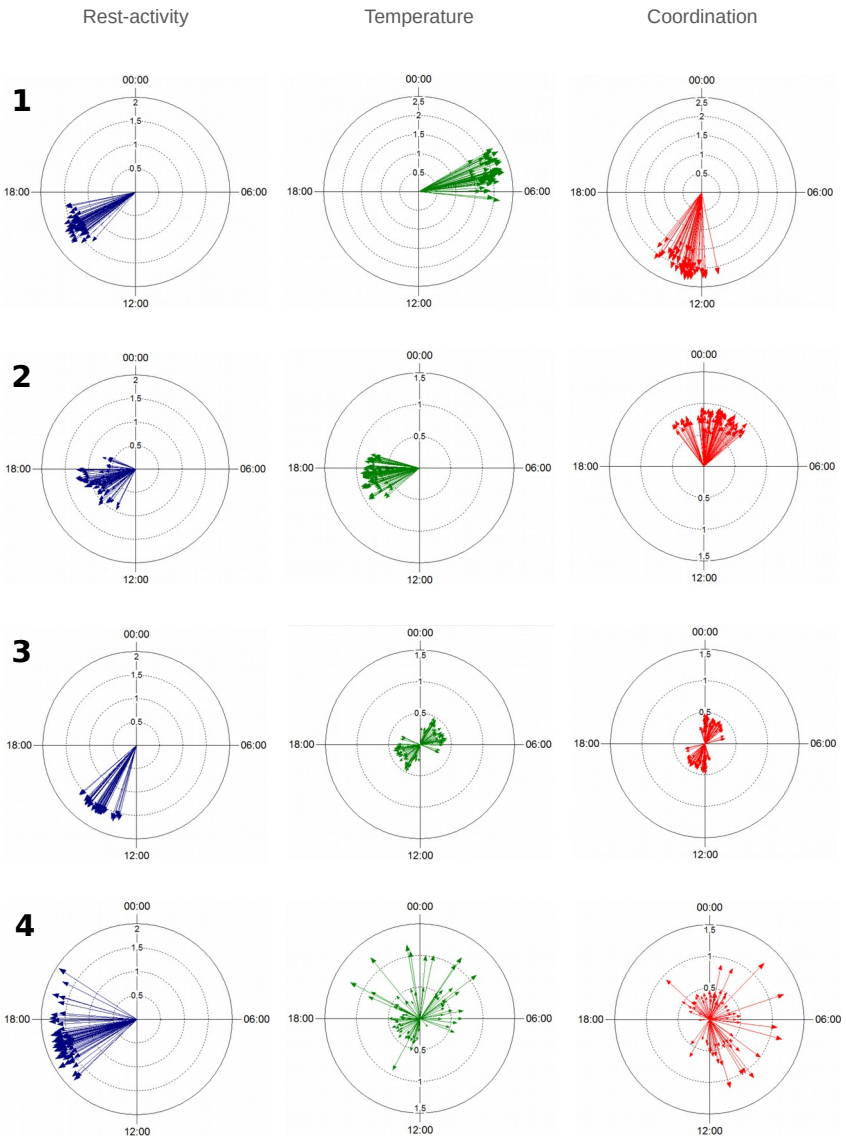

Fig. 4: Inter- and intra-subject variability in circadian acrophases and amplitudes of rest-activity (left panels), temperature (middle panels), and circadian coordination (right panels). Illustrative examples through polar plots in 4 healthy subjects, whose 3-day time series shifted by 6 h (Subjects 1 and 4) or 1 h (subjects 2 and 3) have been analyzed using the sampling-resampling spectrum analysis. The length of each vector represents the amplitude of the dominant period and its direction points toward the timing of the corresponding acrophase. The circadian coordination is estimated through using the activity acrophase in each 3-day time series, as the time reference for the corresponding temperature vector.

Subjects 1 and 2 had both stable rest-activity and temperature 24-h rhythms, and robust coordination, yet with distinct phase relations between rest-activity and temperature rhythms; subject 3 had stable 24-h rhythm in rest-activity and 12-h rhythm in temperature; and subject 4 had moderately stable rest-activity 24-h rhythm, unstable temperature phase, and loose circadian coordination.

Subjects classification according to temperature periods and circadian coordination

Results of the spectral analyses over the complete time series of the 28 subjects in Cohort 1 were very similar to those of the 27 subjects in Cohort 2 (**see Multimedia Appendix 1 and Multimedia Appendix 2**). For instance, a dominant circadian rhythm in rest-activity was identified for all subjects, yet with a dominant circadian rhythm in skin surface temperature for 68% (19/28) of the subjects in Cohort 1 and 74% (20/27) of those in Cohort 2; the dominant temperature period was about 12-h (circa-hemidian) for 25% (7/28) and 22% (6/27) of the subjects in Cohorts 1 and 2, respectively. Atypical patterns were found for 2 and 1 subjects, respectively. Both cohorts of healthy subjects were pooled, so as to further examine the relations between summary statistics of the temperature and activity variables and their spectral properties, as well as the relevance of available covariates, such as sex, age and weight in the 55 healthy subjects. The differences between the acrophases of both rhythms on each tested timespan were taken as estimates of circadian coordination.

Large inter-subject differences characterized the median values of both activity, whose median was 39.8 movements per min [IQ, 19.3 to 54.7], and skin surface temperature, whose median was 35.2 °C [34.7 to 35.8]. The rest-activity rhythm displayed a dominant 24-h period for all 55 subjects. In contrast, the skin surface temperature displayed a dominant period in the circadian range for 39/55 subjects (71%), and in the circahemidian range for 13/55 subjects (27%). Three out of 55 subjects (5%) displayed atypical patterns, one for both variables, due to transmeridian travel, one with a dominant temperature period of 6 h, and one with an unstable temperature pattern. We categorized the subjects as belonging to *Class A*

(circadian rhythms in both variables), *Class B* (circadian activity and circahemidian temperature) or *Class C* (atypical rest-activity and/or temperature patterns, not shown) (**Fig. 5**). For *Class A*, the median circadian acrophases were located at 14:40 for activity (with individual acrophases ranging over 7h44 min, from 12:41 to 20:25), and at 3:33 at night for skin surface temperature, yet with inter-subject differences spread over the 24-h. Thus, the skin surface temperature acrophase occurred at night (22:01 to 7:00) for 31 subjects and during day-time (7:01 to 22:00) for 8 subjects in Class A (p from Fisher Exact <0.001). As a result, the median time interval between both rhythm acrophases was 11h 47 min, yet it had a wide range from 7 min to 12 h among the 39 Class A subjects.

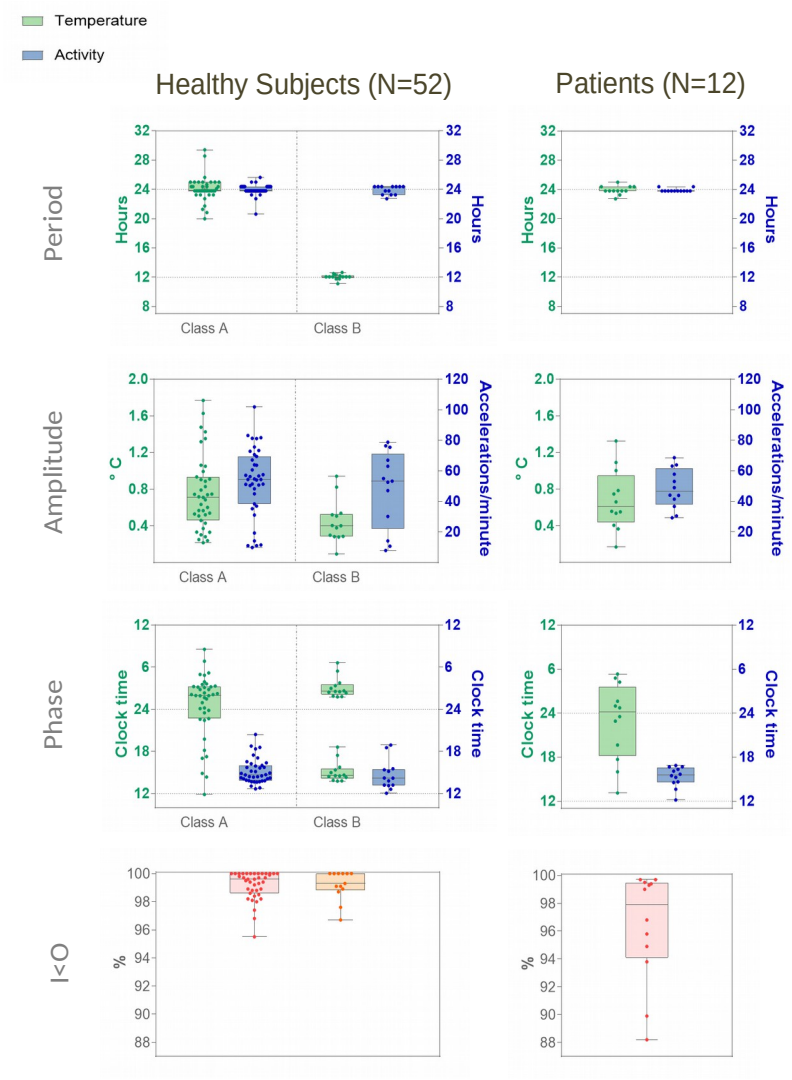

Figure 5: Inter-subject variabilities in main rhythm parameters of healthy subjects (left columns) and cancer patients (right column). Median, interquartiles, range and individual values of dominant periods and corresponding amplitudes and acrophases of temperature (green) and rest-activity (blue), based on spectral analysis of time series over the whole time span. Healthy subjects are classified according to dominant temperature period of ~24 h (Class A) or ~12 h (Class B), while all of them display a dominant 24-h rhythm in activity. The bottom row depicts the distribution of the dichotomy index I<O of the rest-activity pattern in Class A or B healthy subjects, as well as in cancer patients.

Sex and age moderation of temperature but not activity rhythms

Statistically significant pairwise Spearman correlations with |r|>=0.4 were identified for median values and their corresponding dominant rhythm amplitudes for both activity (r=0.77) and temperature (r=0.49). Sex jointly with age had a selective influence on the rhythmic organization of temperature, but not that of rest-activity in the 55 healthy subjects. This was statistically validated by multivariate regression analysis of amplitude and spectral gravity center (or 'mean period') of temperature, as response variables, with age and sex as covariates (**Fig. 6**). Females displayed larger temperature amplitude than males (two-sample t−test, p = 0.005) (**Fig. 6a**). Females also had larger values than males in the estimated gravity center of their temperature spectrum (two-sample t−test, p = 0.03). Overall, the results indicated that females tended to mostly display dominant 24-h rhythm periods with large amplitudes, while 12-h rhythms tended to predominate in males (**Fig. 6c)**. The interaction between sex and both temperature rhythm parameters was mostly apparent beyond 35 years of age (**Figure 6b, d**).

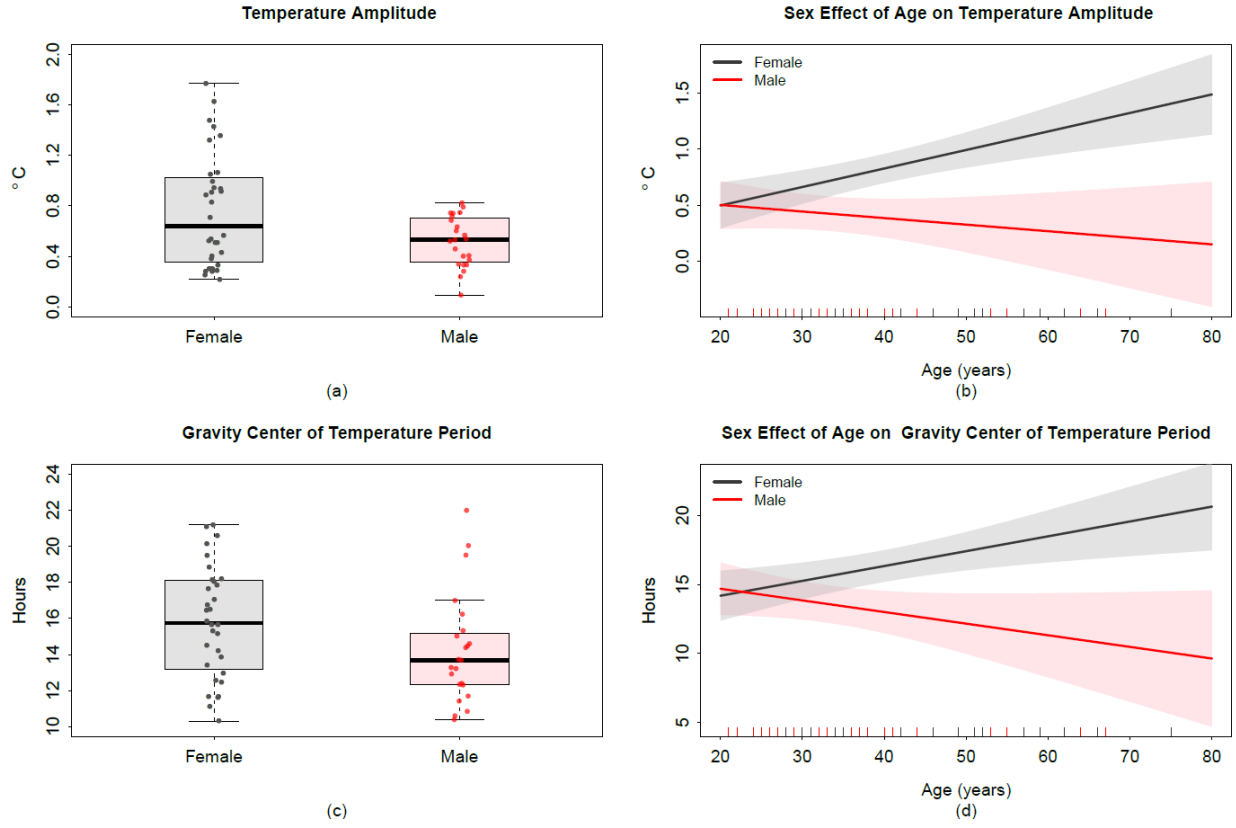

Fig. 6: Sex and sex-age dependencies of circadian amplitude (upper row) and spectrum gravity center of temperature time series (lower row) in 55 healthy subjects.

(a) Box plot of temperature amplitudes of the estimated main harmonic for females (left, N=32) and males (right, N=23). *Note larger mean amplitude in females vs males (t-test with p-value 0.005).*

(b) Sex-specific effect of age on temperature amplitude shown by estimated regression line with 95% confidence bands. The vertical dashes along the horizontal axes show corresponding age of each subject. *Regression analysis shows that sex, age and the interaction term sex*age are of significance, with p-values 0.04, <0.001 and 0.002, respectively.*

(c) Box plot of the estimated gravity center of temperature spectra for females (left, N=32) and males (right, N=23). *Note that females had larger mean values with p-value 0.03.*

(d) Sex-specific effect of age on the gravity center of temperature spectra shown by estimated regression line with 95% confidence bands. *Regression analysis (see Methods) shows that sex, age and the interaction sex*age are of significance, with p-values of 0.03, 0.004 and 0.003, respectively*.

Circadian coordination in cancer patients

Seven male and 5 female patients tested the platform for a median of 19 days, ranging from 4 to 29 days. All the patients had previously received one or more chemotherapy protocols for metastatic gastrointestinal cancer, including colorectal (N=5), pancreatic (N=3), liver (N=2), stomach (N=1) or anal (N=1) cancer. Five patients had co-morbidities (**see Multimedia Appendix 4**). Six patients received chronomodulated infusions, including 2 courses at home, while being telemonitored. Circadian patterns in rest-activity and thoracic temperature were identified in all the patients' records, as shown by dominant 24-h periods (**Fig. 7**). Despite all patients belonging to Class A, large inter-patient variations were found regarding the circadian amplitudes in both rest-activity (range, 29.3 to 68.6 accelerations per minute) and temperature (0.17˚C to 1.33˚C). Individual rest-activity acrophases varied within a 5-h range, occurring between 12:09 and 16:52. In contrast, the circadian acrophases of temperature were located between 22:01 and 07:00 at night for 8 patients, and at daytime for another 4 patients. Inter-subject

variations were also revealed with dichotomy index I<O, whose individual median values ranged from 88.2 % to 99.7 %, with rather low estimated intra-subject coefficients of variations of 0.3 to 6.4 %. Interestingly, the circadian acrophase of temperature was located at daytime for 3 of 6 patients with an I<O under 97.5%, but at nighttime for 5 of 6 patients, whose I<O was over 97.5% (p<0.001 from Exact-Fisher test).

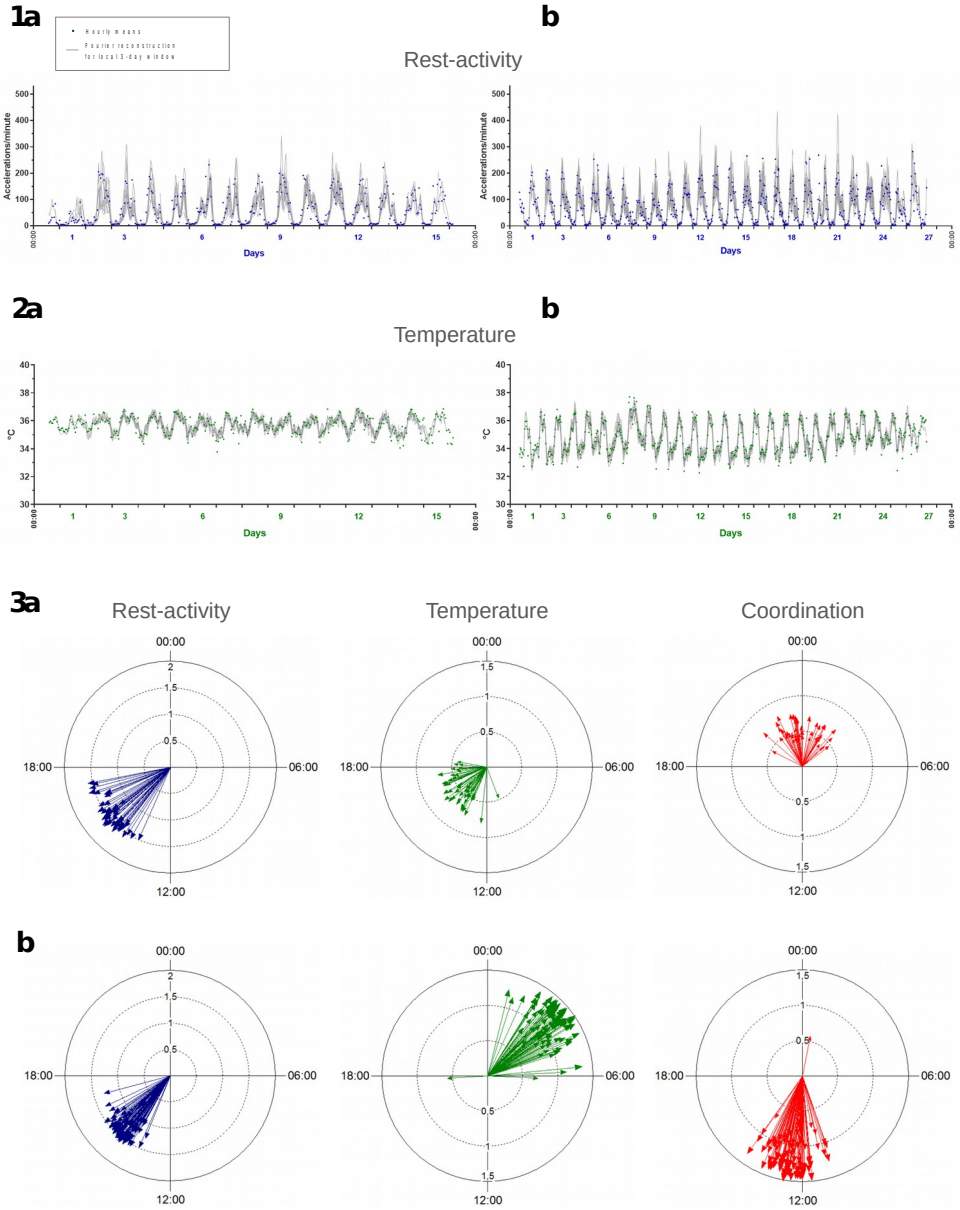

Fig. 7: Inter- and intra-subject differences in circadian patterns in rest-activity and thoracic skin surface temperature as illustrated in two cancer patients.

Panels 1a -2 a: Chronograms in both variables for patient 1, a 53 y-o. male on conventional chemotherapy with oxaliplatin-5-fluorouracil-leucovorin delivered during hospitalization for liver metastases from stomach cancer, on days 1 to 2 of the recording; usual awaking and retiring times were 7:50, and 21:50; mean rest-activity I<O was 99.1%, with intra-subject coefficient of variation of 1.0%.

Panels 1b-2b: Chronograms in both variables for patient 2, a 78 y-o. male with lung and lymph node metastases from rectal cancer; treatment involved intravenous panitimumab and chronomodulated chemotherapy with irinotecan, oxaliplatin, 5-fluorouracil and leucovorin at home, using a four-channel programmable-in-time pump, from day 6 to day 9 of the recording; usual times of awakening and retiring were 7:15 and 23:00, respectively; mean I<O was 98.8%, with a coefficient of variation of 2.0%.

***Panels 3*:** Polar plot representations of amplitude-acrophase vectors of both variables and their coordination, computed according to the sampling-resampling spectrum method over 3-day windows, with 6-h shifts in each 3-day window; for the coordination graph, the acrophase-amplitude vector of temperature is referred to the acrophase of activity taken as zero-phase reference in the same 3-day time window. **3a**, patient 1; **3b**, patient 2.

Relations between I<O and chest temperature timing among the study population

An I<O of 97.5% or less was found in 9 of the 51 subjects with a 24-h temperature rhythm (18% of Class A) and in 1 of the 13 subjects with a 12-h temperature pattern (8% of Class B). We did not consider further the 3 Class C subjects (1 with a high I<O, and 2 with a low one). Interestingly, the average circadian acrophase of chest temperature was localized at daytime, i.e. between 7:01 and 22:00 for 6 of the 54 subjects with a high I<O value (11%), as compared to 6 of the 10 subjects whose I<O was low (60%) ($p<0.001$ from Exact-Fisher test). Indeed, having a high I<O enabled the accurate prediction of a chest temperature occurring at night, while no reliable prediction of temperature rhythm timing could be made win the subjects whose I<O was low (**see Multimedia Appendix 3**).

DISCUSSION

A mobile e-Health platform (PiCADo) consisting of a BLE chest sensor and a pocket size BT/BLE/GPRS gateway effectively measured body accelerations, 3-D orientation, and upper chest temperature every 1-5 min for prolonged timespans, teletransmitting them to a central server every 24 h. This interval hat can be reduced to 1 h. In 67 healthy people or cancer patients, this technology revealed large interindividual differences in circadian coordination that was captured in real time during their daily routine. The multidimensional platform and its capabilities to combine electronic Patient-Reported Outcomes (PROs) with circadian rhythm monitoring and body weight measures meet the expectations of the American Society for Clinical Oncology, regarding the future of e-Health technologies in cancer medicine [52]. Thus, the weekly transmission of electronic PROs significantly improved overall survival in two randomized trials conducted in cancer patients, indicating this information might elicit initially unplanned interventions and/or modify patient's engagement with an oncologic benefit equivalent to that of the addition of an active drug [53, 54]. The PiCADo platform provides a novel framework for the further integration of circadian rhythms and other parameters into proactive timely care interventions and the ready assessment of their efficacy. Such technology enables a novel systems approach for a coordinated medical and care logistics fit for the management of chronic disease and cancer patients, so called Domomedicine [26, 55].

Technology and compliance

The reliability and acceptance of the PiCADo platform is illustrated from the records obtained in the subjects from two countries, including 55 healthy ones and 12 cancer patients at home or during their usual activities, for pre-specified durations of 4 up to 30 days. Indeed, valid time series were extracted from the server, and amenable to longitudinal statistical analyses. These results are in line with previous

ones obtained in 31 cancer patients through a fixed internet platform within the inCASA European project [26]. The current PiCADo platform was developed in order to bypass the limitations of the inCASA platform, through mobile technology, and multi-rhythm monitoring, including skin temperature. Its specifications aimed at the broad integration of circadian rhythms into medicine, as a potential new information for triggering progress in the proactive management of cancer and chronic diseases.

Further real life tests (not shown here) indicated the reliability of combining such rhythm telemonitoring with other physiologic or patient-reported outcomes parameters, such as body weight or self-rated symptoms, through additional BLE-connected devices.

Circadian coordination of healthy people or cancer patients during their daily routine

The current study has highlighted the consistency of the 24-h patterns in both rest-activity and thoracic skin surface temperature from one day to the next both in healthy and cancerous patients. However, marked inter-subject differences were found regarding the dominant period, the spectrum central gravity, and the amplitude and acrophase location of temperature. More specifically, nearly 1/4 of the healthy subjects had a prominent 12-h rather than 24-h periodic temperature rhythm. Sex and age, but not weight were influential on the temperature rhythms, as discussed below. Among the 39 healthy subjects with a predominantly circadian chest temperature rhythm, the acrophase was located at night, as expected [33, 56, 57] for 79 % (31/39), or at daytime for 20 % (8/39). Indeed it is known that skin surface temperature usually increases at night, thus resulting in heat dissipation and the core body temperature drop that has been associated to sleep triggering [57]. In contrast, inter-subject variability was limited for rest-activity, with all the 67 subjects displaying a dominant circadian rhythm, and 97 % (65/67) of them having an acrophase of activity located in the afternoon or early evening. Consistently, only 5 of 55 healthy subjects had a dichotomy index I<O between 97.5% and 95.5%, a rate in good agreement with a prior study using wrist actigraphy in 182 young subjects [27]. Half of the 12 cancer

patients had an I<O ranging between 97.5% and 88.7%, i.e. the same rate as that previously reported using wrist actigraphy in 436 cancer patients [22, 27]. This suggests that there is consistency of both recording methods regarding I<O estimation. There were statistically significant relations between temperature period and amplitude on the one hand, and sex, age and I<O on the other hand, while no such correlations were found for the circadian rest-activity parameters derived from the spectrum. Moreover, the circadian acrophase of thoracic temperature occurred at nighttime, thus indicating physiologic circadian coordination, for 48 of the 54 subjects (89%) whose I<O exceeded 97.5%, while it was located at daytime for 6 of the 10 subjects (60%) with a lower I<O. These findings suggest that low I<O values could reflect non-physiologic circadian coordination. Hence temperature monitoring significantly increased the information already provided by rest-activity regarding CTS function, as suspected in pilot studies [44, 45].

Sex and age as important determinants of circadian coordination and timing

Here, women aged >35 y-o tended to have robust 24-h rhythms in their temperature, with larger amplitudes as compared to those in males. This apparent difference between circadian rhythms in temperature and activity has a neuroanatomic basis, which has been demonstrated in rodents [58]. Thus, the rest-activity and temperature rhythms were shown to be generated by the neurons located in the caudal [59] and subparaventricular zone of the suprachiasmatic nuclei [60, 61], respectively. Since body temperature is an important driver of both the resetting and the coordination of peripheral clocks [8], its rhythm could play a critical role for the circadian timing of medications [13]. The larger amplitude of the circadian rhythm in temperature shown here for women supports the hypothesis that circadian timing of medications is even more critical in women as compared to men. Moreover, larger circadian amplitudes have also been found in females, compared to males, for cortisol secretion, another key driver of peripheral clocks and clock-controlled metabolism and cell cycle determinants of drug effects

[5, 62]. Two separate clinical trials uncovered that the optimal timing of a multidrug chronomodulated chemotherapy protocol could lag 6 h behind in women as compared to men with this same cancer type [63, 64]. Such differences in circadian amplitudes, and time lag between males and females were similar in cancer patients and in mouse models [65, 66]. The sex-related differences in circadian timing system that were discovered here could explain why the same multidrug cancer chronotherapy protocol improved response rate, progression-free survival and overall survival in men, but not in women with metastatic colorectal cancer, independently of all other prognostic factors within a meta-analysis of three randomized international clinical trials involving 842 patients [28].

Study limitations and current perspectives

The main limitations of our study beyond the technological possibilities of the e-Health platform was its exploratory nature, with unbalanced sex and age distribution, as well as a limited number of cancer patients. We did not assess chronotype via an established questionnaire [67], or working hours, although the temperature and activity records provided an objective and quantitative phase assessment [68, 69]. Other indicators of circadian function, such as cortisol or melatonin rhythms or Dim Light Melatonin Onset [70] were not determined, nor did we investigate clock genes polymorphisms [71]. Indeed, genetic variants of human clock genes have been shown to be associated with phenotypic differences, which could allegedly impact on disease processes, including cancer [72]. Moreover, the various biomarker rhythms of circadian function can be differentially altered by disease processes [73].

Comparison with prior work

However, the technology supporting the platform here presented allows to fully integrate the new information brought about by circadian rhythms, jointly with repeated self-assessed symptoms and other measurable parameters. The PiCADo platform represents an answer to the limitations of the current hospital-centered care system, which was designed for responding to acute medical events,

rather than for managing the long term medical care required for cancer and other chronic diseases [74-76]. The latter illnesses not only represent the vast bulk of healthcare payload in western countries, but also their management is suboptimal, given the current hospital logistics constraints [77, 78]. This is especially true, since disease and treatment response dynamics vary from patient to patient, with most events occurring at home and remaining unnoticed, while impacting on daily life, and eventually cumulating and leading to emergency hospitalizations. In the previous inCASA study, we showed the reliability of a fixed internet platform for the remote monitoring of self-rated symptoms, body weight and rest-activity rhythm in cancer patients, and the rather good patient compliance. Moreover, such remote monitoring provided early warning signals of patient deterioration at home that resulted in emergency hospitalization 3 days later. Circadian disruption played a prominent role in the determination of such early warning signaling [26]. Here, we aimed at improving circadian timing disorders detection through combining rest-activity and temperature monitoring, while being also able to integrate self-rated symtoms and body weight measurements, using a mobile, rather than fixed platform. We now believe that such PiCADo e-health platform could shift the current hospital-centered system of care towards a patient-centered system promoting biomedical progress. This would involve the safe delivery of care and support treatments at home or during the patient's daily activities, through adjusting cancer therapies to circadian rhythms, i.e. chronotherapy [26, 79-81]. PiCAdo further provides an ongoing monitoring system of the patient's wellbeing through developing forecasting analytical methodology integrating multiple sources (patient-reported outcomes, circadian rhythms in activity and temperature, physiological measures).

Conclusion

We have shown that such mobile e-health circadian platform allows automatic and non-invasive monitoring of precise circadian parameters in non-hospitalized healthy subjects and cancer patients. Preliminary analyses point to large and unsuspected inter-subject variabilities, which may be of great

importance when administering treatments and preventing emergency situations. Hence it deserves further testing as a tool for the real-time assessment of the CTS of humans of both sexes in various conditions, where two types of studies are currently in progress or about to start, respectively, in France and in the UK. The platform is being used for the determination of the impact of the occupational schedule on circadian function in the CIRCADIEM study, while the service rendered by this circadian e-Health platform is to be investigated further in cancer patients in the IDEAs study. Clearly, such system now needs assessment over months and in large patient cohorts within a prospective clinical trial. E-health circadian monitoring may indeed be of preventive and curative interest in a number of situations involving chronic conditions [82].

LIST OF ABBREVIATIONS

BLE: Bluetooth Low Energy

BT: Bluetooth

CL: Confidence Limits

CTS: Circadian Timing System

GPRS: General Packet Radio Service

IQ: Inter-Quartiles

IQR: Inter-Quartile Range

MDASI: M.D. Anderson Symptom Inventory

PROs: Patient-Reported Outcomes

SCN: Suprachiasmatic Nuclei

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Conflicts of interests:

JB and FL have co-founded ETIC-Systems, a start-up aiming at further developing e-Health connected devices for human health. N.B. and G.B. coordinated the PiCADo project on behalf of Altran Research, an international engineering company. The patent entitled "Procédé de détermination automatique de l'index de Dichotomie I<O d'un individu, Brevet français n° 1562557 du 16-déc-2015, N/Réf : UTT/16/F" involves shares of Université Technologique de Troyes, INSERM, and Altran.

Author contributions: S.K., P.F.I., A.A., M.B., A.U., F.V. and F.L. designed the study, recruited the subjects and followed data acquisition. S.K., Q.H., and B.F. performed the statistical analyses and iconography. M.M., J.B., N.B., G.B. and F.L. conceived the platform, coordinated the technology development, and performed preliminary descriptive analyses. B.F. and F.L. coordinated the manuscript development, and co-directed the work. S.K., Q.H, B.F. and F.L. wrote the manuscript. All authors reviewed the manuscript.

Multimedia Appendix:

Multimedia Appendix 1: **Intersubject variabilities in main rhythm parameters of healthy subjects in Cohort 1.**

Multimedia Appendix 2: **Inter-subject variabilities in main rhythm parameters of healthy subjects in Cohort 2.**

Multimedia Appendix 3: **Polar plots of mean temperature acrophases in study population according to dichotomy index I<O value.**

Multimedia Appendix 4: **Patients characteristics**

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