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Circadian Rhythm Stability Analysis from Actigraphy Data in Persons with Dementia

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***Abstract*— Circadian rhythms strongly influence psychiatric disorders such as dementia. The stability of circadian rhythms is of high interest in medical research and practice, yet the stability in the dynamic sense remains unexplored. In this study we introduce a set of indicators based on stability analysis. Actigraphy data collected from persons with dementia over seven days, four months apart, is filtered, and then frequency-based model fitting is performed, to which both pole-placement and damping factor analysis is applied. Concurrently, a method based on a multi-harmonic sine model is designed in collaboration with clinical experts to obtain an at-a-glance visualization of circadian rhythms. The method is scalable for multiresolution applications. Results show the capabilities of dynamic stability analysis based on actigraphy data.**

***Index Terms*— stability analysis, real-world data, circadian rhythm, actigraphy, dementia**

I. Introduction

Psychiatric disorders are strongly influenced by circadian rhythms [1]. Circadian rhythms are oscillations found in essentially every physiological process in the human body [2]. The suprachiasmaticus nucleus in the hypothalamus is the controller that sets the timing of the rhythms by managing temperature, neuronal and hormonal activity, also including melatonin (night hormone) production. The rhythms manifest as synchronized oscillations of activity and sleep-wake cycles [2] of approximately 24 hours. Circadian rhythms are key regulators of bodily functions such as thermogenesis, immune function, metabolism, reproduction and cell cycles [3]. Circadian rhythms undergo changes throughout the lifespan: the phase of the oscillation shifts from early morning during childhood, to later during adolescence, before returning to substantially earlier again in older adults [2]. This older age shift is often accompanied by further weakening of the circadian rhythms, decreased melatonin production, loss of rhythmicity, poor entrainment to the solar day, and internal desynchronization [4].

Dementia is a progressive syndrome most often caused by neurodegenerative disorders and is characterized by cognitive impairment interfering with daily living and presence of behavioral and psychological symptoms in dementia (BPSD) such as sleep disturbances, anxiety, depression, delusions, hallucinations and agitation [5]. In dementia, circadian rhythms become less robust [6] and their dysregulation potentiates BPSD, in particular agitation, sleep disturbances and sundowning [7]. Various treatment approaches, e.g., chronotherapy [8], require reliable analysis of the circadian rhythm for monitoring and to predict treatment effects.

The stability of circadian rhythms is a topic of high interest in medical research [9], [10], [11], [12]. In this field, the term stability refers to whether or not some characteristics or measured biomarkers of circadian rhythms are constant, most often the phase. Stability in the dynamic systems sense remains unexplored. Thus, in this interdisciplinary study, we perform circadian rhythm stability analysis for persons with dementia using system-related tools to obtain an assessment of the measured circadian rhythms and investigate a potential predictor for future behavior.

Paper organization. First, the circadian rhythm problem statement is discussed in section II, followed by a description of the real world data and study protocol in section III. In section IV we present the stability analysis for persons with dementia using actigraphy data. Results are presented in section V and conclusions in section VI.

II. Circadian Rhythm: Problem Statement

Circadian rhythms are quantified in phase (the timing of a reference point in the rhythm relative to a fixed event), period, and magnitude (as the double of amplitude, measured between the maximum and minimum of the wave), all of which assume a sustained periodic rhythm [13]. The gold standard biomarker for circadian phase is the dim-light melatonin onset, i.e., the timepoint when melatonin production rises in strict dim light conditions during the evening [14]. This procedure requires hourly samples of melatonin in blood, saliva or urine, while complying to a strict protocol of light exposure, dietary intake and activity [14]. This is not feasible for people with dementia and proxy measures for circadian rhythms are employed, one of which is the assessment of rest-activity rhythms with actigraphy data [15]. An actigraph is a wrist-worn device which can quantify movements over several days, usually equipped with accelerometer, and rarely gyroscope or magnetometer.

Circadian rhythm analysis traditionally reduces the rhythm to a single cosine wave, for which parameters such as the mesor (wave vertical bias), amplitude and phase are extracted (cosinor analysis [16]). Activity data seldom resemble a

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cosine wave, thus non parametric circadian rhythm analysis (NPCRA) utilizes statistical summaries, for instance: interdaily stability (IS), intra-daily variability (IV), averages of the least/most active five/ten hours (L5/L10), relative amplitude between M10 and L5 (RA) [17], [18]. Our interest is on $IS = N\sum_{h=1}^{p}(\bar{X}_h - \bar{X})^2(p\sum_{i=1}^{N}(X_i - \bar{X})^2)^{-1}$, which is a misnomer, as it does not evaluate system stability in the dynamics sense, and on $IV = N\sum_{i=2}^{N}(X_i - X_{i-1})^2((N-1)\sum_{i=1}^{N}(\bar{X} - X_i)^2)^{-1}$ (N number of data points, p data points per day, $\bar{X}$ mean of all data, $\bar{X}_h$ hourly means, X_i individual data points). These indicators were originally defined for $p = 24$ and while studies attempted to modify them for larger dataset sizes with varying reliability based on monitoring period [19], they do not capture the temporal dimension.

Moreover, circadian rhythms are composed of more than one harmonic (e.g., the sleep-wake cycle). For instance, nighttime disturbances and daily activities are not accounted for by the traditional indicators. For persons with dementia, the ability to track activity changes that happen with shorter periodicities is paramount for proper care.

Indicators with predictive properties are needed in dementia research, and thus the dynamic properties of the system (human body) must be considered, especially acknowledging that multiple dynamics can be involved in driving the observable outcomes of circadian rhythms.

Thus, in this study, we explore the stability of the human body as a system in a closed care loop, with day and night movement levels as output, and for unknown inputs. We therefore must consider an analysis based on frequency response. At the same time, this method should produce indicators that are easily understandable by clinicians and caregivers with no or little systems and mathematics background; thus, stability quantifiers must carry real-world significance that can be described through lay terminology.

III. Study Protocol: Real World Data

Participants. In this analysis we use data collected during the COSMOS study, a cluster-randomized controlled trial (2014 to 2015) aiming to improve the quality of life of nursing home (NH) patients. The study included 723 patients from 67 NHs in Norway, with a median Mini-Mental State Examination (MMSE) score of 11 points. The MMSE scale assesses cognitive function impairment [20] on a 30-point scale, with $0-11$ severe, $12-17$ moderate, $18-23$ mild, and $24-30$ none. Inclusion criteria: participants of ≥ 65 years living in the NH for at least 2 weeks. Patients with a life-expectancy of < 4 weeks were excluded [21].

Ethics. The trial was approved by the Regional Committee for Medical and Health Research Ethics, West Norway (REK 2013/1765) and registered at clinicaltrials.gov (NCT02238652). Data availability statement: the data used in this study is subject to restrictions and is available from BSH upon reasonable request.

System structure. The COSMOS study implemented the multicomponent complex intervention over 4 months, consisting of communication, systematic assessment and treatment of pain, medication review, organization of activities,

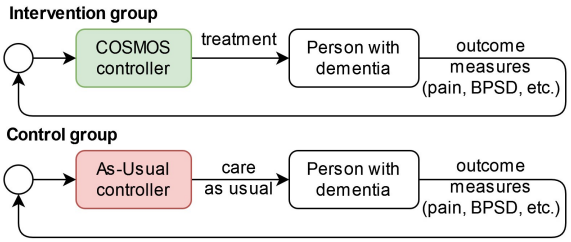

Fig. 1. System interpretation of the COSMOS intervention.

and safety. The control group received care as usual during this time, while the intervention group received the COSMOS complex intervention as treatment. Both are systems in closed loop (figure 1), where the COSMOS and the As-Usual controllers are represented by the formal caregivers deciding on the course of treatment or provided care; the two controllers work on different time samples: daily-weekly-monthly for the COSMOS treatment (depending on the intervention component), while As-Usual might not change the care command during the 4 months.

Measurements were collected twice, at the beginning of the period (baseline) and at the end: clinical assessment measures (full list in [22]) and 1-week continuous actigraphy.

Pain was assessed with the MOBID-2 Pain Scale [23]. The scale has two parts: a) musculoskeletal pain via 5 actively guided movements; b) another 5 items on pain from head, skin, and internal organs. Each item is rated on a $1-10$ point scale, with 0 no pain and 10 the worst pain possible, which are then combined by the rater into a total $1-10$ pain score. A total score ≥ 3 is considered clinically significant pain.

The Cohen-Mansfield Agitation Inventory (CMAI) is a 29-item instrument (range $29-203$) rating the frequency of manifested agitation and other behavioral disturbances [24]. CMAI items are defined on a $1-7$ point scale (1 never, 2 $<$ 1/week, 3 $1-2$ times/week, 4 several times/week, 5 $1-2$ times/day, 6 several times/day, 7 several times/hour). From the CMAI, we use the cumulative score on items $1-5, 7, 9-12, 14, 20-21$ representing: hitting, kicking, grabbing people, throwing things, scratching, hurting self/others, tearing/destroying things, making physical sexual advances, pacing and aimless wandering, trying to get to a different place, repetitious mannerisms, and general restlessness.

Nighttime disturbances were assessed by the Neuropsychiatric Inventory – Nursing Home version (NPI-NH) [25], which measures the frequency and severity of 12 symptoms defined over natural sets: frequency $F \in \{0,\ldots,4\}$ (0 symptom not present, 4 present daily); severity $S \in \{1,2,3\}$ (1 mild symptom, 3 severe). The score for each symptom is given by $F \times S \in \{0,\ldots,12\}$. Scores $F \times S \geq 4$ are associated with clinically significant symptoms.

Actigraphy data was collected using a Philips Actiwatch Spectrum [26], which a wrist device equipped with a 3-axis accelerometer. The measured acceleration is then scaled into so-called "activity counts", quantifying the amount of movement of the wrist per minute via the sum of scaled peak accelerations measured every 15 seconds.

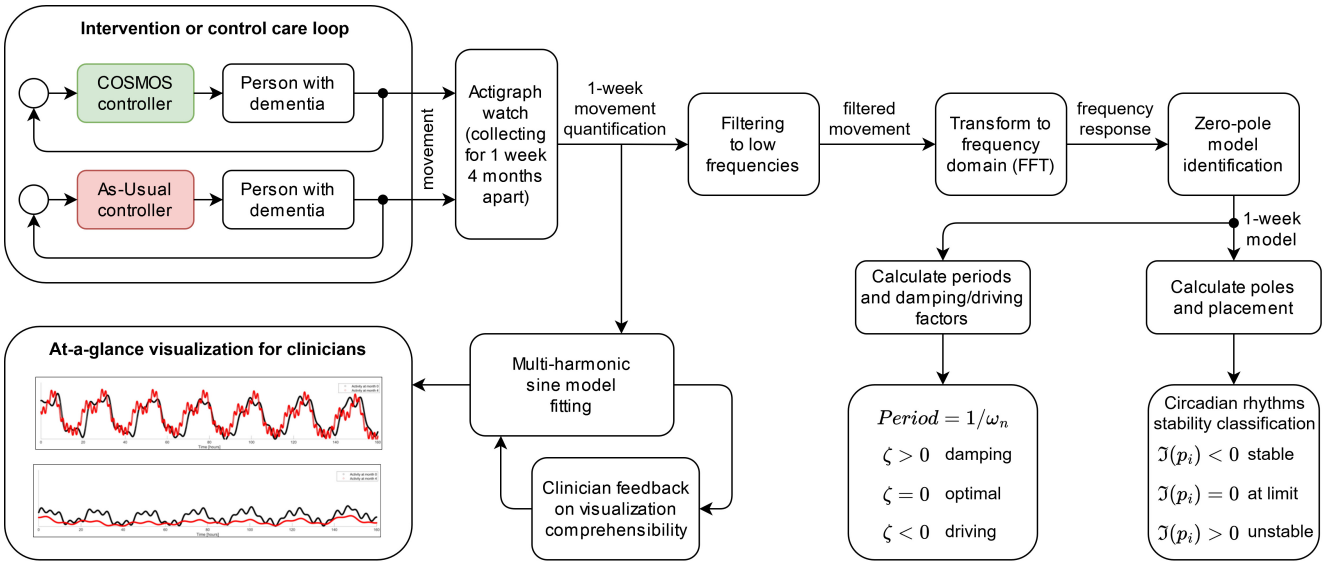

Fig. 2. Concept for stability analysis of circadian rhythms for persons with dementia using actigraphy data with at-a-glance-visualization design.

IV. Stability Analysis from Actigraphy Data

The analysis in this section concerns the stability of circadian rhythms for the person with dementia as described in figure 1. From a systems point of view, the body of the person with dementia as it responds to treatment, care, or other social inputs, is a nonlinear system for which one single comprehensive model does not exist. However, the manifestation of circadian rhythms as observable movement (measured in this case by actigraphy) is, or can be approximated by, a multi-harmonic sine wave. This behavior is particular to second-order systems with complex conjugate poles. Thus, we propose that the circadian rhythms of a person (dominant cycle of 24 hour, or secondary cycles with periods smaller than 24 hours) can be described by the position of conjugate pole pairs: on the imaginary axis for optimal behavior of periodicity at the so-called stability limit, shifted toward the left-hand side plane for damping behavior, or toward the right-hand side plane for driving behavior. Moreover, in the bodies of persons with dementia changes are slow, with dynamics spanning months, therefore it is plausible that 1-week observations can be locally approximated with linear system representations, which will describe the status of the person during that period.

With these considerations, we propose that the 1-week snapshot of the circadian rhythms can be approximated with a zero-poles linear model. Let q be the number of circadian rhythms to be analyzed. The proposed model is then:

$$G(s) = \frac{s^q + z_{q-1}s^{q-1} + \cdots + z_0}{s^q + p_{q-1}s^{q-1} + \cdots + p_0}, \tag{1}$$

where the anticipatory component corresponds to the treatment of the intervention or the care-as-usual routine.

For visualization, we propose a multi-harmonic sine model based on the first h harmonics:

$$V(t) = \sum_{i=1}^{h} a_i \sin(b_i t + c_i). \tag{2}$$

We arrived at this at-a-glance visualization in collaboration with our clinician colleagues who provided feedback on comprehensibility. In this study, the preferred multi-harmonic models had $h \in [q; 2q]$, for $q \leq 12$.

Figure 2 illustrates the concept for stability analysis of circadian rhythms for persons with dementia using actigraphy data with at-a-glance-visualization design. The filtering process aims to reduce the noise in the raw data caused by very small hand movements. The frequency domain response is chosen to account for all types of period inputs to the system, which are mostly unknown and unmeasured (day/night cycles, care routines, etc.). The calculation of periods from natural frequencies ω_n is necessary for comprehensibility by clinicians. Damping factors correspond to a decrease in rhythm amplitude, while driving factors to an increase. The circadian rhythms stability classification is based on the placement of conjugated pole pairs in relation to the imaginary axis of the complex plane, while any $|\zeta| \geq 1$ associated with real poles represents a total loss of periodicity.

V. Results and Discussion

Due to attrition, only 37 participants have a near-complete dataset of outcome measures and actigraphy. For our analysis, we selected 8 participants covering small and big changes in BPSD, to serve as a proof-of-concept: 4 persons from the intervention group and 4 from the control group.

We applied the procedure described in IV. All calculations and visualizations are obtained in Matlab 2019a. Filtering is Gaussian-weighted moving average (*smoothdata* function), while fitting is performed with the *tfest* function in its default configuration [27]. The model fitting for visualization is based on trust-region reflective least squares (*fit* function). In this study, we choose $q = 6$ and $h = 8$.

Figure 3 shows the frequency responses for all participants as raw and filtered data, as well as the response of the fitted models. The focus in this study is on low frequencies, which

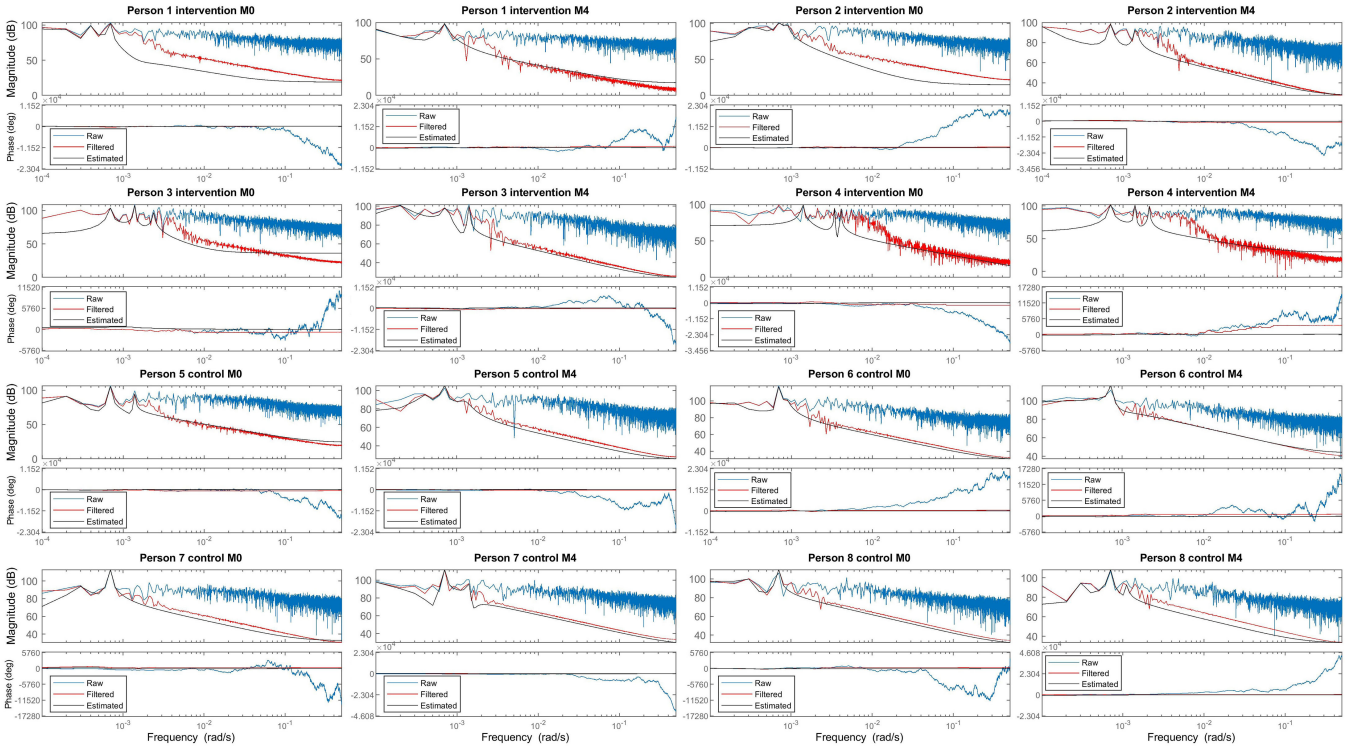

Fig. 3. Bode plots for system estimation results vs. the filtered and raw actigraphy data.

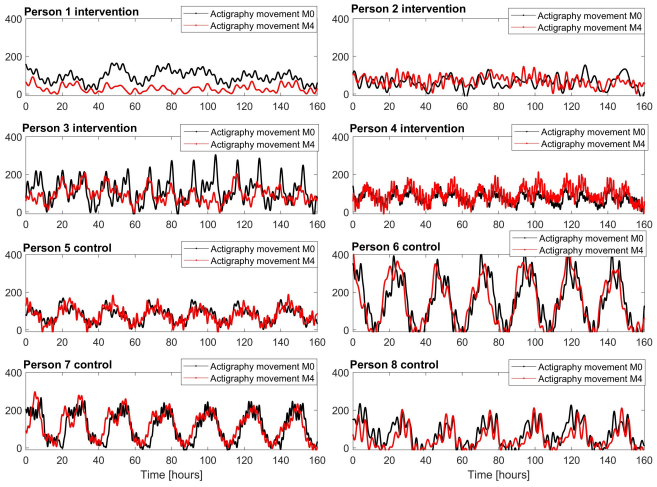

Fig. 4. Visualization of movement with multiple harmonic sine estimation.

the models fit well. The fitting percentages are between $15.47 - 86.39\%$. Interestingly, the fit percentages are on average 39.72% for the intervention group and 74.47% for the control group. At the same time, the higher frequency movement is more present in the intervention group, which is an effect of the multicomponent intervention, specifically the daily and weekly care activities. This means that both filtering and model fitting should be tailored based on the amount of caregiver interactions and/or other social activities.

Figure 4 shows the result of the visualization with a multi-harmonic 8-sine wave model. We arrived at this format through an iterative interdisciplinary design procedure together with our clinician team members.

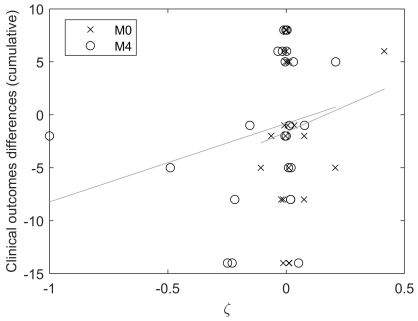

Fig. 5. Cumulative differences in traditional outcome measures vs. the dampening/driving factors at month 0 and month 4.

Table I presents the outcome measures for all participants at both collection points (baseline M0 and after four months M4), alongside all six poles of the identified models (presented as three complex conjugated pairs, and in one case two pairs and two first-order poles), the associated damping/driving factors for each pair (and in one case for each first-order behavior), and the first three or four dominant periods of the circadian rhythm associated with each pair (in one case for each first order behavior). Figure 5 shows the differences $M0 - M4$ between cumulative traditional outcome measures and ζ for all participants: negative differences signify worsening of symptoms, whereas negative ζ signifies increase in oscillation amplitudes (and vice versa).

However, because the traditional measures are state descriptors (status of symptom) and the system parameters such as dampening/driving factors, poles, and periods are dynamic descriptors (circadian rhythm changes over time), a correla-

TABLE I

RESULTS OF THE CIRCADIAN RHYTHM STABILITY ANALYSIS VS. TRADITIONAL MEASUREMENT SCORES.

Person	Group	MMSE	MOBID-2		CMAI		NPI-NH		Periods [hours]		ζ		Poles $\cdot 10^{-5}$	
			M0	M4	M0	M4	M0	M4	M0	M4	M0	M4	M0	M4
									11.3	16.7	0.011	-0.228	-0.92 $\pm i$ 69.3	-3.70 $\pm i$ 70.3
1	I	12	0	0	15	28	0	1	4.29	2.84	-0.012	-0.247	0.49 $\pm i$ 40.6	15.1 $\pm i$ 59.3
									2.51	2.47	0.013	0.052	-0.18 $\pm i$ 15.3	2.38 $\pm i$ 10.1
									5.18	18.9	0.075	-0.217	1.78 $\pm i$ 86.2	-2.66 $\pm i$ 143
2	I	1	0	3	29	34	0	0	2.55	2.45	-0.012	0.019	0.85 $\pm i$ 68.2	-1.36 $\pm i$ 71.2
									2.02	1.21	-0.020	0.018	-2.55 $\pm i$ 33.5	1.99 $\pm i$ 8.97
									2.56	8.75	-0.001	0.209	-3.08 $\pm i$ 236	0.55 $\pm i$ 139
3	I	13	7	6	30	22	8	12	1.26	2.36	0.005	0.030	-0.73 $\pm i$ 138	-2.25 $\pm i$ 73.8
									0.73	1.25	0.013	-0.003	0.10 $\pm i$ 68	-4.16 $\pm i$ 19.4
									1.25	2.45	-0.001	-0.009	0.16 $\pm i$ 413	-0.79 $\pm i$ 210
4	I	21	5	7	14	13	12	3	0.50	1.23	0.001	-0.008	-0.49 $\pm i$ 343	0.12 $\pm i$ 141
									0.42	0.83	-0.003	0.003	0.27 $\pm i$ 138	0.67 $\pm i$ 71.1
									7.60	4.60	0.034	0.077	-0.95 $\pm i$ 138	19.6 $\pm i$ 126
5	C	21	0	1	14	14	0	0	2.51	2.51	-0.007	0.014	0.50 $\pm i$ 69.5	-0.99 $\pm i$ 69.4
									1.25	1.36	0.006	-0.153	-0.78 $\pm i$ 22.9	-2.95 $\pm i$ 37.7
									11.8	3.48	0.076	0.0004	5.34 $\pm i$ 84.8	0.35 $\pm i$ 71
6	C	1	0	3	37	36	0	0	2.50	2.45	-0.002	-0.005	0.18 $\pm i$ 69.8	-0.02 $\pm i$ 50
									2.05	23.7 & 3.19	-0.062	-1 & -1	-1.12 $\pm i$ 14.7	7.35 & 54
									6.40	40.5	-0.106	-0.489	-0.76 $\pm i$ 69.2	-2.86 $\pm i$ 138
7	C	7	1	4	22	24	0	0	3.22	2.52	0.207	0.010	-11.2 $\pm i$ 52.9	-0.69 $\pm i$ 69.2
									2.51	1.26	0.010	0.020	2.9 $\pm i$ 27	2.1 $\pm i$ 3.75
									12.6	5.68	0.414	-0.034	0.68 $\pm i$ 69.6	1.77 $\pm i$ 112
8	C	16	3	3	23	22	9	4	5.14	2.52	0.0005	0.002	-0.02 $\pm i$ 33.9	-0.14 $\pm i$ 69
									2.50	1.55	-0.009	-0.015	-5.71 $\pm i$ 12.5	1.06 $\pm i$ 30.6

Note. Groups I intervention, C control; M0/M4 month 0/4. MMSE $\in [0;30]$ (low score: impaired cognitive function); MOBID-2 $\in [1;10]$ (high score: high pain levels); selected CMAI $\in [11;77]$ (high score: high agitation levels); nighttime disturbances NPI-NH $\in [0;12]$ (high score: frequent, severe).

TABLE II

INTERDISCIPLINARY CLINICAL/SYSTEMS INTERPRETATION OF RESULTS OF THE CIRCADIAN RHYTHM STABILITY ANALYSIS VS. TRADITIONAL MEASUREMENT SCORES, OVER A 4-MONTH PERIOD.

	Pain	Movement agitation	Nighttime disturbances	Periods [hours]	Dampening or driving factors	Pole characteristics and stability (real part)
1	no pain	increase	very slight increase	1 large increases 2 small decrease	increase from 3 around 0 to 2 driving 20%	increase from 1 to 2 unstable 1 unstable becomes dominant
2	significant increase	increase	none	1 increases significantly 2 small decrease	increase from 3 around 0 to 1 driving 20%	decrease from 2 to 1 unstable with 1 stable larger in size
3	slight decrease	decrease	increase	1 increases significantly 2 small decrease	increase from 3 around 0 to 1 dampening 20%	maintains 2 stable all larger in size
4	increase	none	significant decrease	all increase slightly but remain small	all 3 maintain around 0, slightly larger	maintains 2 unstable small size variations
5	slight increase	none	none	1 decreases ($\sim$half) 2 remain small	increase from 3 around 0 to 1 dampening 15%	maintains 2 stable 1 unstable becomes dominant
6	significant increase	approx. constant	none	periodicity disrupted by 2 first-order behaviors	increase in driving to 100%	two unstable become real losing periodicity
7	significant increase	approx. constant	none	1 increases significantly 2 small decrease	1 driving increases to 50% 1 dampening increases to 20%	1 stable decreases significantly maintains 1 unstable
8	constant	approx. constant	decrease	2 decrease ($\sim$half) 1 remains small	2 maintain around 0 1 dampening decreases 40% to 0	increase from 1 to 2 unstable 1 stable loses dominance

tion analysis between them is not suitable. Therefore, we proceed to an interpretation of both outcome measure types from the clinical and the systems perspectives. Thus, table II shows the interpretation of the periods, dampening/driving factors and pole configurations. The loss of periodicity is validated against the interpretation of the traditional outcome measures. For instance, participants 1 and 2 experience increased agitation, reflected by the appearance of driving factors in the M4 model compared to M0. Participant 4 experiences increased pain but decreased nighttime disturbances, reflected by the unstable poles. Participant 6 loses periodicity, as shown by the visualization in figure 4.

When it comes to predicting the overall improvement or deterioration of the health status based on the circadian rhythms, the driving/dampening factors themselves, as well as the positions of the poles, give an insight on how the system response would evolve without changes in inputs (e.g., treatment). We surmise these model parameters have the potential to become predictors, but different data is necessary for proof, collected over longer periods and from complementary sensors (e.g., heart rate, temperature) in addition to movement.

For all participants IS $\in [0.0131;0.0644]$, with differences between the M0 and M4 measurements of maximum 0.88%, which does not properly reflect the changes in periodicity. Similarly, IV $\in [0.3716;0.8473]$, with the exception of one

measurement (person 1, M4) which was 1.0733; according to [18], values of IV<1 correspond to healthy persons, which is clearly not the case here, and thus IV does not suit our focus population, i.e. persons with dementia.

VI. Conclusions and Future Work

In this paper we propose a circadian rhythm stability analysis method from actigraphy data for persons with dementia based on frequency domain transfer function identification and a visualization procedure with multi-harmonic sine models. Results show that dynamic and stability analysis of actigraphy has the potential to inform on the evolution of circadian-related health status for persons with dementia. Our proposed method is also compatible with multiresolution analysis at different time scales for various rhythms. In the next step, we aim to incorporate the anticipatory behavior from zeros in the analysis, as well as other factors that can affect circadian rhythms, such as medication reviews and progression toward the end of life. Ultimately, we will include the results of stability analysis into a classification algorithm that accounts for measurements with traditional scales and for systematic medication reviews, developed around reasoning based on clinical expert knowledge.

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