Real Time Telemetric Monitoring of the Circadian Rhythm via a Wearable Device for Cancer Patients undergoing Chemotherapy

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1) Introduction

Wearable devices allow for non-invasive telemonitoring of patients. Physiological data, such as physical activity (PA) and body temperature, can be collected in the daily living environment of the patient without the need for hospitalization. Thus patients can be admitted to *"virtual wards"*. The devices can be used to monitor the Circadian Rhythm (CR), which regulates many critical cellular processes (Schibler et al. 2015 Cold Spring Harb Symp Quant Biol), and to detect adverse events which pose a risk to health. The appraisal of the CR in real time could lead to chronopharmacological strategies and personalized medicine.

Disruptions of the CR in cancer patients are associated with poorer treatment outcomes, and short progression-free and overall-survival (Lévi et al 2014 Chronobiol. Int. 31 (8)). The MultiDom clinical trial (NCT04263948) telemonitors patients with pancreatic cancer undergoing standard chemotherapy aiming to reduce the rate of patients undergoing toxicity-related emergency admissions (Bouchahda et al. 2023 BMJ Open. 13(6)). Figure 1 summarises the MultiDom protocol.

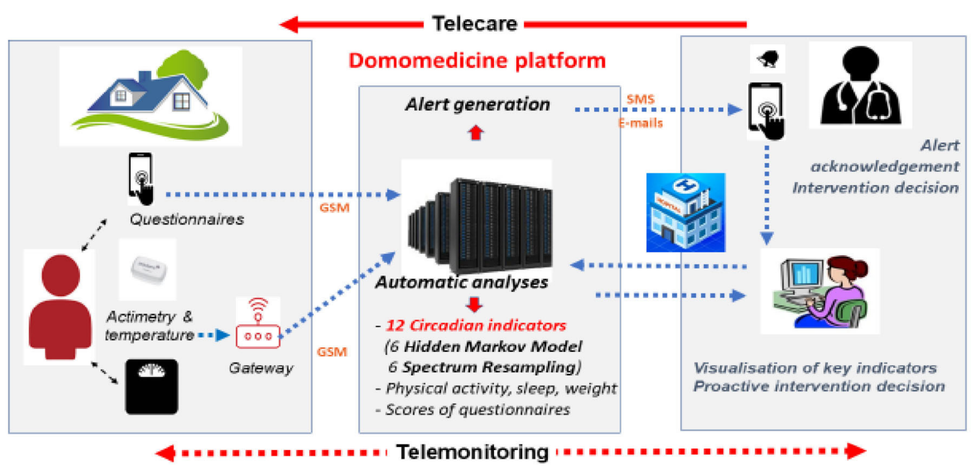

Figure 1: Diagram illustrating the MultiDom protocol, source Bouchahda et al. 2023 BMJ Open. 13(6).

Our Aim is to compute in real time "circadian parameters" (e.g. amount of rest and its regularity) from actimetry that are of interest to daily remote monitoring and can trigger proactive intervention.

2) Hidden Markov Models

Hidden Markov Models (HMMs) have two building blocks:

1. The hidden state process: states are given by Rest (includes sleep), Moderate and Intense, Activity. States are hidden (i.e. not observable) and we want to learn them. The current state S_t depends on the past only via S_{t-1} (Markov property). The transition probability of moving from one state to another is given by $\pi_{ij} = P(S_t = j|S_{t-1} = i)$.
2. The emission process: emissions (observations) are given by the activity as recorded by the sensor. The current observation Y_t depends only on S_t, i.e. $P(Y_t|S_t)$. Figure 2 is a graphical representation of a HMM.

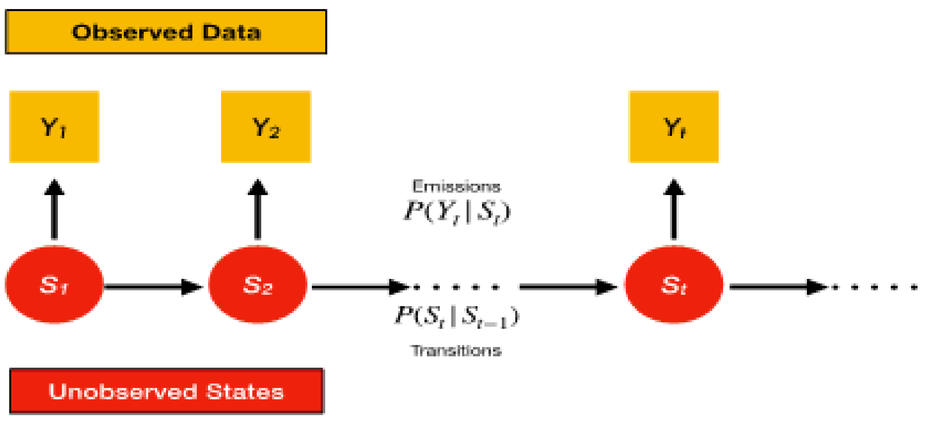

Figure 2: Graphical representation of a HMM.

To incorporate circadian rhythm we assume that the transition probabilities of the Markov chain follow a circadian oscillation, this is obtained via cosinor oscillators (Cornelissen 2014, Th. Bio and Med Mod.) and a multinomial logistic link function. We are also considering P-splines as an alternative. The resulting Markov chain is non-homogeneous which poses serious challenges to the estimation. Indeed, during the day some transition probabilities can be either 0 or 1 creating a problem known as separation (Gosh et al. 2018, Bayesian Analysis). Under separation posterior means might not exist, and even if they exists mixing can be slow (i.e. our inference is inefficient). For these reasons we will use state of the art MCMC gradient based techniques.

We are interested in studying changes in the CR as patients undergo treatment. To allow comparisons before and during treatment we need to maintain consistency in the state interpretation. Hence, we estimate the HMMs during treatment by keeping the emission parameters of the baseline (i.e. before treatment started). For the treatment period, we take windows of 2 days in overlapping mode over one day. This is a compromise between having small windows and thus detecting disruptions as soon as possible, and having enough data to obtain reasonable estimates.

3) Preliminary Results and Conclusions

Baseline Activity and State Estimation

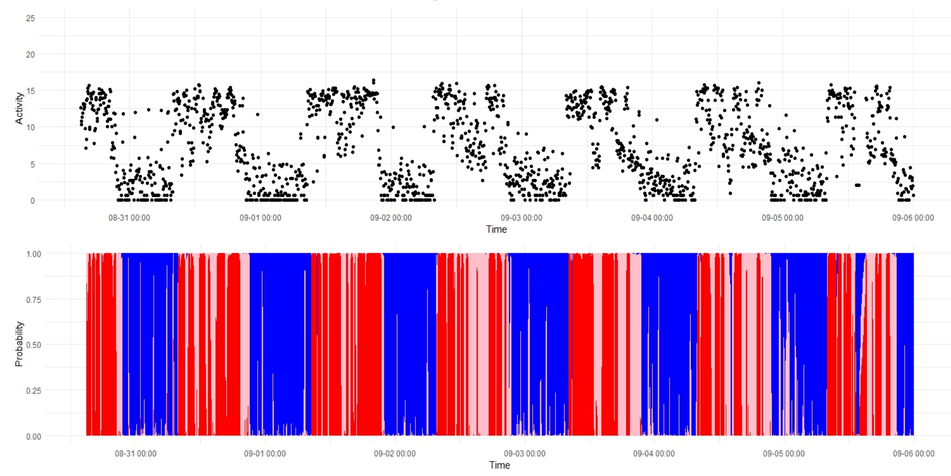

Figure 3: Top panel: raw activity data shown as 5 minute square rooted for Patient 4002 during baseline. Bottom panel: State probability plot; blue, pink and red are Rest, Moderate and Intense Activity respectively.

In this work we provide tools for Medical Experts to monitor in real time the CR of patients as they undergo chemotherapy and inform their decision making. Thanks to our Bayesian approach we can provide uncertainty quantification for the circadian parameters. To the best of our knowledge this is the first work to do so. Future work will investigate which parameters are the most significant for monitoring to trigger timely interventions from Medical Experts. Both Patients and Medical Experts involved in MultiDom were keen on the use of telemonitoring systems, in particular Patients felt safer compared to standard practice (Bouchahda et al. 2023 BMJ Open. 13(6)). The encouraging results of this work will help further develop the current domomedicine platform.

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