Robust Individual Circadian Parameter Estimation for Biosignal-based Personalisation of Cancer Chronotherapy

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Abstract—In cancer treatment, chemotherapy is administered according a constant schedule. The chronotherapy approach, considering chronobiological drug delivery, adapts the chemotherapy profile to the circadian rhythms of the human organism. This reduces toxicity effects and at the same time enhances efficiency of chemotherapy. To personalize cancer treatment, chemotherapy profiles have to be further adapted to individual patients. Therefore, we present a new model to represent cycle phenomena in circadian rhythms. The model enables a more precise modelling of the underlying circadian rhythms. In comparison with the standard model, our model delivers better results in all defined quality indices. The new model can be used to adapt the chemotherapy profile efficiently to individual patients. The adaption to individual patients contributes to the aim of personalizing cancer therapy.

Index Terms—cancer, chronobiology, circadian rhythm

I. INTRODUCTION

Cancer is a major public health problem all over the world. It is the leading cause of death in economically developed countries and the second leading cause in developing countries. There is also a big impact of cancer through a huge amount of financial costs for both the person suffering from cancer and the society. The general aim is to increase the overall survival rate. Therefore, the treatment efficiency for patients suffering from cancer has to be improved [10].

For this purpose circadian drug delivery in chemotherapy is used. Here, the tolerability and efficiency of anticancer drugs are improved on the basis of the circadian timing system in humans [13]. Today, often the standard chemotherapy as well as the radiation dose are chosen individually according to the tumour type. The new approach, considering the circadian drug delivery, further adapts the chemotherapy profile to circadian rhythms (chronomodulation) of the human organism. This reduces toxicity effects of the chemotherapeutic drugs and at the same time enhances the efficiency. To access circadian rhythms [19] in human, previous work dealt with the requirements to measure a marker rhythm which characterizes the timing of the internal circadian system [11]. Such a marker rhythm has to be periodic and easy to measure over a long period of time with non-invasive methods.

Up to now, the state-of-the-art was a fixed chronomodulated chemotherapy profile for all patients [16]. This fixed profile was extracted from experimental models of the rest-activity rhythm [7, 13]. To personalize profiles, information out of biosignals (e.g., rest-activity, temperature) was required to access the patient-specific circadian rhythms. Such biosignals containing cycle phenomena are often modelled using the Cosinor model [6, 17]. To model the rhythms, a cosine wave is fitted to the data using optimization algorithms. In general, the parameters of a cosine wave are used to describe the underlying rhythm [21]. However, the Cosinor model is not able to model different lengths of intervals within one period of a cycle phenomenon [19].

Therefore, the estimation of such rhythms containing different lengths of intervals within one period of a cycle phenomenon is not adequate using the Cosinor analysis [1]. This results in an increasing need for novel models considering the different lengths of intervals [3, 4]. This leads to a better description of individual differences in individual patients to further optimize the benefit of chronomodulated chemotherapy [7, 13]. The analysis of such models and the extraction of relevant information to characterize the patients is an important topic in research [3, 9, 12, 14].

To achieve this aim we developed a new method called Extended Cosinor model [20]. This model is able to represent cycle phenomena containing different lengths of intervals within one period. Therefore, a new segment-wise defined function is developed consisting of two cosine waves. With the different circular frequencies of the two cosine waves it is possible to model the different lengths of intervals. Also through the segment-wise definition of the model function it is possible to model the superior periodicity of the underlying rhythm.

This more detailed model of cycle phenomena in biosignals can be used to adapt the chronomodulated chemotherapy efficiently to individual patients. This contributes to the aim of personalizing cancer therapy.

II. METHODS

A. Extended Cosinor model

For the representation of the anti-periodicity within rhythms the Extended Cosinor model was developed. The model is able
to consider different lengths of two intervals (e.g. day and night, rest and activity) within one period. At the same time the model is able to consider the periodicity of the superior rhythm (e.g. 24-hour cycle). As a basis for the Extended Cosinor model, a new segment-wise defined model function is developed ($f_{\text{cos,Extended}}$). This model function consists of two cosine half-waves. The circular frequencies of the two cosine waves are used to model the different lengths of the intervals within one period. See Figure 1 for an example of the newly developed model function, where two cosine waves were combined to a new function.

![Model function of the Extended Cosinor model](image)

**Fig. 1.** Model function of the Extended Cosinor model: The two shifted cosine half-waves are shown in red ($f_{\text{cos1}}$) and green ($f_{\text{cos2}}$). Due to the fact that $\phi_1$ is equal to zero in this case, the intersection is at $\pi/\omega_1$. 

### B. Using the Extended Cosinor as a model for rhythms

For modelling rhythms with the Extended Cosinor model, the model function $f_{\text{cos,Extended}}$ has to be fitted to the original data extracted from the measured biosignals. For this purpose, a numerical optimization algorithm was used to estimate the parameter vector of the model function. Therefore, a quality index describing the goodness of the model was used to optimize these parameters. Furthermore, constraints are defined within the optimization algorithm. These constraints force the parameters of the model function to be set in a predefined interval. These intervals influence the shape of the function following characteristic patterns. Therefore, the constraints within the optimization algorithm are required for a better representation of the patterns within a rhythm (see Figure 2). All models and algorithms used were implemented using the Matlab toolbox Gait-CAD [15].

### III. Results

For the evaluation of our model we used two databases (Database A and Database B). Database A was created as part of a study in 2013 [8, 18]. Two biosignals, the temperature and the rest-activity signal, were recorded using wireless sensors (sampling rate of $\frac{1}{5}$ min). Both biosignals were monitored for 4 days in 10 patients suffering from cancer (for more details see [20]). Database B was created in connection with the PICADO project in 2012 [3, 8]. Here also the temperature and the rest-activity signal were recorded in 34 healthy people over a period of 4 days (sampling rate of $\frac{1}{10}$ min). For evaluation purposes we used the rest-activity signal in both databases as an example of a biosignal. The Cosinor model, as the standard model for representing rest-activity rhythms is compared with the new Extended Cosinor model using the quality indices listed in Table II.

**TABLE II**

| Quality index | Description | Abbreviation | Values for a good model |
|---------------|-------------|--------------|-------------------------|
| $Q_1$         | Sum squared errors | SSE | Lower |
| $Q_2$         | $R^2$ adjusted | Adjusted R squared | Higher |
| $Q_3$         | RMSE         | Root mean squared error | Lower |
| $Q_4$         | $r_{xy}$     | Correlation coefficient | Higher |

The results of modelling all rest-activity rhythms in Database A are listed in Table II. Here, the bold black values state the best results for each quality measure. As shown in the results the Extended Cosinor model is superior to the Cosinor models in all quality indices. An example of one rest-activity rhythm modelled with the Cosinor and Extended Cosinor model is shown in Figure 3.
For Database B, Table III lists the results of modelling the rest-activity rhythm. Here, also the Extended Cosinor model was superior to the Cosinor model regarding all quality indices. Moreover, Figure 4 shows one example for modelling a rest-activity rhythm in Database B.

### TABLE III

**Evaluation of different methods for the rest-activity time series in Database B. Here bold values represent better results.**

| Quality Index | Cosinor model | Extended Cosinor model |
|---------------|---------------|------------------------|
| $Q_1$ Mean ± STD | $2.92\times10^6 ± 2.92\times10^6$ | $2.67\times10^6 ± 2.65\times10^6$ |
| $Q_2$ Mean ± STD | $0.339 ± 0.136$ | $0.367 ± 0.135$ |
| $Q_3$ Mean ± STD | $0.338 ± 0.136$ | $0.367 ± 0.135$ |
| $Q_4$ Mean ± STD | $37.6 ± 23.7$ | $36.7 ± 23$ |
| $Q_5$ Mean ± STD | $0.573 ± 0.124$ | $0.599 ± 0.115$ |

The developed Extended Cosinor model provides better representation of rhythms containing intervals with different lengths in comparison to the Cosinor model. This advantage is based on the fact that the Extended Cosinor model in contrast to the Cosinor model is able to model different lengths of intervals within one cycle period. Furthermore, the underlying model function of the Extended Cosinor model provides more parameters in comparison with the Cosinor model. The higher number of parameters can be used for further accessing of the rhythms.

In this paper a new model (Extended Cosinor) representing cycle phenomena in rhythms is presented. The new model is evaluated against the standard Cosinor model using rest-activity rhythms as one exemplary biosignal. The Extended Cosinor model provides a better representation of rhythms containing intervals with different lengths within one cycle period.

The new model can be used to access biorhythms of individual patients. In the context of chronomodulated chemotherapy according to the biorhythms of the patients. However, there are some limitations so far. If the biorhythms are too disrupted, the quality of modeling is not as good as modelling normal rhythms. Therefore, future research has to handle the problem of adapting the constraints for model generation to cope with such phenomena and further adapt these constraints to every individual rhythm. It is suggested that adapting the constraints improves the model quality for individual patients and therefore makes a further step towards the personalization of chemotherapy.

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