Closed-loop control for optimising chemotherapy infusion

-A feasibility study-

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Shaping future proposals: Closed-Loop control systems for optimized treatments

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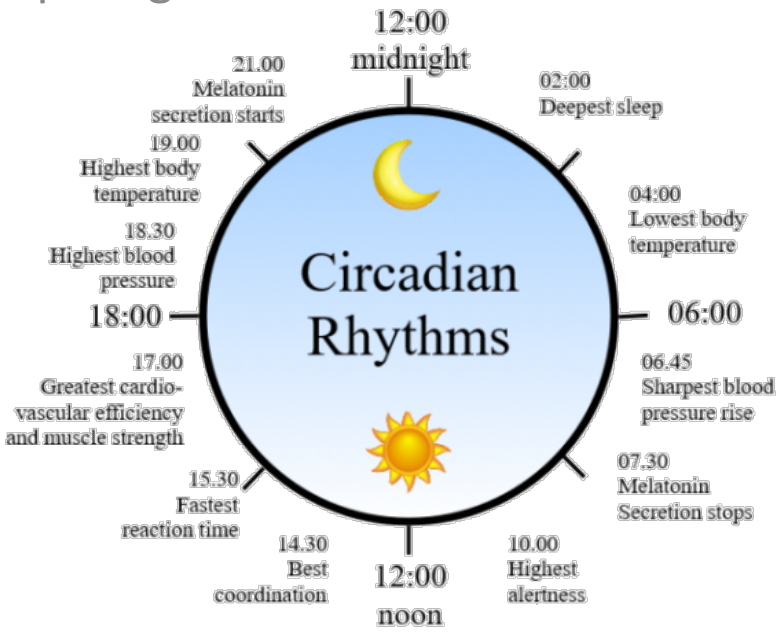
UNITED KINGDOM · CHINA · MALAYSIA

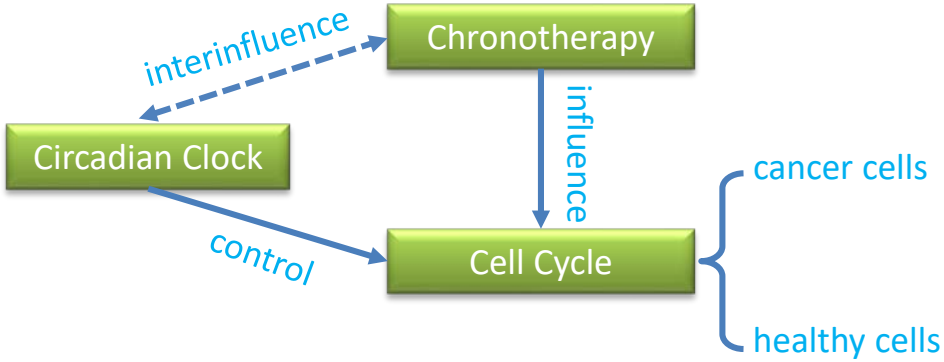
Project Overview

"Inner clock adapts our physiology to the dramatically different phases of the day, […] regulating critical functions such as behaviour, hormone levels, sleep, body temperature and metabolism".

(from 2017 Nobel Prize in Physiology or Medicine motivation*)

Circadian rhythms change the efficacy and side effects of chemotherapy throughout the day. Chemotherapy in turn alters circadian rhythm. This creates a closed-loop requiring control.





*https://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html

Project Overview

Circadian rhythms can be monitored using :

- Blood
- Salivary
- urine hormone tests.

BUT, they are not practical at home and are not real-time monitoring.

We aim to combine **artificial intelligence** and **signal processing** with commercial sensors to monitor circadian rhythms in real time. Is this feasible?






Open Questions

1. ***How often*** should sensor read-outs be made to accurately determine circadian cycle? Can we use commercial wearable devices?
2. ***Who benefits most*** from coordinating chemotherapy with circadian rhythm (e.g., gender, age, tumour staging/position)?
3. **Which measurements should be prioritised** when designing a closed-loop control intervention for chemotherapy?
4. ***How should we balance toxicity/side effects in healthy tissue*** against cell kill in tumour? Is this patient/tumour-specific?
5. **Which control approach is more effective** (e.g., state space mechanistic, machine learning, system identification)?
6. **How precisely will the loop be closed**?
7. **How accurate can predictions based on the circadian cycle be**?

Project Research Questions

- Research Question 1: can circadian rhythm be measured in real-time?
- Research Question 2: which measurements can be used to predict (and how accurately) circadian cycles (and patient responses) using artificial intelligence?
- Future Step: to provide fundamental knowledge to develop closed-loop controllers for delivering chemotherapy.

Project Objectives

Initial 6 months

- Pilot on healthy subjects.
- Improving and tuning the acquisition protocol.
- Dataset preparation.
- Preliminary model development and validation.

Research Question 1

Next steps

- Revise ethical approval
- Pilot on patients.
- Refine acquisition protocol.
- Dataset preparation.
- Model testing on patients.
- Model improvements…

Research Question 2

Project Update

Pilot study on healthy subjects

Signal pre-processing:

- Filtering
- Synchronise signals
- Visual inspection of signals and trends
- Dataset preparation

Preliminary data analysis:

- Can we gauge cortisol/melatonin level using other than hormones?
- Which Heart Rate Variability features (time, frequency and non-linear domains) can be used?
- Can statistical analysis identify significant and relevant features?
- Can Artificial Intelligence be used to automatically detect cortisol level?

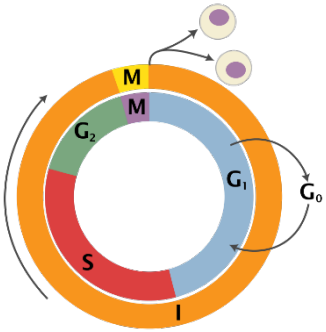
Project Update

Pilot study on healthy subjects

- Many HRV features (11 out of 14) changed significantly between peak and trough of cortisol level.

- An Artificial Intelligence model was able to recognise peak and trough of cortisol level with satisfactory performances.

A mathematical modelling approach



In general, the cell cycle is divided into 5 consecutive phases:

(1) G0: the cells are quiescent but can be recruited to the cell cycle.
(2) G1: the cells are in the pre-DNA synthesis or growth.
(3) S: the cells are in DNA synthesis.
(4) G2: the cells have synthesized DNA but have not started mitosis.
(5) M: the cells are progressing through mitosis.

- Simultaneously, deterministic modelling has been used to implement models explaining how the cell cycle changes over time.

What are the next steps?

Pilot on Patients

- Cancer patients recruitment in Wrexham Hospital-Ethical Approval in place, but it required a minor amendment according to pilot results.

- Differences in the circadian cycle before and after, will be associated with the therapeutic response and PROMS.

What are the next steps?

1. Machine-learning methods used to construct models for healthy subjects will be adapted to estimate circadian cycles in quasi-real time for patients.

2. Can these models be used to gauge therapeutic response?

Gaps and challenges

3. The design and feasibility of a controller that alters cancer therapy based on circadian alterations and predicted therapy responses will be investigated.

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