Biology-inspired Frequency Modulation for Full-body Synthetic Molecular Communication

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***Abstract*—Molecular communication (MC) is a step towards the future internet of bio-nano things (IoBNT) and a possible connection between life sciences and engineering for personalized medicine. To achieve this goal, we have to enable reliable communication through the human circulatory system (HCS). In this work, we introduce a novel frequency modulation (FM)-based communication approach for full-body MC. The presented approach encapsulates two different information states in an oscillating system inspired by the hypothalamic–pituitary–adrenal (HPA) axis of the human endocrine system. While the primary oscillation is produced by changing a feedback delay of one of the involved molecules, the secondary oscillation is driven by a changing intensity of the same molecule. We qualitatively compare our approach with amplitude modulation-based communication through the HCS and discuss its benefits for long-term MC-based monitoring in IoBNT applications.**

***Index Terms*—Molecular Communication, In-body Communication, Closed-loop Feedback System**

I. Introduction

Over the past decades, molecular communication (MC) has become an important future communication approach [1]. The concept of transmitting information via the exchange of molecules means that communication becomes possible where it was infeasible before. It is supposed to enable the future internet of bio-nano things (IoBNT) which connects life sciences and engineering for personalized medicine [2]. Possible applications in this area, such as Health Digital Twins, benefit from the ability to communicate the state of in-body implants to gateways readable from the outside [3], [4]. To enable this communication, the planned MC pathways must be able to communicate through the full body via the human circulatory system (HCS). At this point in research and time, this task still poses a problem.

Research shows that the complexity of an MC network topology has an immense impact on the received signal [5]. The HCS has a highly complex topology and makes reliable communication using the existing approaches very complicated, as most of those approaches are based on amplitude modulation (AM) [6]–[8]. They emit different numbers of molecules for different signals on the transmitter side and then detect those varying molecule levels on the receiver side. This approach faces some problems when considering full-body MC through the HCS, though. The received number of molecules depends highly on the location of the receiver and the volume of blood that reaches it. Age and activity are only two factors of many that influence how much blood is pumped into which part of the HCS over a given time period [9], [10]. This means that the number of detected signaling molecules will vary greatly in AM-based transmissions through the HCS. To enable MC based on AM, the decoding thresholds for the used particle levels would have to be highly adaptable, reacting to long-term and short-term changes. This is why in this work, we propose an alternative: frequency modulation (FM) based on existing communication processes in the human body.

Our solution for full-body MC using FM-based communication is inspired by the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is part of the gut-brain axis and an essential part in the human endocrine system. Its dynamics have only recently become the focus of MC researchers. While the Gut-Brain-Axis was analyzed from different viewpoints and possible interactions with it were predicted [11], [12], its potential in inspiring full-body MC has not been considered, yet. In the HPA axis, information is not only contained in the amplitude of the signal but also in its frequency. Imitating the oscillating system of the HPA, we designed an FM-based communication framework for full-body MC. While AM-based approaches struggle with communicating through the HCS, we will show that FM is more robust and is an opportunity to achieve full-body MC.

In this work, we present our biology-inspired FM-based communication approach for synthetic full-body MC The proposed approach encapsulates two different information states in an oscillating system, which can robustly communicate information from one position in the human body to another.

Our contributions can be summarized as follows:

- We design an FM-based full-body MC system,
- we translate a mathematical model of the communication in the HPA axis to a communication approach that lets us encode information for synthetic full-body MC, and
- we compare the formulated approach with an AM-based approach and show the superior robustness of our approach for full-body communication.

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II. Related Work

The concept of synthetic MC based on the communication processes in the HPA axis is a novel contribution, but the employed modulation approach and the consideration of full-body systems have been the subject of several related works. In the following, we will give an overview of the use of FM in MC and of full-body MC.

While AM is the prevalent choice in current works, FM has been tackled in MC research [8]. As a theoretical base, Huang *et al.* [13] derived a frequency-domain channel impulse response (CIR) for an MC channel with dispersion. Mahfuz *et al.* [14] compared binary transmission in MC for AM and FM. They found that the inherent properties of the signal propagation in MC led to the signal becoming unrecognizable after short distances. Chou [15] evaluated FM for MC and developed a decoder that would reduce the inter-symbol interference (ISI). In these cases, FM is used in artificial systems with much shorter transmission distances and more static network characteristics than what we consider here. Akyol *et al.* [16] on the other hand, implemented FM in a microdroplet-based MC testbed. Their work showed the applicability of FM to simple microfluidic systems. While in the mentioned setups, AM was still a viable option, it becomes less of an option for more complex and dynamic systems like the HCS.

The topic of full-body MC has seen a rise in contributions over the last years. While Chahibi and Balasingham [17] already considered communication through the HCS for targeted drug delivery systems ten years ago, Lekić *et al.* [18] recently proposed the adaptation and evaluation of targeted drug delivery systems with MC based on semantic communication concepts. They interpret the interaction of the drugs with the treated disease and the success of the treatment as factors driving the communication in a semantic context. Using the resulting system, they analyze the limits of the channel capacity of the drug delivery system. Lotter *et al.* [12], too, transfer the concepts of communication theory to a biological process. They propose the optimized modulation of the Gut-Brain-Axis for personalized treatment options. Using machine learning (ML), they design a system that lets them identify the modulating factors for recorded Gut-Brain-Axis dynamics. Ortlek and Akan [11] analyze the dynamics of the Gut-Brain-Axis in delayed differential equations (DDEs) and their meaning in a semantic communication system. They evaluate the impact of short-term and long-term stress signals on the system. While in the recorded work, the description and interaction with biological full-body MC system is the focus, we here instead propose to use the communication in the HPA-axis as an inspiration for full-body synthetic MC.

III. Natural Oscillations in the HPA Axis

The hypothalamic–pituitary–adrenal (HPA) axis is part of the human endocrine system and a major component in the body's stress response [19]. It is a closed-loop system based on the complex interaction of many different elements that can be condensed into the interaction between three main components [20]. Adrenocorticotropic hormone (ACTH),

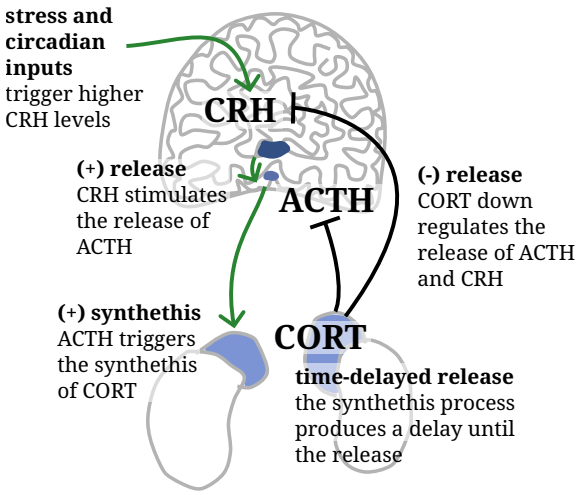


Fig. 1: The HPA axis is a closed-loop feedback system. Stress and circadian inputs drive the release of CRH in the hypothalamus. The CRH in turn triggers the release of ACTH in the anterior pituitary. Increasing levels of CRH and ACTH trigger the synthesis of glucocorticoids, CORT in humans, in the adrenal gland. The time needed for the synthesis process introduces a time delay into the system. The time-delayed release of the CORT then reduces the CRH and ACTH via a negative feedback loop.

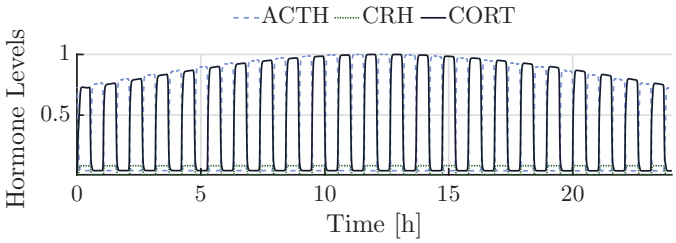


Fig. 2: The hormone levels of ACTH, CRH, and CORT naturally oscillate over time due to the time-delayed negative feedback of the CORT and the circadian inputs to the CRH [21].

corticotropin-releasing hormone (CRH), and glucocorticoids, cortisol (CORT) in humans, affect each other's hormone levels with positive and negative feedback loops. A schematic of the system is shown in Fig. 1.

Stress and circadian inputs induce the release of CRH in the hypothalamus. The CRH then induces the release of ACTH in the anterior pituitary. The hormones travel through the body and trigger the synthesis of CORT. With a time delay, the CORT is released and travels back to the brain. There, it negatively impacts the release of CRH and ACTH. The described system exhibits circadian and ultradian oscillations, as shown in Fig. 2. While the circadian oscillations are induced by changing circadian inputs triggering the increased or reduced release of the CRH and ACTH, the ultradian oscillations are inherent in the delayed feedback system. They originate in the time delay between the reception of ACTH and CRH at the adrenocortical gland and the release of the newly synthesized CORT [21].

In this work, we model the described dynamics with the three DDEs system introduced by Walker *et al.* [21]. In

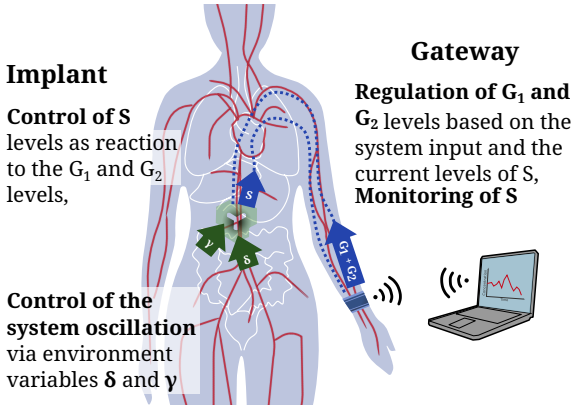


Fig. 3: The proposed system model encapsulates two implant environment states in the variables δ and γ. They impact the oscillation behavior of the system via the levels of component S. At the gateway, the current levels of S are monitored while the gateway states G_1 and G_2 control the continued running of the system.

their model, each equation represents the level of one of the involved hormones. CRH, ACTH, CORT react each others levels and their previous levels. The equations for ACTH and CRH do not contain a delayed component. Their output reacts immediately to changes in the hormone levels. The CRH and ACTH levels are inhibited by the currently detected CORT levels in the blood. They are driven by a changing parameter p_1 that represents the circadian and stress level inputs. The resulting ACTH levels drive the release of CORT with a delay δ. The complete system shows the circadian and ultradian oscillations visible in experimentally collected data [22].

IV. Full-body FM Synthetic MC

In order to achieve communication between outside entities and in-body implants or nanomachines, we propose a system model inspired by the endocrine system. Based on the biological communication system in the HPA axis, we design a full-body communication system for FM synthetic MC. In the following, we will introduce the general system architecture, and following this, we describe the mathematical model used.

A. System Model

Fig. 3 visualizes our system model. As depicted, we are considering communication between a gateway and an in-body implant. The gateway can be positioned anywhere on the body, and the implant is positioned in a fixed location in the HCS. The goal of the system is to monitor the state of the implant at the gateway. This state can be, for example, the temperature, number of specific biomarkers, pH value, or similar parameters of the implant environment. The implant senses this state of the environment and communicates it to the gateway, where it can be used for long-term monitoring in personalized medicine.

Similarly to the biological system of the HPA axis, we assume three communication components. The components G_1 and G_2 are released at the gateway, and the component S is released by the implant based on its sensor readouts. While components G_1 and G_2 are responsible for the continuation of the communication process, component S is responsible for the oscillation of the system. At the gateway, a constant baseline for the number of released particles of G_1 and G_2 is set. The released number of component particles is defined by this baseline and positively impacted by the number of detected circulating G_1 component particles as well as negatively impacted by the number of detected S component particles. While the G_1 particles travel through the HCS and influence the future gateway behavior, the G_2 particles travel through the MC network and impact the levels of S released at the sensor. Analogous to CORT's reaction to ACTH in the HPA axis, S reacts in a delayed fashion to the detected levels of component G_2. By linking the delay δ between the detection of G_2 and the release of S to the environment parameter that is to be observed, the oscillation of the system can be controlled. Taking temperature as an example, the delay of the system could be lower the higher the temperature of the environment. With a chemical process that happens faster the higher the surrounding temperature, this goal is achievable. A lowering of the temperature then induces a higher delay, which induces lower frequencies in the communication systems' oscillations. These changes in the oscillation frequency are observable at the gateway, independent of the gateway position. Potentially, the implant could even be mobile, as the movement of the gateway and the implant should only change the amplitude of the detected signal and not its frequency.

Additionally, the amplitude of the S component can be used to introduce a secondary oscillation analog to the circadian oscillation in the HPA axis. By tying a detectable environment parameter to the period of the oscillating amplitude of S, an oscillation with a lower frequency can communicate a second environment state. This could, for example, be parameters that are expected to vary more slowly over several days. With the given system, long-term developments could then be monitored and potentially inform medical decisions.

B. Mathematical Model

We base the mathematical model of our system on the DDE system by Walker *et al.* [21] and adapt it to fit our needs. The modified model can be summarized as

$$\begin{aligned} \frac{dg_1}{dt} &= \frac{(sg_1)^2}{p_4 + (sg_1)^2} - p_5 - p_6 g_1, \\ \frac{dg_2}{dt} &= \frac{p_1}{1 + p_2 g_1 s} - p_3 g_2, \\ \frac{ds}{dt} &= \gamma g_2(t - \tau) - s, \end{aligned} \tag{1}$$

where g_1, g_2, and s are the levels of G_1, G_2, and S, respectively, and the variables p_1 to p_6 are constants. The variable τ is the value of the implant sensor input controlling the ultradian oscillation. The value of γ follows a sine as

$$\gamma = p_8 \cdot \sin\left(\frac{2\pi}{\alpha} \cdot (t + p_7)\right) + p_9, \tag{2}$$

where α is the value of the implant sensor input defining the circadian oscillation, and p_7 to p_9 are constants. The resulting system models the communication component levels like the

HPA axis model by Walker *et al.* [21] but moves the input for the secondary oscillation to the implant side.

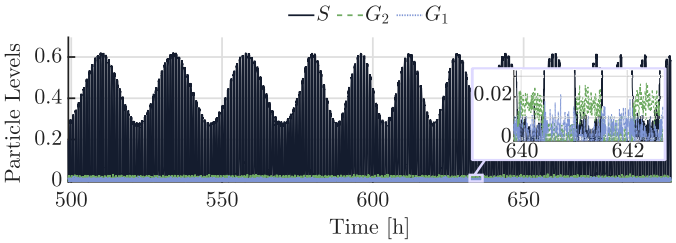


Fig. 4: The recorded number of molecules at the gateway shows the two oscillations changing over time. The overlay box shows a zoomed-in view of the signal to better display the lower amplitudes of the signals G_1 and G_2.

The signal detected on the receiver side records the two oscillations. Fig. 4 shows the changing levels of S over time based on Eq. (1). While the levels for G_1 and G_2 are relatively low with a minimal oscillation amplitude, the levels for S clearly show the two oscillations. The oscillation triggered by δ lets the detected number of S oscillate between 0 and a maximum value $S_{\max}$. The current value for $S_{\max}$ is determined by the input for α. Both oscillations can be robustly detected by looking at the signal in the frequency domain, as we will show in the following section.

V. Evaluation

In the following, we qualitatively evaluate the applicability of the proposed FM-based communication versus a simple AM-based approach for in-body MC. We first describe the evaluation setup. Following this, we consider the detectability of the modulated frequencies and compare the performance of the AM-based and the FM-based full-body MC for different gateway positions.

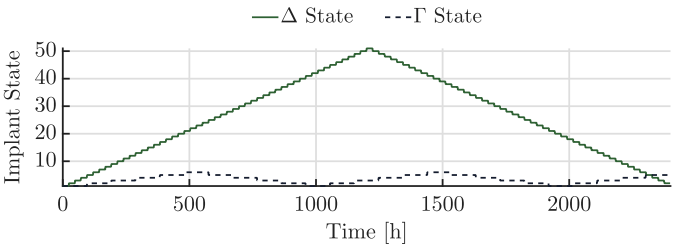
A. Evaluation Setup

In this evaluation, we consider the communication between the gateway and the implant for the system described in Section IV-A. The implant environment has two states, Δ and Γ. Using FM or AM, the implant sends the state of the environment to the gateway, where it has to be interpreted. The gateway is located at the right hand or the left foot for these experiments. It could potentially be located anywhere on the body. The used states and arrival likelihoods for the two positions are shown in Table I. The values of the implant states over time are visualized in Fig. 5a.

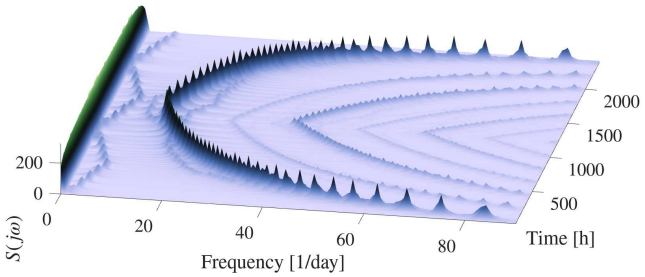
The transmission of the environment states is represented in the system via the value of S over time. In the FM approach,

TABLE I: Evaluation parameters

Parameter	Description	Value
Δ	Primary state of implant	ID = 1...51
Γ	Secondary state of implant	ID = 1...5
p_{rh}	Probability of blood reaching right hand	0.0136 [23]
p_{lh}	Probability of blood reaching left foot	0.0175 [23]



(a) The implant states Δ and Γ are changing over time.



(b) The fast Fourier transform (FFT) at the gateway over time.

Fig. 5: The FFT of the signal at the gateway in (b) shows the changing implant states of (a) over time. The primary oscillation of the Δ state shows up in the FFT in its highest peak, while the secondary oscillation of the Γ state is clearly visible in the first peak directly after the DC component.

the two states are transmitted in the two oscillations of the system. The state Δ is captured by the delay δ and drives the primary oscillation of the system. The Γ state gets translated into the period γ and is detected as the secondary oscillation at the gateway. Both variables impact the implant's release of S in response to the incoming levels of G_1 and G_2. The DDEs to calculate the component levels over time are evaluated in MATLAB[1] and the system constants are set based on the biological values for the HPA axis following Walker *et al.* [21] and shown in Table II. The number of S molecules recorded over time is analyzed via a FFT.

In the AM approach, the two states are transmitted directly in the number of released S molecules at the implant. Its reaction of the implant to the environment states Δ and Γ can be summarized as

$$S(t) = \Delta(t) \times 10 + \Gamma(t) \times 1000. \tag{3}$$

The state Δ produces an increasing molecule release in steps of 10 according to the state ID. State Γ triggers changes in steps of 1000 molecules according to the state ID. The factors 10 and 1000 are chosen so that $S(t)$ is unique for each state combination and which can be clearly identified at the receiver side. To keep the system simple, we here assume

[1]The code will be made available on GitHub at the time of the conference.

TABLE II: System constants

Parameter	p_1	p_2	p_3	p_4	p_5	p_6	p_7	p_8	p_9
Value	10	15	7.2	0.05	0.11	2.9	10	0	26

that particles, once released, only pass through the HCS once. More realistic assumptions would introduce more ISI and make the differentiation of states harder at the gateway. On the gateway side, the received number of S can be compared to predefined thresholds to identify the transmitted states.

B. Detectability of the Oscillations

At the gateway, the received number of S particles over time must be translated to the correct state. In the proposed FM-based communication approach, the states are encoded in the system's oscillation frequencies. We therefore analyze the recorded number of particles with the FFT of the received signal over time. We show the transmitted implant states over time in Fig. 5a and the FFT on the receiver side in Fig. 5b. In this evaluation, we use an FFT of the number of particles for component S over a full day.

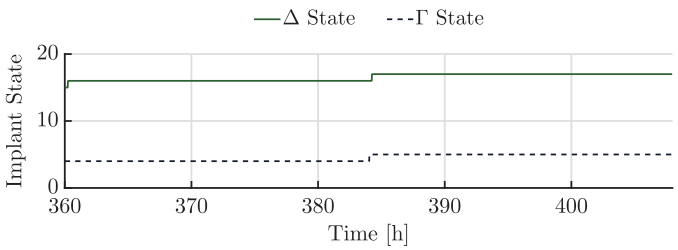
The FFT clearly illustrates how the two states were received at the gateway. The primary oscillation depends on the Δ state and changes every 24 hours in this evaluation. The state first increases from its minimum 1 to its maximum 51 and then decreases again to 1. The changed state is clearly visible in the FFT in the highest peak after the DC component. The peak moves from over 90 oscillations per day down to just below 20 oscillations and then increases again to 90.

The Γ state changes every four days and varies in a zigzag pattern between ID 1 and ID 5 and back. The resulting secondary oscillation shows up in the FFT in the first peak and varies, according to the input Γ state, between 6 and 2 oscillations a day. The zigzag pattern of the changing Γ state is clearly visible in the FFT. In the FFT, we can see that the frequency for the Γ state also introduces additional peaks around the peak of the Δ state.

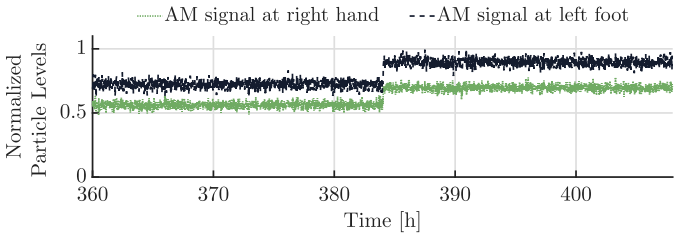
The chosen pattern with the Δ state changing every 24 hours and the Γ state changing every 4 days was chosen, so that both states would be easily recognizable in one FFT over a full day's signal with measurements once a minute, as shown in Fig. 5b. Both states can change at a different pace and will still be detectable in an FFT. The length of the signal and the number of measurements per minute that are considered in the FFT must then be adapted to pick up the correct frequency.

C. AM vs. FM in Full-body Molecular Communication

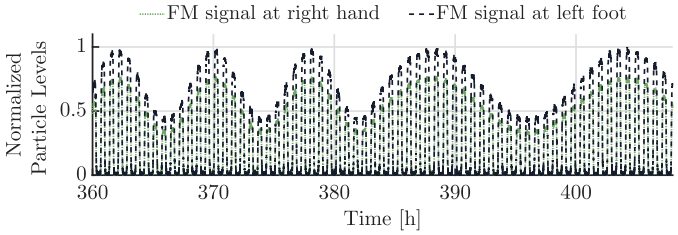
As most research up to date has focused on AM-based communication, it makes sense to discuss why, in this specific case, communication with an FM-based approach is more appropriate. In this subsection, we will therefore qualitatively evaluate the applicability of AM-based and FM-based MC to full-body communication. To visualize the differences between the two and showcase the robustness of our proposed approach, we include Fig. 6. It shows a detail snapshot of a two-day time period in the simulation for two potential gateway positions. It includes the transmitted states at the implant at that time in Fig. 6a, the particle levels for the AM transmissions in Fig. 6b and for the FM transmission in Fig. 6c, as well as the matching FFT in Fig. 6d.



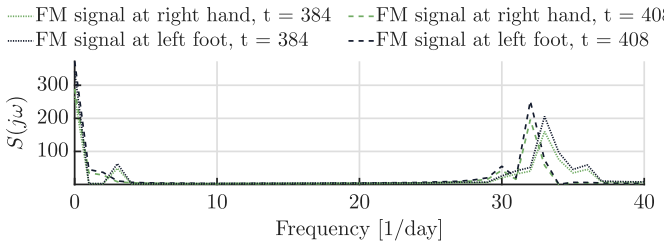
(a) The states transmitted by the implant.



(b) The received number of molecules of component S in AM transmission for two gateway positions.



(c) The received number of molecules of component S in FM transmission for two gateway positions.



(d) The FFT of the received signal for two different gateway positions.

Fig. 6: In the shown time period, the Δ state and the Γ state at the implant change as shown in (a). In (b), we observe that the different positions mean that different thresholds are necessary for the AM transmission. While the amplitude of the recorded signals also changes in FM approach for the different positions as shown in (c), it is robust to the changing amplitude and reliably produces the same output for the FFT as visualized in (d).

Fig. 6a shows the changing states between hours 360 and 408 of the simulation. At time 384, both the Δ and the Γ state increase to the next higher state ID. In Fig. 6b, we observe the changing level of component S for the AM transmission at this time period for two different gateway positions. With a change in the transmitted states, the number of transmitted particles also changes. Looking at only one gateway position, the two signal levels are clearly distinguishable. Once we consider a second position, the problem becomes apparent. The first signal level at the left foot is level with the second signal level

at the right-hand gateway. The gateways would therefore have to be aware of their position, and the thresholds will have to adapt the current flow behavior towards the gateway to enable reliable identification of the correct Δ and the Γ states.

Fig. 6c shows the signaling particle levels for the same time period using our proposed FM transmission scheme. The figure shows that at the left foot, clearly more particles are detected than at the right hand. This only impacts the maximum number of received particles, though. The oscillation is similar enough for both gateway positions. This becomes apparent when looking at Fig. 6d at the FFTs at the two gateway positions. The frequency response for the right hand and the left foot and very similar and detects the same frequencies for the Δ and the Γ states. At both gateway positions, the change of the two states is clearly visible in the FFT. The Δ state switches from 35 to 34 oscillations a day, and the Γ state switches from three to two oscillations a day.

The presented comparison shows us that our FM communication approach is more robust to changes in the gateway position. As different percentages of blood travel to the different parts of the HCS, changing numbers of particles will be detected at the different blood vessels and the gateway positions connected to them. This amplitude change happens not only for distinct positions, though, but may also occur naturally at the same blood vessel. Depending on the activity of the body, the heart will beat faster or slower. This means that more or fewer particles are transported to the same blood vessel [9]. We would therefore have to build gateways that are highly adaptable and continuously react to those changing particle levels to enable full-body MC based on AM. With our FM-based approach, the system becomes more robust to the natural changes in the blood flow through the HCS.

VI. Conclusion

In this work, we presented a biology-inspired frequency modulation scheme that enables full-body MC through the HCS. We adapted a DDE system to model the particle distribution and used it to show the superiority of FM for robust communication in complex MC networks. The approach is a step towards the implementation of long-term monitoring for personalized medicine. In our future work, we will extend this approach to include gateway-side interventions and evaluate the communication scheme in particle simulations of the HCS.

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