Towards T-cell based Bio-Robots: Synergy between Molecular Communications and Bio-Mechanics

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***Abstract*—In this paper, we report on our ongoing work in the field of bio-inspired micro robotics. We discuss, how different scientific disciplines, including molecular communications, have to be combined to realize systems capable of tasks like tumor clearance and pathogen elimination.**

I. Introduction

Molecular communications (MC) is a bio-inspired communication paradigm utilizing molecules as carriers of information. It has been proposed as one of the key communication paradigms for the bio and micro/nano domain. Since MC originated historically from communications engineering, it has been developed in a similar way, i.e., viewing the communication system as an isolated engineering system[1]. In bio-micro robotics however, this approach might not be appropriate as the communication system is an integral part of the overall system and cannot be clearly separated from it. Moreover, a common opinion in bio-micro robotics is, that respective systems should not be engineered from scratch, but by modifying pre-existing biological organisms accordingly [1]. As a consequence, it is crucial to understand, model and analyze these organisms to predict and optimize the effect of modifications. In this work, we follow this approach: Inspired partly by the well-known CART-therapy, we propose to use cytotoxic T-cells as bio-micro robots. We sketch a computational modeling framework to simulate the interplay between biological signaling, communications and mechanics ultimately enabling cell locomotion. In future works, we will implement and refine the preliminary framework presented in this abstract.

II. Biological System and Computational Model

A. Considered Scenario

In the following, we consider the simple scenario depicted in Fig. 1: We assume a T-cell crawling on a flat surface. On its membrane surface it exhibits G-protein coupled receptors (GPCRs) used for sensing the environment. Specifically, it uses these sensing units to determine the local concentration of chemo-attractants, i.e., molecules emitted by a source towards which the T-cell aims to crawl. This scenario arises, when other immune cells (e.g., macrophages) encounter pathogens or tumor cells and emit chemokines to attract cytotoxic T-cells. In our simplified scenario, we assume that the source is located at the coordinate origin and that the T-cells surface elements are described by a vector $\mathbf{r} = [\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_I]^T$. The vectors $\mathbf{r}_i,\ i \in \{1, 2, .., I\}$, are three dimensional vectors indicating the spatial location of a GPCRs on the cells membrane as a function of time.

B. Molecular Communications and Signaling Perspective

From an MC perspective, the molecule source is the transmitter (TX). However, in contrast to classical digital communications, in this scenario the TX continuously releases molecules. The released molecules diffuse across the medium

[1]In classical engineering this reductionistic approach is often well justified, because the electrical communication systems are typically much faster than the processes generating the transmitted information, e.g., sensors, actuators, etc..

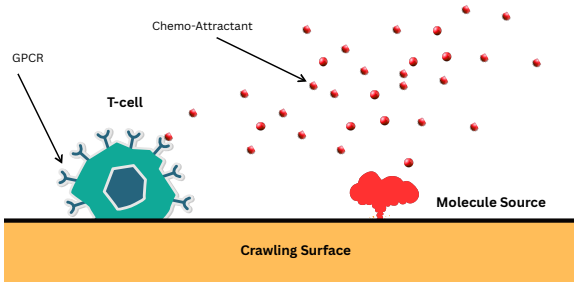

Fig. 1: Considered Scenario: A molecule source emits chemoattractive molecules. A T-cell senses these molecules using GPCRs and uses this information to crawl towards the source.

(i.e., the channel) until they eventually reach the T-cell (i.e., the receiver (RX)). At the RX the chemo-attractant molecules are sensed and converted into intracellular signals, which control the movement of the T-cell towards the source. Using the standard MC-TX models (e.g., point source) and assuming that the release rate Q from the TX is either constant or at least varies much slower than the time scale of molecule transport process (e.g., diffusion) the concentration $C(\mathbf{r}_i)$ at any location $\mathbf{r}_i$ can be computed according to

$$C(\mathbf{r}) = Q(t)g(\mathbf{r}) \tag{1}$$

Thereby, $g()$ describes the static space dependent transfer characteristic. The equation (1) can be used to compute the local concentration on the surface of the T-cell. Next, we discuss how the T-cell translates this information to an intracellular signal. We interpret this as part of the RX, i.e., we interpret the RX as a system which samples the channel at different locations $\mathbf{r}$ and translates it into signals $\mathbf{a} = [a_1, a_2, ..., a_I]^T$ and $\mathbf{m} = [m_1, m_2, ..., m_I]^T$ which control the the movement of the cell (see II-C). The conversion between extracellular chemo-attractant concentration and signaling molecules inside the T-cell is achieved using GPCRs, which can be modeled as shown in our previous work [2]. As the key intracellular signaling molecule downstream of the GPCR we consider the GTPase Rac, to which we attribute the following functions [3], [4]:

1) It promotes actin polymerization
2) It inhibits another GTPase called Rho, responsible for myosin contraction

These two functions link the molecular signaling to the biomechanics and, hence, the locomotion of the T-cell. Specifically, actin polymerization tends to expand the cell locally, while myosin activation tends to contract locally. As a consequence, areas with high local Rac concentration tend to expand, while those with low local Rac concentration tend to contract. Moreover, the probability of adhesion to the nearby surfaces is also higher in high Rac regions. A simplified schematic of Rac-induced local and global morphological and biophysical effects is shown in Fig. 2. Crawling emerges by a combination of protrusion formation and attachment in the front and

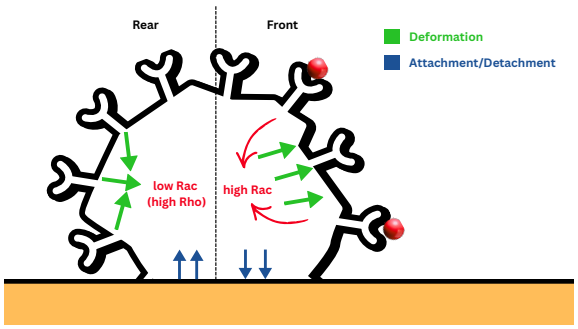

Fig. 2: Simplified crawling model based on Rac signaling: Front and rear can be determined by concentrations of external chemo-attractant molecules (red spheres), which translates (red arrow) to local Rac concentrations. In regions of high Rac, actin polymerization (not shown) leads to outward deformation. Lack of Rac (via missing inhibition on Rho) leads to inward deformation via myosin (not shown) contraction. Cells adhere more strongly to nearby surfaces at high local Rac.

contraction and detachment at the rear. Since Rac is degraded strongly inside cells we assume, that its concentration is elevated predominantly near the respective receptors and hence in the proximity of the surface. It is therefore justified, to associate always one Rac signal a_i with one $\mathbf{r}_i$. As a starting point we choose

$$a_i = [\mathrm{Rac}]_i = \frac{S(C(\mathbf{r}_i))}{\sum_i S(C(\mathbf{r}_i))}, \tag{2}$$

where $S(.)$ is the receptor saturation curve (e.g., $S(x) = \frac{x}{K+x}$ with half saturation constant K). The scaling $\frac{1}{\sum_i S(C(\mathbf{r}))}$ models the adaptation of local receptor signaling strength to overall signal strength (see App. III), a well established conceptual mechanism responsible for the polarization of eukariotic cells [5].
The concentration of Rho can be modeled based on the Rac concentration according to

$$m_i = [\mathrm{Rho}]_i = \frac{K_h}{K_h + [\mathrm{Rac}]_i}, \tag{3}$$

with K_h the half saturation constant.

C. Link to Bio-Mechanics

In the following, we will discuss, how molecular signals can be mapped to forces on the cell. To model the mechanics, we consider a simplified model of the T-cell, which focuses on the cortex, i.e., the active outer shell of the cell. This model will be derived based on the energy approach discussed in [6]. Therefore, the cells cortex is separated into elements obtained by triangular meshing. Each triangle i corresponds to a receptor patch $\mathbf{r}_i$ and therefore has associated signals a_i and m_i. Edges of the triangles are represented by spring with resting length l_0 and spring constant k. Additional springs accounting for bending angle between triangles, normal forces on the crawling surface, etc., will be incorporated successively. The signals a_i and m_i interact with the springs by increasing and decreasing resting lengths, respectively. Under the common assumption of overdamped dynamics, the ODE describing the system dynamics can be written in the general form [6]:

$$\mathbf{R}(\mathbf{r})\dot{\mathbf{r}} = \mathbf{F}(\mathbf{r}, \mathbf{a}, \mathbf{m}), \tag{4}$$

where $\mathbf{R}(\mathbf{r})$ is the dissipation matrix (accounting especially for friction with the crawling surface) and $\mathbf{F}(\mathbf{r})$ the acting forces. These forces can be computed as gradients of a global energy function [6], which allows great flexibility for incorporating various biomechanical properties (e.g., incompressibility of the cell interior).

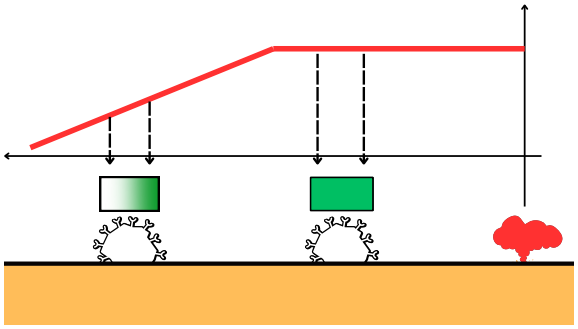

Fig. 3: Challenge of static gain in T-cell gradient sensing

III. Conclusion and Outlook

In this work, we presented a simplified mathematical abstraction of T-cell locomotion, focusing on signaling and its connection to biomechanics. In future works, this model will be implemented in software and is expected to provide novel insights into the challenges and opportunities of MC in the context of bio-micro robotics and engineering in general. Moreover, the model can be used to test and optimize modifications of T-cells for various tasks.

References

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Appendix 1: Motivation for Adaptation of Local Receptor Gain to Global Signaling Strength

We motivate the need for a local adaptation of signaling strength to global signaling intensity by contradiction: Assume, there were no global adaptation of local signaling intensity. Moreover, assume that $Q(t)$ from (1) can be arbitrary positive. Since the GPCR has some saturation dynamics, it would always be possible to create a scenario as depicted in Fig. 3. The graph depicted in red represents the local Rac concentration as a function of distance[2], which becomes increasingly flat as we approach the source. While the T-cell on the left operates in a region where a clear concentration difference can be sensed between front and rear, this is not possible for the T-cell on the right, due to receptor saturation. Hence, a model with static gain cannot approach an arbitrary source arbitrarily close. This contradiction can be resolved by acknowledging that, while Rac-signaling itself is highly localized, GPCRs might in parallel transfer information from one receptor patch to another, enabling cell-wide signal adaptation through MC.

[2]It would also be possible to plot over the chemo-attractant concentration; the conversion is achieved by (1)