Leader-Follower Optimization of Large Bacteria Population

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***Abstract* — We consider heterogeneous populations of engineered bacteria consisting of a few leaders that can sense various targets and then guide the follower bacteria towards these targets inside the human body. The follower bacteria represent the majority of the bacteria population and carry the payloads towards the region of interest for diagnostic or drug delivery purposes. Despite the appeal for healthcare applications, the modeling and control of such a heterogeneous bacteria population remains an open problem. Towards this end, we define an optimization problem that aims at finding the optimal percentage of leaders that need to be used in a heterogeneous bacteria population in order to minimize the average hitting time needed to reach a targeted region inside the human body.**

***Keywords* — Bacteria population, leader, follower, collective dynamics, dense networks of swarms.**

I. INTRODUCTION

The mathematical characterization of the collective dynamics of engineered micro-robotic swarms can be used for detection of silent progression of diseases [3]. However, for targeted drug delivery within the human body, the efficient modeling, analyzing and control of such dense networks of swarms represent a major challenge [2].

In this paper, we propose a new idea of using bacteria leaders which are engineered to detect abnormal behavior, such as unusual oxygen consumption, to minimize the time needed by bacteria population to reach a particular target inside the human body for diagnostic or drug delivery purposes. This is possible because bacteria leaders can be engineered to excrete chemo-attractants such that the follower bacteria can sense them and use chemotaxis to swim up the attractants gradient towards the abnormal regions.

II. PROPERTIES OF LEADERS AND FOLLOWERS

An important objective of synthetic biology is to reliably engineer bacteria, such that it can respond to environmental signals according to a pre-determined genetic program [4]. The design framework uses standard biological parts of wide variety of cellular functions ranging from transcription factors and enzymes, to gas vesicles and molecular chaperones.

In this paper, the sensory systems inside the leader bacteria are the "eyes" targeted to detect abnormal behavior. More precisely, the transmembrane sensor systems and synthetic gene networks of bacteria leaders are capable of sensing a desired signal, and transducing the signal to a cytoplasmic response regulator which regulate the state of flagella motor and the production of chemo-attractants. Then the chemo-attractants diffuse in the environment and can be sensed by the follower bacteria. For example, bacteria can sense oxygen by direct interaction of a membrane protein receptor (e.g. FlixL), or by a cytoplasmic transcriptional factor (e.g. Fnr), or redox-responsive regulatory systems [1]. In turn, and different from bacteria leaders with engineered "eyes", bacteria followers can be engineered to deliver therapeutic agents to targeted regions [4].

III. MODELING OF DENSE NETWORKS OF SWARMS

In order to characterize the dynamics of heterogeneous bacterial populations, we introduce a Langevin-type of model which tracks the trajectories and speed of swimming bacteria in a 3D space. Of note, the speed of the leaders is affected by their capabilities of sensing a pre-determined signal (e.g., oxygen consumption), while the speed of followers is influenced by the diffused chemo-attractant excreted by the leaders and the hydrodynamic interactions in viscous liquids.

Towards this end, we first study the dynamics of swimming bacteria by charactering the movement of leaders, diffusion of chemo-attractants, and chemotactic motion of followers. Second, we formulate a dynamic optimization problem which for a pre-defined time interval seeks to find the minimum number of leaders required to guide under certain environmental scenarios the bacterial population to the targeted region in minimum time.

Our results show that by introducing a small percentage of bacteria leaders, the average hitting time of the bacteria population from initial positions to target regions can be significantly reduced. Therefore, introducing heterogeneity and division of labor in bacteria population are crucial for solving the diagnostic and drug delivery problems.

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