Addressing by Concentrations of Receptor Saturation in Bacterial Communication

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ABSTRACT

Engineering of molecular and nano-scale communication networks may benefit future applications which interact with biological systems. Molecular communication networks are composed of bionanomachines which can interact with biomolecules or cells through transmission of molecules. One promising approach for generic communications is directional transport of molecules, such as by bacteria, to transmit molecules to another bionanomachine at a specific spatial location in an environment. In this paper, bacteria move to spatial locations relative to molecular beacons. Each molecular beacon emits a different type of molecule to produce a concentration gradient. A bacterium has a chemotactic pathway tuned for estimating its direction relative to the concentration gradients, and the specific concentrations at which the chemotactic pathway saturate represents a specific spatial address. Through simulation modeling, receptor parameters of bacteria were tuned to target various spatial addresses, and the latency and success rate of communication were characterized for receivers positioned at each spatial address.

Categories and Subject Descriptors

C.2.1 [**Network Architecture and Design**]: Distributed networks

Keywords

localization, bacteria propagation

1. INTRODUCTION

Applications which modify or control biological systems benefit from the ability to dynamically self-organize biological components. Such applications include medical applications to sense and interact with cells, environmental applications to detect and remove waste molecules, or self-organization to arrange biological components into products [1, 2, 11]. For example, in drug delivery systems, drug carriers move about a biological system, identify a location of interest, and perform biological processes at the location. Or for example, in tissue engineering, cells at relative locations differentiate into specific types of cells to form patterns of cell types.

Molecular communication is one promising approach to expand the ability for biological components to self-organize or interact. Molecular communication is the process of releasing molecules (e.g., ions, peptides, DNA) to transmit information. For example, information may be encoded in the concentration or timing of molecules released [9, 12]. One promising area in molecular communication is communication using motile cells, such as bacterial carriers [7]. Passive molecular communication mechanisms, such as diffusion, are slow and blindly search about an environment for a receiver; whereas, motile cells can sense conditions, such as concentration gradients, and propagate directionally through an environment towards a receiver [6]. Bacteria have been observed to self-organize into a variety of patterns during growth [3], and engineered control over these processes at a finer granularity may lead to novel patterns or dynamic control over cellular self-organization processes.

Generic addressing is an essential communication functionality especially as the number of bionanomachines increases. Most existing approaches within the research area of engineering molecular communication consider addressing by types of molecules. For example, a destination is represented by a type of molecule and router cells transmit using a type of molecule for each hop within a network [5]. In this paper, we design spatial addressing as a generic mechanism to propagate bacteria containing information to a subset of nanomachines. In our prior work, a bacterium acted as an active carrier of information and used accurate distance measurements to several beacons to target specific locations relative to the beacons [10]. In this paper, we redesign bacterial transporters using a saturation-based spatial addressing which is less likely to suffer from local minima. We then simulate a more realistic model of bacterial chemotaxis which considers bacterial sensing and motor activity. We apply a simple evolution of bacterial parameters to improve the success rate and latency of transmitting to receivers at specific spatial addresses.

Section 2 describes the design of beacons and bacterial propagation in the proposed system. Section 3 describes an evolution-based simulation of bacterial design to optimize the success rate of transmission to several spatial addresses. Section 4 concludes the paper.

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2. SPATIAL ADDRESSING BY CONCENTRATIONS OF SATURATION

In the proposed system, beacons produce molecular concentration gradients distributed spatially through an aqueous environment. Bacteria sense the concentration of each type of gradient molecule over time and control flagella to move relative to the concentration gradients. This section details these components and how they are integrated to produce addressing based on saturation of bacteria receptors.

2.1 Beacon model

Beacons release molecules to produce concentration gradients. Each beacon releases a different type of molecule so that a bacterium can distinguish between different beacons. For simplicity we assume beacons produce a steady state concentration gradient by releasing molecules at a constant rate in a 3-dimensional space. Flows are assumed to not be present. At a distance r from beacon $i, i \in I$, concentration for the type of molecule released by beacon i is

$$C_i(r) = \frac{N}{4D\pi r} \quad (1)$$

where N is the rate of molecule release from the beacon [4].

2.2 Bacteria propagation

The model applied this paper is based on related work which has developed a simulation model that characterizes the bacterial chemotaxis [13]. Subsequent chemical pathways within the bacterium convert the receptor activity into signals which control propagation of the bacterium and are described in [13]. Bacteria propagate by rotating flagella which determine whether the bacterium continues along its current direction ("run") or whether the bacterium randomizes its direction ("tumble"). The bacterium also experiences random rotational and positional perturbations. Based on the rate of concentration change, the bacteria changes the frequency of its tumble behavior. When the bacterium senses that it is moving in a direction in which conditions are becoming more favorable, the bacterium continues moving in the direction. When the bacterium senses that it is moving in a direction in which conditions are becoming less favorable, the bacterium is more likely to tumble and thus avoids moving in the less favorable direction.

2.3 Address Representation

In the proposed system, a spatial address is a location relative to beacons and each beacon produces independent concentration gradients by releasing different types of molecules. A desired spatial address is specified by the distances to each of the beacons. For a bacterium targeting a distance from a given beacon, the bacterium is designed to have its receptors become saturated at the concentration corresponding to the target distance for the given beacon. At concentrations above the saturation concentration, the receptors no longer respond to concentration changes for the given beacon.

Fig. 1 illustrates the concentration gradient of a beacon from the perspective of a bacterium which has receptors that saturate at some concentration. The saturation concentration of a beacon is illustrated as a circle around each beacon. Ideally, the bacterium has a sharp threshold for saturation

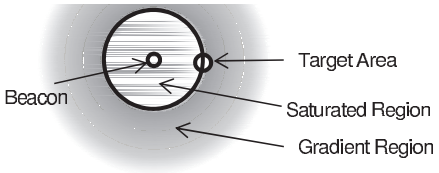

Figure 1: Saturation circle of a single beacon.

such that at concentrations less than the threshold (i.e., farther away than the desired distance), the bacterium follows the concentration gradient to move closer to the beacon. At concentrations greater than or equal to the threshold (i.e., at the desired distance or less), the bacterium ignores the type of molecule. If all chemotactic pathways are saturated, the bacterium responds as if there is no concentration gradient or roughly as a random walk through the environment.

Modification of the receptor numbers and activity is one approach for modifying the saturation concentration. The following summarizes several parameters of the model for receptors in [13] which we consider in this paper to modify the saturation concentration of receptors. Bacteria have Tar and Tsr receptors which react to the rate of aspartate concentration change over time. Receptors are clustered together in order to amplify a detected concentration, and a cluster contains certain numbers of Tar and Tsr receptors. Molecules in the environment bind to and release from Tar receptors with kinetics K_a^{on} and K_a^{off} respectively. Molecules in the environment bind to and release from Tsr receptors with kinetics K_s^{on} and K_s^{off} respectively.

2.4 Unreceivable State

In spatial addressing, the key difference between receivers is their location. Thus, an active bacterium may encounter and be received by an receiver at an incorrect location. If it arrives at an incorrect receiver, then an error in communication occurs. To reduce the chances of this, bacteria are assumed to start in an unreceivable state. This state gives the bacterium some time to bypass incorrect receivers while propagating to the target location. After some preset amount of time, the bacterium then enters a receivable state and transmits information to the first receiver it encounters. The bacterium is more likely to arrive at the correct location if it has sufficient time to propagate past incorrect locations and if it has a spatial distribution closely matching the target location when entering the receivable state.

2.5 Absence of Local Maxima

The usage of saturation concentrations avoids local maxima by ensuring that there is always a path to the target location with the same or increasing strength. Strength S for a spatial location L is the sum of beacon concentrations where the max concentration of each beacon is limited by the saturation concentration

$$S(L) = \sum_{i \in I} \min(C_i(r_i(L)), M_i) \quad (2)$$

where I is the set of indices for beacons, $r_i(L)$ is the distance from the location L to beacon i, and M_i is the saturation

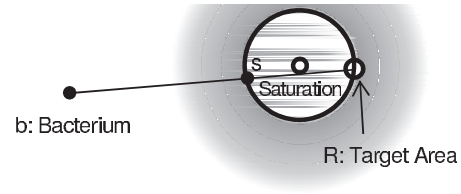

Figure 2: Regions in which saturated and unsaturated beacons appear relative to a bacterium and a target area.

concentration for beacon i. The concentration of receptor saturation of a beacon thus causes the strength for the beacon to be constant within the distance corresponding to the saturation circle.

Fig. 2 illustrates the line from a bacterium b to a target location R. For each given beacon, R is on a circle of saturation. On the line from b to s, distance to the center of the beacon is strictly decreasing, and thus strength is strictly increasing. On the line from s to R, strength is constant due to saturation. Thus, strength going along the direct path from b to R is non-decreasing. Since this is true for all beacons along the direct path, the total strength summed from all beacons is a non-decreasing function along the direct path. Since there is always a non-decreasing path to R, there are no local maxima.

3. OPTIMIZING ADDRESSES THROUGH EVOLUTION

3.1 Simulation Configuration

We integrated an existing simulation model described by [13] with our simulation of bacterial coordinates [10]. The existing simulation model in [13] produces a reasonably accurate model of the bacterial chemotactic pathway and molecular motors. In this paper, we consider a 2-dimensional space in which molecules independently diffuse away from 3 beacons to produce three independent concentration gradients. Positioning of components is relative to a point at coordinates (0 μm, 0 μm). For simplicity, the 3 beacons are positioned 500 μm from the point and form an equilateral triangle. (The results are expected to generalize to other beacon arrangements, but the bacteria may need to be tuned accordingly.) A bacterium decides to tumble based on a logical "or" of the 3 concentration gradients. This roughly produces the behavior of tumbling when the bacteria is moving away from any unsaturated beacon. The beacons produce a concentration gradient of $C_i(r) = 16/r$ molecules/μm^3. In this paper, we did not consider the impact of the specific concentration of the gradient.

Transmitters are positioned randomly within 1000 μm of the point (0 μm, 0 μm). We consider a simple addressing by which receivers are at 7 different locations. 3 locations correspond to the beacons, 3 locations at the mid-points between combinations of two beacons, and 1 location is at the median of all three beacons. Each simulated configuration was run with 1000 bacteria and each bacterium starts at a different transmitter.

3.2 Bacteria evolution

The specific configuration of a bacterium determines the range of concentrations to which the bacteria is sensitive as well as the concentration at which the receptors become saturated. Bacteria configurations were evolved for each of the 7 different target locations. Fig. 3 illustrates the locations for the 3 beacons used for all simulations. For simplicity, the concentration sensing pathway is assumed to be independent for each beacon (i.e., each beacon produces a different type of molecule and the bacterium has independent receptors and signal transduction for each type of molecule). For a given beacon, parameters which were allowed to mutate include the number of Tar and Tsr receptors per cluster and the reaction rates for the receptors (K_a^{on}, K_a^{off}, K_s^{on}, and K_s^{off}). Thus, the pathway for a beacon has 6 parameters and the pathways for all 3 beacons have a total of 18 parameters.

Each pathway corresponding to a type of beacon molecule was initialized to have the default parameters given from related work or initialized to become saturated very easily. This results in 7 initial bacterium configurations in which each configuration corresponds to different combination of easily saturating pathways. For example, one configuration has the pathway for the first beacon saturate easily and the pathways for the second and third beacon as default chemotactic behavior.

The positional error rate of a configuration was measured as the mean distance of the 1000 bacteria to the target location after 20 minutes of propagation. The next configuration to run was generated from three parent configurations which had the lowest positional error rates. Each parameter of the next configuration was selected randomly from one of the parents. Then each parameter was mutated as follows. The number of Tar and Tsr receptors per cluster was equally likely to remain the same, increase by 1, or decrease by 1 (a negative number of receptors is simulated as 0). The reaction rates for K_a^{on}, K_a^{off}, K_s^{on}, or K_s^{off} were equally likely to be multiplied or divided by a number drawn uniformly from the range (1, 2). A total of 300 configurations were simulated for each target location.

3.3 Simulation Result

Fig. 3 illustrates the positional error rate of 1000 bacteria achieved for each target location after evolution. Each "+" represents the most fit configuration where fitness is the mean distance of bacteria from the target location. The center of an "+" is the mean location and the length of the edges of the "+" represent the standard deviation (i.e., square root of variance) for the configuration in the x-axis and y-axis. For bacteria targeting locations on beacons, the bacteria are well localized and had the lowest mean error of around 50 μm. For the bacteria targeting the mid point between two beacons, the bacteria are more loosely localized and had a mean error of around 80 μm. For the bacteria targeting the median location of the three beacons, the mean error was relatively high at 130 μm. Further optimization may yield improvements in targeting locations. By symmetry, the three cases targeting the location of each beacon are equivalent; however, one case has much lower error rate (33 μm , 59 μm , and 59 μm mean error) and the others can also be reconfigured to have a matching error rate.

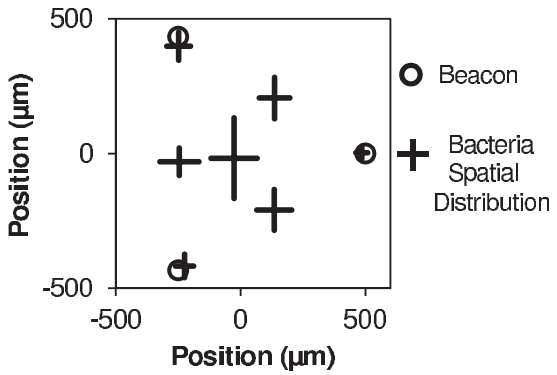

Figure 3: Spatial addresses with three beacons. Each + represents the mean and standard deviation along the x and y-axis for the location of each of the 7 evolved bacteria population configurations after 20 minutes of propagation.

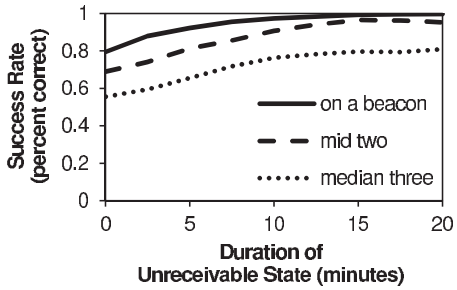

Figure 4: Duration of unreceivable state versus percent successfully arriving at the correct receiver. Bacteria target locations on a beacon, at the mid point of two beacons, or at the median of all three beacons.

Fig. 4 illustrates the success rate of receiving versus the duration of the unreceivable state of bacteria. Bacteria propagate for some amount of time before they activate, after which they are received by the first receiver they contact with a total 1 hour propagation. Success rate is the percentage of bacteria which arrived at the correct receiver. Bacteria required around 15 minutes in order to propagate past incorrect receivers. As expected, the overall success rates were inversely proportional to the variance in the spatial distribution (given in fig. 3) for each of the target locations. Note that the unreceivable state represents one form of propagation latency, and bacteria must still randomly encounter the correct receiver after entering the receivable state.

4. CONCLUSION

In this paper, we proposed a spatial addressing of bacteria based on receptor saturation in concentration gradients produced by beacons. We modeled the system and showed that the bacteria are searching through a strength function with no local maxima. We then simulated the system using a model of a bacteria chemotaxis pathway. The bacteria were evolved for 7 different target locations and had some success in targeting the different addresses. This indicates that spatial addressing may be feasible using the proposed approach and that the number of addresses was increased relative to the case of just using the beacons themselves as addresses.

Future work includes optimizing accuracy of spatial addressing, designing dynamic targeting of different locations, applying other motility models such as gliding with pseudopod extension [8], identifying fundamental limits in resolution of spatial addresses, and scaling the system to larger numbers of beacons.

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