Towards an end-to-end model for yeast cell communications using pheromones

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***Abstract*—It is well established that Molecular Communications (MC) fall short of validation, especially at the microscale level for cell to cell communications. We are working towards the development of a new testbed, involving yeast cells facilitating information exchange using pheromones. The testbed will be used to validate an end to end (E2E) communication model of the system involving the transmitter, diffusion channel and receiver dynamics, for system simulation and analysis. In this paper, we report progress towards the development of such a model. We highlight the most important biological processes involved in the considered setup, and how their characterization yields mathematical models different than the ones considered so far in the MC literature. As such, the system poses unique challenges that we aim to address in the near future.**

I. Introduction

Molecular Communications (MC) deals with the use of communications theory principles to characterize information exchange using molecules, often among living entities [1]. Numerous efforts have been documented, developing practical testbeds to validate the developed theoretical findings [2]. At the microscale level a number of efforts have been reported, with the most significant for cell to cell communications involving prokaryotic cells e.g. bacteria [2], [3]. However, eukaryotic cells exhibit a higher degree of similarity to human cells and can thus prove to be helpful, in bringing MC principles closer to human health applications [1]. Within the PheroMolCom project, we aim at developing a new testbed for MC using yeast cells [4]. Yeast is a well studied model organism and the wealth of existing fundamental knowledge readily available in the literature, coupled with its genetic amenability, render it an ideal candidate for validating molecular cell to cell communications. One of the project objectives is the development of an E2E communication model to be validated with experimental results. Towards this end, in this paper we report progress on the development of such a model.

II. System Description

S. cerevisiae cells use pheromone to establish links between their two mating cell types: Matα and Mata. Matα haploid cells secrete α-factor pheromone, a 13 residue peptide, whereas Mata cells secrete a-factor, which is a 12 amino-acid long peptide. The E2E model, inline with the existing literature, comprises of three main components: the Transmitter the Fluidic Channel and the Receiver.

A. Transmitter

A straightforward approach towards pheromone stimulation of the diffusion medium, is the direct α-factor injection into the channel. However, a more challenging next step will be to consider Galactose stimulation of a Matα cell, as suggested in [4]. Galactose stimulation, will trigger a signaling pathway which involves transcriptional induction of Matα which will be integrated in front of the GAL1 promoter, and will replace the GAL1 coding region. This will lead to the synthesis of α-factor inside the Matα cell, followed by the secretion of the α-factor molecules to the extracellular space. Relevant literature currently used as a baseline for the development of the complete model, includes [5]- [7].

B. Diffusion channel

We consider a fluidic environment, where the propagation of α-factor molecules takes place via diffusion. Hence, we adopt a Reaction Diffusion (RD) equation to describe this physical process in the fashion of [8]. The α-factor binding to Mata receptors initiate a set of cascaded chemical results, known as the pheromone response pathway. As soon as the pheromone reaches the receiver cell, a protease called Bar1 is secreted from the Mata cell, and starts cleaving the α-factor particles, thus causing severe pheromone degradation [8], [12]. This is the natural response of a Wild-Type (WT) Mata cell, and together with pheromone related, self-degradation mechanisms have to be accounted for in the modelling procedure [8]. In search of a characterization of the α-factor concentration in both space and time, we consider the following equation [8]:

$$\frac{\partial \alpha}{\partial t} = \nabla^2 \alpha - k_B B - k_\alpha \alpha + S \tag{1}$$

where $\alpha \rightarrow \alpha(x, y, z, t)$ represents the pheromone concentration) and $B \rightarrow B(x, y, z, t)$ represents Bar1 protease concentration. The degradation rate k_B represents the rate at which Bar1 cleaves the α-factor, while k_α is the pheromone autodegradation rate which is related with its protein chemical structure in yeast cells. This partial differential equation is different from other ones that have been considered in the MC literature, as for example the work in [9] where pheromones have been considered for information exchange in plants. Beyond that, a closed form solution that yields a complete characterization in both space and time is missing in the literature, as it poses significant challenges currently being addressed. It

must be noted, that solutions at steady state can be found in [8], which, however, do not account for the time aspect thus rendering them unsuitable for the posed aims. Furthermore, adopting the approach in [10]- [11], three types of noise are considered: $\tilde{n}_s$ (sampling noise during secretion), $\tilde{n}_c$ (particle counting noise due to Brownian motion), $\tilde{n}_l$ (ligand binding noise due to uncertain receptor availability upon pheromone arrival). Their combination results in $\alpha_F = \alpha + \tilde{n}_s + \tilde{n}_c + \tilde{n}_l$.

C. Receiver

The binding of α-factor at the Mata triggers the "pheromone response pathway", starting with the activation of the receptors lying at the Mata cell's surface. Such activation, signals the activation of another, pre-existing heterotrimeric protein within the cell, called G-protein [12]. After a set of cascaded chemical reactions, a chemical compound called Mitogen Activated Protein Kinase (MAPK) gets activated (phosphorylated), which in turn phosphorylates another protein called "Ste12" located in the cell's nucleus. This protein acts as a transcription factor, as it is responsible for the initiation of the transcription of other output genes responsible for yeast mating. By binding to the promoter of mating genes located at the Mata DNA, Ste12 initiates the transcription/translation of one such mating gene known as "Fus1" [12], [13]. To account for the aforementioned processes we base the developed model on the models of [12], [13] which are appropriately coupled. This coupling is necessary since in [12] the Fus1 gene is not accounted for. Moreover, in [13], although Fus1 is included in the modelling procedure, the authors consider the MAPK directly as the input, thus failing to provide a complete model for the receiver response. As highlighted in [13], Fus1 depends heavily on the activated form of Ste12, thus motivating the consideration of Fus3PP and the activated Ste12 as the pivotal points, linking the two models as in Fig1. The resulting model provides a more comprehensive view of all the intracellular reactions linking the α-factor concentration at the input, to the Fus1 mRNA output, capturing the time dynamics of each chemical compound involved in the response. Further refinement of the model and better tuning of the considered parameters, together with pheromone levels will be driven by the obtained experimental results.

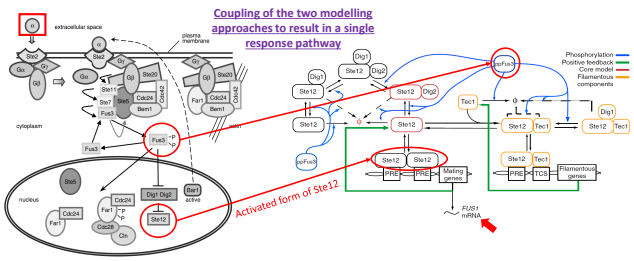
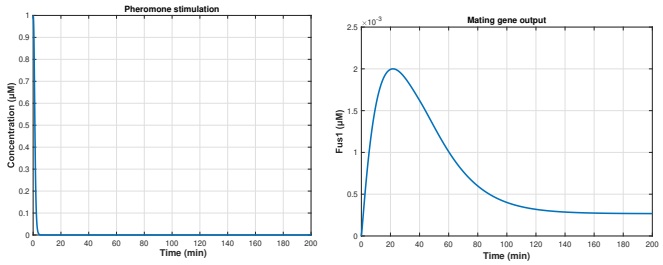


Fig. 1. The models of [12], [13], coupled by the MAPK Fus3PP.

The resulting Receiver model led to the computation of Fus1, whose mRNA level is plotted in Fig.2b. In Fig.2a, we present the α-factor input, which immediately gets degraded by Bar1 [12]. The parameter values and initial conditions are drawn from [12], [13]. Due to lack of space we do not include the complete model here but this will be made available on the project's website (http://pheromolcom.frederick.ac.cy/).



(a) α-factor at the input of the Mata cell (b) Mating gene expression dynamics

Fig. 2. Simulation results

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