Programmable Metabolic Disruption in Yeast Cells via Targeted Terahertz Excitation of Enzymes

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ABSTRACT

Standard practices in microbiology often require genetically modifying the operation of cells. The process is particularly complex and time-consuming as it involves manipulating cells at the gene level. To overcome these challenges, we introduce a conceptual design for a non-contact and non-invasive procedure that utilizes terahertz waveforms. We propose a method to suppress gene expression by targeting the enzyme associated with the gene. Building on techniques from the reported literature, we outline a procedure in which terahertz waveforms transfer energy to a targeted enzyme within yeast cells. Upon energy transfer, the enzyme unfolds, which prevents it from catalyzing the associated metabolic reactions. As a result, this makes the cell deficient in a particular gene expression on demand.

CCS CONCEPTS

• **Applied computing** → **Health informatics**; • **Hardware** → **Biology-related information processing**.

KEYWORDS

Metabolic exchange, cell to cell communication, nano communication, terahertz radio

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1 INTRODUCTION

Research on yeast cells advances innovative therapies that can be applied directly to human cells, due to the genetic similarities between them. [1, Fig. 9.23]. Experimental work includes studying the drug tolerance of yeast cell communities and their extended lifespan [3]. These experiments rely on discovering metabolic cooperation among heterogeneous yeast cells, where cell biomass is observed to increase as a consequence of a natural balance between auxotrophes [2].[1] As an example, the process reported in [2] promotes auxotrophes among co-cultured yeast cells as a result of four different plasmid segregation.[2] The technique involves preparing yeast cells in which genetic information is deleted from the strain and restored in the form of four different plasmids. The resulting procedure is complex and time-consuming as it requires complex genetic manipulations with little experimental diversity per experiment.

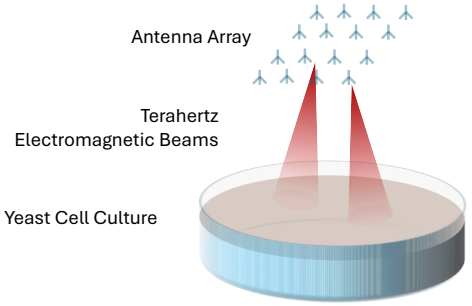

Figure 1: Proposed setup to promote auxotropes within cultured yeast cells.

In this work, we explore an alternative strategy for generating auxotrophs and circumventing the complex and time-consuming process of standard genomic procedures. We use findings from the field of nano communication to realize novel experimental opportunities in the field of life sciences. As follows from the central dogma of living cells [1, Fig. 1.2], genes are transcribed into ribonucleic acid (RNA) molecules, which are later translated into proteins, some of which are the required enzymes to catalyze metabolic reactions [1]. Our proposal involves blocking specific enzymes as a catalyst and preventing the development of certain metabolic pathways. As illustrated in Fig. 1, we suggest a configuration in which an array antenna projects directed beams onto a culture of yeast cells, utilizing terahertz band electromagnetic radiation [4]. The antenna is designed to radiate at the resonant frequency of enzymes selected for expression by specific genes. In this way, we mimic a selected gene knock-out, rendering the cell auxotrophic in itself, and utilize a non-contact, non-invasive procedure to alter the cell.[3]

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[1] Auxotrophy refers to the deficiency of a cell to produce a given metabolite, i.e., substrates or products of metabolic chemical reactions.
[2] Plasmids refer to circular deoxyribonucleic acid (DNA) molecules that carry a particular gene [1, page 331]. Plasmid segregation refers to the stochastic loss of plasmids during the cell division process.
[3] We provide access to the code related to this work in https://github.com/tkn-tub/bioelectrodynamics

2 CONCEPT

We develop our concept using the *in-silico* model Yeast-GEM of the *Saccharomyces cerevisiae* (baker's yeast), strain S288C [7]. The Yeast-GEM model comprises a total of 1161 genes that produce the enzymes necessary to catalyze 2709 different reactions. To illustrate, we select a non-redundant metabolic pathway in which a single gene produces the enzymes necessary to catalyze a specific metabolic reaction. We select to illustrate the reaction related to Pyruvate metabolism[4] as catalyzed by the gene YDR272W (aka GLO2). GLO2 encodes the Glyoxalase II enzyme, which catalyzes the hydrolysis of (R)−S−lactoylglutathione to produce (R)−lactate, glutathione and a hydrogen proton.[5] Inhibiting the Glyoxalase II enzyme is equivalent to silencing the corresponding gene GLO2.

Using terahertz radiation, we can modulate the functionality of the Glyoxalase II enzyme as a catalyst in the reaction. Enzymes are highly specific catalysts that rely on their three-dimensional structure to bind to chemical substrates [1, Chap. 5]. Whenever the enzyme unfolds, it ceases to catalyze the reaction mentioned above. To accomplish this procedure, we follow the approach in [4] aiming to unfold the mentioned enzyme. Unfolding happens due to increased enzyme energy as transferred from two components: (i) the natural impacts of other molecules with the enzyme in the cell and (ii) the external force applied by the terahertz electromagnetic field. Considering these two energy sources, the enzyme will be unfolded with probability [4, Eq. (39)]

$$p_U = 1 - p_F = 1 - \frac{1}{1 + \exp\left(\frac{\Delta E - \langle E_{tot}\rangle_{ss}}{k_b T}\right)}, \tag{1}$$

where p_U and p_F denote the steady-state unfolding and folding probabilities of the enzyme, $\Delta E = E_f - E_u$ is the enzyme free-energy, k_b is the Boltzmann constant, T is the temperature of the cell in the units of Kelvins, and $\langle E_{tot}\rangle_{ss}$ is the total steady-state energy of the enzyme. As such, the unfolding probability will approach one with the term $\langle E_{tot}\rangle_{ss}$, as ΔE and T will already be given by the 3D structure of the enzyme and the temperature of the cell.

The concept involves increasing the total steady-state energy ($\langle E_{tot}\rangle_{ss}$) with the terahertz radiation, causing the enzyme to unfold, and preventing the associated chemical reaction. This term ($\langle E_{tot}\rangle_{ss}$) is the sum of the enzyme kinetic and potential energies, see [4, Eq. (26)]. Both types of energy are evaluated considering the contributions from enzyme interactions with other molecules within the cell (Brownian motion) as well as the electric field of terahertz radiation [4, Eqs. (27) and (31)]. The contribution related to Brownian motion is fixed and can be evaluated with enzyme properties as system parameters, such as mass ($\approx 5 \times 10^{-23}$ kg), spring constant (in the range 10^{-2} to 10^{-1} N/m),[6] and temperature. The interaction with the terahertz waveform requires evaluating the protein size, as well as parameters associated with the electric fields, such as the absolute and complex permittivity of the medium (the cytosol of the cell, where this enzyme operates), and the complex permittivity of the protein.[7]

[4]Pyruvate is a molecule used by the mitochondria for generating adenosine triphosphate (ATP) [1, page 451]

[5]See Saccharomyces Genome Database https://yeastgenome.org/locus/YDR272W

[6]Spring constant is in the range of experimentally measured for the Lysozyme protein

[7]These parameters are to be evaluated theoretically, as there are no reported experimental measurements.

Regarding the antenna design, the concept requires evaluating the transmit power and the carrier frequency of the array. The beamwidth and the number of beams will depend on the requirements for the targeted area within the Petri dish, as described in [6]. The transmit power and frequency must be selected to maximize the selectivity of the terahertz waveform with respect to the target enzyme. In the context of this experiment, it refers to unfolding the Glyoxalalase II enzyme while avoiding other proteins within the cell. Such a criterion would require stating a maximization problem similar to [4, Eq. (45)].

Following this process, there is potential for other enzymes as well. The model's stoichiometric matrix[8] reveals that approximately the 14.6 % of metabolites are substrates only, i.e., not produced by metabolic pathways within the cell, and 19 % are products only, i.e., not consumed by any metabolic pathway. These figures reveal the potential for making the cell auxotrophic by targeting specific enzymes.

3 CONCLUSION

This work traces a terahertz-based methodology to knock-out the expression of genes within yeast cells. Relying on the interaction between proteins and the terahertz signal, this methodology allows to transfer the necessary electromagnetic energy to the cell, blocking enzymes from catalyzing metabolic reactions. The methodology stands for a non-invasive and non-interaction setup, where cell genes can be selectively knocked out. Future work is in the direction of determining the enzyme-related parameters, evaluating the unfolding probability, and designing the antenna array.

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[8]The stoichiometric matrix reflects the number of metabolites consumed or produced per chemical reaction; see [5, page 89].