

Mathematical modeling of the regulation of NCgl2816-lddD, brnEF, vanABK and mtlTD operons in *Corynebacterium glutamicum*

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Motivation and Aim: *Corynebacterium glutamicum* is one of the model organisms and one of the most demanded in the field of industrial biotechnology. Various strains of *C. glutamicum* are used to produce more than 70 chemicals [1]. An important rule is the influence of transcription factors on the level of gene expression. However, there is still no complete network of transcriptional regulation in bacteria. Such a network would allow scientists to more easily determine where to manipulate bacteria in order to increase the yield of the target product. Mathematical models are created to help understand how transcription factors can affect the level of gene expression. That is, to determine their contribution to the regulation of any operons. This allows us to consider target genes and/or transcription factors in terms of point selection of candidates that need to be tested by modeling before genetic modifications can be made in bacteria. In this study, we constructed and analyzed mathematical models of the following operons: NCgl2816-lddD, brnEF, vanABK, and mtlTD. The NCgl2816-lddD operon is responsible for lactate utilization, brnEF is a transporter of branched-chain amino acids or L-methionine, vanABK, whose genes are involved in vanilate utilization, and mtlTD is responsible for mannitol catabolism in the bacterium. These operons were chosen, firstly, because experimental data were found for them, and secondly, to demonstrate the independence of the choice of any operon, as study would be similar.

Methods and Algorithms: To create a model of transcriptional regulation of an operon, we need to know the following information: transcription factors (TFs) and their binding sites located on DNA, the number of TFs regulating a given operon, and the type of regulation. For the selected operons, we found this information about the participants of regulation from the articles. We then generate frame models from this data using Operon_Equations [2]. The Operon_Equations reconstructs the mathematical model in differential equations in terms of generalized Hill functions. However, such models may exhibit general behavior and have unknown parameters. We used WebPlotDigitizer (version 4.6) [3] to extract experimental data from article figures to verify our models and determine the parameters for each model. The Scipy package was used to fit the parameters.

Results: The following information was obtained from the articles: NCgl2816-lddD, vanABK and mtlTD are characterized by repressive effects of TFs, while brnEF is characterized by activation effects. Moreover, an effector is required for each of them.

No such study has been performed for RamA as a TF of *NCgl2816-lldD*, but some experiments indicate that RamA is a TFs relative to *NCgl2816-lldD*, so we decided to include it in our study. We created mathematical models for four operons: *NCgl2816-lldD*, *brnEF*, *vanABK*, and *mtlTD*. For each of them, the parameters were matched according to the selected values within the life capacity of the bacteria. Verification of these models has been carried out.

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References

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