INTEGRATIVE DYNAMIC MODELING OF TRYPTOPHAN PRODUCTION IN *ESCHERICHIA COLI*

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Introduction. Tryptophan is an aromatic amino acid widely used in the production of medicine or as a food additive. The microbial production is performed with model organisms like *Escherichia coli* or *Corynebacterium glutamicum*. The repletion of metabolic precursors (4) and the modification on regulatory pathways have yield results in the over-production of Tryptophan. Reaching only 80% of the theoretical yield, and therefore it is considered that there is room for the manipulation of the strains and achieves the optimal production. The causes of the limitations in the production are mainly explained due to the tight regulation of the metabolic pathways leading to tryptophan. It is well known the control at the level of enzymes, transcription and translation. To explore the possibilities to increase the production, the exploration of rational strategies based on mathematical models have been proposed to simulate the metabolism and overcome the different types of control. Some mathematical models are focused on regulation (2), whereas others include metabolic and regulatory pathways (3). The aim of this work is to build an integrative dynamic model, including metabolic, regulatory and signaling pathways to simulate the tryptophan metabolic synthesis and optimize the production using Escherichia coli as a model organism.

Methods. The first step in the reconstruction of the integrative dynamic model consisted in simulate the metabolic capabilities of *E. coli* for tryptophan production using as a template the Genome Scale Metabolic Model, iAF1260 (GSMM) (1). For the simulations, COBRA Toolbox (5) was used comparing the results from MOMA and FBA algorithms to optimize the production of tryptophan and using different carbon sources; glucose, xylose and maltose. The single and double mutant analysis was performed as well as the over expression of different enzymes. Based on theses simulations, in the second step, the number of the metabolic reactions was defined as well as the control at different levels and the identification of parameter to build the model and integrate regulatory information. The final step will consist in use the experimental data available to

Results. The simulations using the GSMM of E. coli do not results in better yields in tryptophan production points candidates of the main pathways and precursors that can have an immediate effect on tryptophan synthesis. Simulations also shown that the preferred carbon source is glucose

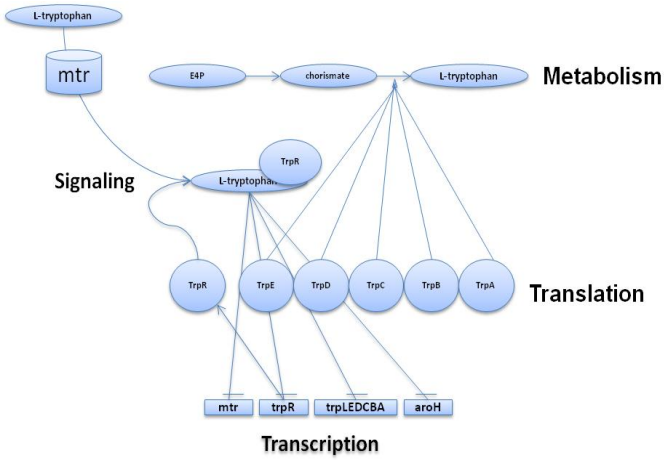

Fig.1 Scheme representing different levels and molecules involved in tryptophan synthesis .This information will be considered as part of the dynamic model.

Table 1. The best results of the calculated yields using different carbon sources. For the calculations the GSMM of *E coli* was used and single and double deletion mutants were simulated.

Carbon source	Deletions	Yield (%)
Glucose	Single deletion	50.1
Xylose	Double deletion	39.2
Maltose	Double deletion	34.1

Conclusions. Based on the *in silico* performance in tryptophan production, the first template of the metabolic pathways was constructed, and it accounts for 25 metabolic reactions and its regulation.

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