## B-30   METABOLIC MODELLING OF STRINGENT RESPONSE IN RECOMBINANT *ESCHERICHIA COLI*

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Recombinant protein production in *Escherichia coli* often derive cellular stress responses characterized by several biochemical reactions, most of which controlled at the genetic level. Drainage of precursors and energy often results in nutrient starvation, especially amino acid deprivation inducing the cellular stringent response. The production of a specific nucleotide, ppGpp, catalyzed by the enzyme RelA, is the primary signalling and initiating event in the stringent response, when an uncharged tRNA attaches to a ribosome. This nucleotide interacts with RNA polymerase to control its activity in a promoter-selective mechanism, which ultimately leads to the inhibition of synthesis of stable RNAs (rRNAs and tRNAs), which results in the decrease of ribosome concentration and, therefore comprising the overall protein synthesis machinery. Moreover, this stress response also leads to the activation of synthesis of specific mRNAs coding for proteins involved in proteolysis and other stress factors.

To gain a better understanding of the dynamics of the stringent response, a mathematical model was developed. Here we propose an hybrid modelling approach based on cooperation between kinetics-based dynamic model and FBA-based static model. FBA simulation was used to incorporate valuable data in the kinetic model of the *E. coli* stringent response, i.e. amino acid synthesis. The model integrates the main cellular events involved in stringent response: the amino acids biosynthesis and the individual tRNA charging reactions, detection of uncharged tRNA by the ribosome and consequently activation of the enzyme relA, ultimately leading to the formation of ppGpp. The effect of ppGpp on the control of transcription rate is also predicted.