

Impact of negative feedbacks on *de novo* pyrimidines biosynthesis in *E. coli*

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Regulatory processes via negative feedback loops play an essential role in biological systems like metabolic pathways and molecular genetic circuits. They are able to orchestrate intracellular processes, sustain the cellular homeostasis and possess living systems to adapt to variable environmental conditions. Theoretical analysis of mathematical models describing cellular processes controlled by negative feedback loops demonstrates the possibility of oscillatory dynamics in these systems, while a combination of positive-negative feedbacks and doubled negative feedbacks contribute to the manifestation of more complex dynamic modes including quasiperiodic, chaotic and even hyper chaotic. Furthermore, features of the dynamic modes depend not only on the number and type of regulatory feedbacks, but also on their length, i.e. a number of intermediate steps between regulatory element and its target.

From this perspective, an investigation of dynamic modes of key metabolic systems regulated by negative feedbacks, such as a system of pyrimidines biosynthesis, is of particular research interest. Herein, a new mathematical model of pyrimidine nucleotides biosynthesis is presented that includes all experimentally verified negative feedback loops regulating enzymatic reactions. Computational analysis of the model demonstrated the existence of stationary and oscillatory modes of the system behavior under particular sets of kinetic parameters. It is worth to note that values of the parameters fit into physiological bounds of the studied metabolic system. It was shown that an emergence of the oscillatory pattern in the biosynthesis depends on a variation of two parameters indicating Hill coefficient (h_{UMP_1}) for nonlinear impact of UMP on the carbamoylphosphate synthase activity and parameter r that designates an impact of the non-competitive mechanism of UTP inhibition in the regulation of an enzymatic reaction of UMP phosphorylation. Finally, it was proposed that the biosynthesis of pyrimidine nucleotides in *E.coli* follows the oscillatory pattern which emerges depending on the regulatory mechanism of the UMP kinase activity.

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