

STOCHASTICITY IN PROTEIN LEVELS DRIVES COLINEARITY OF GENE ORDER AND ENZYMATIC STEPS IN METABOLIC OPERONS OF *ESCHERICHIA COLI*

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It is well established that in bacterial genomes gene order is not random. Genes within the same operon often encode enzymes involved in the same metabolic pathway or proteins interacting in the same complex. However, it is almost completely unexplored if gene order within operons is governed by chance or might be under selection. Here we ask if gene order within metabolic operons reflects the functional order of the encoded enzymes acting in the same biochemical pathway (colinearity). We hypothesize that colinear arrangement might be adaptive by enabling the temporal ordering of enzymes in linear metabolic pathways. Using a stochastic kinetic model of gene expression and metabolic pathway operation we not only show that a colinear arrangement can increase pathway productivity, but also find that the advantage of colinearity is greater in lowly expressed operons which show metabolic stalling owing to stochastic protein loss. To see if these theoretical predictions are upheld, we investigated the metabolic operons and biochemical pathways of *Escherichia coli*. We show that, on average, colinearity of intra-operonic gene order is significantly higher than expected by chance. Furthermore, in accordance with our stochastic stalling hypothesis, we found that colinearity is more pronounced for lowly expressed operons. These results support the view that stochasticity is a pervasive problem to a cell and that gene order evolution can be driven by the selective consequences of fluctuations in protein levels.