Operon organization in different *E. coli* multi-gene networks correlates with noise reduction

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***Short Abstract* — Many biochemical subsystems in bacteria are expressed via cotranscription into polycistronic messenger RNA from multi-gene operons. To determine how operon organization affects post-transcriptional dynamics, we defined a number of network classes representing several bacterial subsystems and compared effects of intrinsic gene expression noise in them. We found some subsystems that minimize physiologically relevant noise when the genes are transcriptionally coupled, and others where the uncoupled architecture minimizes noise. Comparing the results to operon formation patterns in naturally occurring *E. coli* networks suggests that reduction of gene expression noise may be an evolutionary force for operon maintenance.**

Keywords* — operon noise chromosome evolution *E. coli

CO-TRANSCRIBED polycistronic operons are a distinct structural feature of bacterial chromosomes [1]. The presence of operons is usually explained by horizontal transfer of intact systems, but (i) operonic structure occurs in essential systems that horizontal gene transfer cannot explain [2] and (ii) organization of genes into operons results in co-variation of the gene products in the post-transcriptional network [3], suggesting that dynamical properties, including noise, may be a driving factor in chromosome evolution. To test the hypothesis that post-translational dynamics substantially depend on operon organization, we constructed mathematical models that capture noise levels in several classes of simple two-gene systems.

The classes represent simplified versions of networks that occur repeatedly in bacteria, including linear metabolic pathways, redundant metabolic pathways, cooperative gene regulation, covalent modification, and stoichiometric protein-protein interactions. Our analyses using linear noise approximations and numerical stochastic simulations give two consistent predictions. First, noise is reduced in linear metabolic pathways and stoichiometric interactions when the genes are in the same operon. Second, noise is similarly reduced in metabolic or gene regulatory redundancy when the genes are in separate operons. We discovered that in two-component systems (a type of covalent modification network), feedback to both genes simultaneously can impart adaptable functionality, trading off between high signal capacity and fast signal response in different stress conditions [4].

To determine patterns of operon membership in naturally occurring forms of these five simple network motifs, we used the databases KEGG [5], EcoCyc [6], and RegulonDB [7] to identify network instances and examine whether or not the genes predominantly appear in the same operon in *E. coli*, the most well-characterized bacterium. In each case, the key step in this analysis is to determine a method of creating a randomized control set that accounts for confounding factors, such as spatial biases [8] and differences in gene regulation. Compared to the randomized controls, networks show a statistical trend toward the operon organization pattern that reduces noise.

Therefore, we hypothesize that post-translational dynamics, including noise, may have been a central factor in maintaining operons during bacterial evolution. As a next step, algorithms to simulate long-term evolution of these simple network classes will directly test the interaction between population dynamics and noise that give rise to various linkage patterns in bacterial chromosomes.

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