entaining cues or intercellular communication (32), which suggests that the circadian network is strongly resistant to biochemical noise. Recent work has asserted that this oscillator relies on posttranslational molecular events (33). Perhaps a core posttranslational oscillator, which can rely on large numbers of molecules and avoid the small-number stochasticity of gene expression, is required for robust oscillations.

Cellular control mechanisms may exist to enable the switch between globally noisy or globally “quiet” states of gene expression. Queitsch et al. demonstrated that reduction of heat-shock protein 90 (Hsp90) chaperone activity in Arabidopsis thaliana increases morphological diversity in inbred lines, in addition to revealing otherwise silent genetic variation among different lines (34). Hsp90 chaperone activity is hypothesized to reduce the effect of stochastic molecular events that might otherwise result in developmental variability.

There may exist buffering agents that reduce either the magnitude of noise in gene expression or the impact of such noise on cellular or organismal phenotype. These buffering agents may be regulated, especially in times of stress, to produce a phenotypically diverse population. Waddington’s theories of canalization and genetic assimilation propose that wasteful phenotypic variability in a population is suppressed when the population is well adapted to its environment (35). However, if environmental conditions shift, phenotypic noise becomes advantageous because a noisy population will produce some members that are better adapted to the new environment. Recent work supports the idea that it is advantageous to increase variability in times of stress and decrease variability when organisms are well adapted to the environment (36). Regulation of global noise factors could provide a molecular basis for such evolutionary flexibility.

Concluding Remarks

Many questions remain concerning the generation of noise in gene expression and its consequences for cellular behavior. The presence of stochasticity in gene expression has been confirmed to result in noise in protein abundance, but other sources of noise may result in phenotypic variability. Beyond the identification of true examples of phenotypic consequence, much work must be done to understand how cellular processes behave robustly in the presence of underlying stochasticity. Such work often requires a nontraditional collaboration between mathematicians, physicists, and in vivo experimentals. Many biologists are beginning to focus on the limitations and benefits that stochasticity creates for biological systems, and we expect that future investigations will reveal results both unexpected and unpredictable.

Fig. 4. Control of noise. (A) Infrequent transcription results in high intrinsic noise in protein levels (left). Frequent transcription and inefficient translation results in low intrinsic noise (right). (B) Infrequent promoter transitions between inactive and active states followed by efficient transcription results in inefficient transcription result in low intrinsic noise (right). (C) Increases in gene copy number through polyploidy (top right) or gene duplication (bottom right) result in decreased intrinsic noise relative to a single gene copy (left). (D) Negative feedback, as when a transcription factor represses its own transcription (right), results in decreased noise relative to a linear pathway (left).

References and Notes

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