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## The interplay between feedback and buffering in cellular homeostasis

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Negative feedback and buffering, the use of reservoirs of molecules to maintain concentrations of key molecular species, are the primary known mechanisms for robust homeostatic regulation. However, the fundamental principles behind their combined effect have not been elucidated. Here, I will present our recent research on the interplay between buffering and negative feedback in the context of cellular homeostasis. This research shows that negative feedback counteracts slow-changing disturbances, whereas buffering counteracts fast-changing disturbances. Furthermore, feedback and buffering have limitations that create trade-offs for regulation: instability in the case of feedback and molecular noise in the case of buffering. However, because buffering stabilizes feedback and feedback attenuates noise from slower-acting buffering, their combined effect on homeostasis can be synergistic. These effects are consistent with experimental observations of both ATP homeostasis and pH regulation *in vivo*. The methodology is based on control theory and complexity-aware minimal modelling. The discussed principles are crucial for studying robustness and homeostasis in biology and biotechnology.

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