Mishra *et al.*[1] describes the first practical buffer device for the control of gene expression in eukaryotes[7].

The authors compare two gene circuits, unbuffered and buffered. The unbuffered circuit contains an inducible transcription factor that regulates a GFP reporter. When additional binding sites for the reporter are added, the response of GFP expression to time-varying changes in the level of transcription factor is significantly attenuated and delayed. In the buffered circuit, the authors introduce a 'load driver' between the input and output modules of the circuit.

The load driver is implemented as a phosphotransfer cascade whose fast dynamics bridge the slower input and output stages. The input to the load driver is a protein kinase that initiates phosphorylation of the cascade. The output is a transcription factor that requires phosphorylation for activation. The device incorporates negative feedback because the output transcription factor is dephosphorylated at a rate that is proportional to how much of it is free rather than bound to downstream promoters (**Fig. 1b**). The negative feedback and the short timescale of protein phosphorylation, compared with the long timescale of gene expression, allow the load driver to quickly adjust its output to match its input. By increasing the abundance of protein components in the load driver, the system can be made almost insensitive to downstream load, much like increasing the power of the unity gain buffer in electronics. As proof that the scheme works, Mishra *et al.*[1] show that when the buffered circuit is loaded, it performs almost exactly as if it were unloaded.

Many problems will have to be solved before synthetic biologists can routinely use load drivers to create large-scale gene circuits. For example, the load driver described by Mishra *et al.*[1] can be used for only one connection in a given circuit, owing to the specificities of the proteins involved. In principle, many of the naturally occurring phosphorylation cascades could be repurposed as load drivers, but ideally the proteins that serve as load drivers will be designed from the bottom up using custom DNA-binding, protein-protein interaction and phosphorylation domains so that engineers can build as many as needed. In the meantime, the authors list several phosphorylation cascades that differ in their protein interaction specificities and architectures and that might be repurposed to buffer multiple connections in a larger circuit.

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As the work of Mishra *et al.*[1] shows, synthetic biology is moving from an initial focus on assembling libraries of parts to tackling major roadblocks in the assembly of genetic circuits. Progress in the field to date has largely been based on a methodical engineering approach. The development of the genetic load driver was preceded by many theoretical papers detailing mathematical analyses of retroactivity[8]. Building on this foundation, Mishra *et al.*[1] provide a thorough mathematical analysis of the performance and tunability of their load driver device, using timescale separation from nonlinear dynamical systems theory and disturbance rejection from control theory. It is increasingly clear that these fundamental concepts, and related principles from analog computation[9], will underpin the development of a robust, modular synthetic biology, just as these same tools enabled robust electronic circuits.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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