### Highlights

* Automatic reconstruction of genome-scale small molecule regulatory network
* Reveal a fundamental tradeoff between regulatory capacity and enzymatic activity
* Condition-dependent regulatory capacity of small molecule interactions in E. coli
* Identification of conserved small molecule regulation across kingdoms of life

### eTOC Blurb

Reznik et al. report a computational pipeline for the genome scale reconstruction of metabolic small molecule regulatory networks. They describe general design principles underlying small molecule regulation, and prove a fundamental tradeoff between the activity of a metabolic enzyme and the extent to which it is regulated.