by neutral theory as unnecessary to describe the patterns of species abundances (*21*). Additionally, a recent statistical analysis has called into question the necessity of local interactions to describe patterns of diversity (*22*). Our results run counter to these arguments, as we found support for regional species richness patterns being driven by local species-specific ecological interactions and a local mechanism to explain variation in regional species richness.

It is possible that the patterns found here were generated by mechanisms unrelated to conspecific density dependence that could create spatial separation of adults and conspecific seedlings [e.g., timber harvesting, succession, the mass effect (*23*)]. For example, recruitment differences between early successional and late successional species could imitate patterns of CNDD in forests. To test whether CNDD varies with forest age, we reanalyzed the data set by stratifying the data into early (0 to 39 years), middle (40 to 79 years), and later (80+ years) successional forests. The patterns of CNDD were robust and consistent between age classes, indicating that our results are not contingent on successional dynamics or indirectly on timber harvesting, which has the effect of setting back forest age (figs. S8 to S11).

Janzen (*1*) and Connell (*2*) originally hypothesized that CNDD generated by host-specific seed predators could help maintain the high species richness in tropical forests. We found that CNDD is a strong mechanism maintaining species richness in eastern U.S. forests, but CNDD may also explain the latitudinal gradient in species richness if CNDD becomes stronger with decreasing latitude. We tested this hypothesis in eastern North America, where there is a latitudinal gradient of tree species richness that peaks in the southern Appalachian region (*20*). We found evidence that CNDD could maintain this gradient in tree species richness, as the average regional strength of CNDD was significantly negatively correlated with latitude, ranging from boreal to subtropical forests (Fig. 4). Our results suggest that the strength of CNDD would increase with decreasing latitude into species-rich tropical forests.

Our analyses of the FIA database provide robust evidence that CNDD is pervasive in forest communities and can significantly affect species relative abundance and species richness within and between forests. Further, our results show that species-specific processes acting on seedlings translate into patterns in the abundance and diversity of trees. Several potential interactions could generate CNDD, including intraspecific competition, autotoxicity, seed predators, and soil pathogens. Much research has demonstrated that the soil microbial community can drive CNDD in multiple plant communities, including tropical forests, temperate forests, grasslands, and sand dunes (*18*, *24*). In particular, two studies measuring soil community feedbacks, presumably driven by soil-borne pathogens, have identified a positive relation between strength of CNDD in the greenhouse and relative abundance in the field (*8*, *25*).

Local interactions have previously been considered a local filter on species diversity, but our findings indicate that local interactions feed back to regional species richness and abundance. Further, the prevalence of CNDD across many forest types and diverse species indicates the pervasive importance of these interactions. Our results show that CNDD is a general mechanism structuring forest communities across a wide gradient of forest types and can maintain the latitudinal gradient of tree species richness.

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**Supplementary Materials**
www.sciencemag.org/cgi/content/full/336/6083/904/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S12
Table S1
References (*26*–*28*)

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# Randomized Government Safety Inspections Reduce Worker Injuries with No Detectable Job Loss

**David I. Levine,[1] Michael W. Toffel,[2]* Matthew S. Johnson[3]**

**Controversy surrounds occupational health and safety regulators, with some observers claiming that workplace regulations damage firms' competitiveness and destroy jobs and others arguing that they make workplaces safer at little cost to employers and employees. We analyzed a natural field experiment to examine how workplace safety inspections affected injury rates and other outcomes. We compared 409 randomly inspected establishments in California with 409 matched-control establishments that were eligible, but not chosen, for inspection. Compared with controls, randomly inspected employers experienced a 9.4% decline in injury rates (95% confidence interval = −0.177 to −0.021) and a 26% reduction in injury cost (95% confidence interval = −0.513 to −0.083). We find no evidence that these improvements came at the expense of employment, sales, credit ratings, or firm survival.**

The U.S. Occupational Safety and Health Administration (OSHA) is one of the most controversial regulatory agencies in the United States. Some evidence indicates that OSHA penalties deter injuries (*1*), and OSHA supporters argue that inspections save lives at low cost to employers and employees and that additional regulation would reduce tens of thousands of occupational illnesses and hundreds of worker fatalities (*2*, *3*). At the same time, critics fear that OSHA destroys jobs without meaningfully improving workplace safety (*4*, *5*) and have urged the agency to shift its emphasis from worksite inspections to voluntary safety programs (*6*). Even if inspections do improve workplace safety, they might not be socially efficient if

[1]Haas School of Business, University of California, Berkeley, Berkeley, CA 94720, USA. [2]Harvard Business School, Boston, MA 02163, USA. [3]Department of Economics, Boston University, Boston, MA 02215, USA.

*To whom correspondence should be addressed. E-mail: mtoffel@hbs.edu

the cost of remediating hazards outweighs the benefits. The economic theory of perfectly competitive labor markets (with full information, perfect mobility of labor, and so forth) implies that remediating hazards will cause wages to decline so much that employees on average do not benefit from the increase in safety (*7*). If product markets are also perfectly competitive or if wages are sticky, then many inspected firms will either go out of business or at least suffer lower sales, lower employment, and worse credit ratings (*8*).

The debate has persisted in part because prior research has yielded widely varying results. For example, some studies find that OSHA inspections have little or no correlation with subsequent workplace injury rates (*9–11*), whereas others find that OSHA inspections correlate with a decline in injury rates (*1*, *12–14*). Similarly, workplace-safety inspections correlate with lower productivity in some studies (*15*) but not in others (*16*).

These widely varying results may be due in part to the substantial challenges of measuring the causal effect of OSHA inspections. One challenge arises because most OSHA inspections target workplaces with recent accidents or safety complaints, and these workplaces typically have a combination of ongoing safety problems and a random event ("bad luck") that year. Thus, a cross-sectional analysis revealing a positive correlation between inspections and subsequent injuries does not imply that OSHA inspections cause injuries; it could just be due to ongoing safety problems that spurred the inspection. At the same time, because the random element that contributes to an accident or complaint is temporary, injuries rates often revert to prior levels (*17*), and so inspections often precede a decline in injuries without necessarily causing the improvement, potentially biasing a panel data analysis of targeted inspections.

In addition, most previous studies of the effects of inspections analyze data from logs of workplace injuries that OSHA requires companies to maintain at each workplace. OSHA mandates better recordkeeping when its inspections find incomplete logs, which can erroneously make it appear as if inspections cause higher injury rates. For example, the injury rates reported by very large manufacturing plants more than doubled in the late 1980s after OSHA imposed multimillion dollar fines on a few such plants for poor recordkeeping (*18*).

Fortunately for evaluation purposes, California's Division of Occupational Safety and Health (Cal/OSHA) randomly selected workplaces in high-injury industries for inspections in 1996 to 2006 (*19*). By focusing on these inspections, we simulated a randomized controlled trial that can provide unbiased estimates of the effects of OSHA inspections. To do so, we matched on observables to construct a control group of very similar facilities that were eligible for randomized inspections but not selected.

In addition, we analyzed injury data from the workers' compensation system. Unlike OSHA-mandated logs, workers' compensation data are less likely to be affected by improved recordkeeping after OSHA inspections. Finally, because injuries are not the only outcome that might be affected by OSHA inspections, we also analyzed employment, company survival, and compensation to look for unintended harms from inspections.

The starting point of our analysis was to understand how Cal/OSHA selected establishments for randomized inspections. In each year of our study period (1996–2006), Cal/OSHA identified a list of industries with high injury rates—typically based on data from the U.S. Bureau of Labor Statistics (*19*)—for that year's randomized inspections. For each of these industries, Cal/OSHA used Dun & Bradstreet and other sources to compile a list of establishments with 10 or more employees, then randomly selected a subset of each list. These subsets were then sent to the appropriate northern or southern district managers (each district covers roughly half the state). Within each district, inspectors attempted to inspect all of the randomly chosen establishments, although managers could prioritize on the basis of factors such as avoiding industries they felt were not as dangerous and skipping workplaces that had had an OSHA inspection in the prior 2 years. Our procedure for choosing a sample adjusts for these factors. Specifically, we found controls in the same industry, and we dropped all treatments and potential controls that had had inspections in the prior 2 years.

We obtained data on these inspections from U.S. OSHA's Integrated Management Information System (IMIS). We obtained annual establishment-level data on payroll and on the number and value of workers' compensation claims from the Uniform Statistical Reporting Plan database of the Workers' Compensation Insurance Rating Board (WCIRB). For all California establishments tracked by Dun & Bradstreet, we obtained annual establishment-level data on company names, addresses, whether the establishment was a stand-alone firm (not a branch or subsidiary), Standard Industrial Classification (SIC) and North American Industry Classification System (NAICS) industry codes, sales, and employment from the National Establishment Time-Series (NETS) database.

We began constructing our analysis sample by identifying in OSHA's IMIS database the 1752 establishments at which Cal/OSHA had attempted a random inspection at least once during our sample period. Because injury data from workers' compensation systems are available primarily at the company level, we restricted our analysis to single-establishment firms. Because Cal/OSHA performed random inspections only at establishments with at least 10 employees, we included only establishments with at least 10 employees in the random inspection year or either of the two preceding years. The pipeline of how we linked these treatments and a set of potential controls to the several data sets and then restricted potential controls to resemble treatments by requiring them to be in the same industry and the same region of California, to be classified as a single-establishment firm, to have 10 or more employees, and so forth is shown in table S1. When more than one potential control matched the industry and region of a particular treatment, we selected the one with the most similar number of employees.

This matching process resulted in a matched sample of 409 pairs of single-establishment firms, whose industry distribution is reported in table S2. At 7% of the treatment establishments in our sample, Cal/OSHA did not carry out the inspection, typically because the inspector could not find the establishment, the establishment had gone out of business, or the inspector determined that the establishment was not eligible for a random inspection after all (for example, if the inspector found out the establishment had fewer than 10 employees). As we could not filter the control sample on these criteria, we included as treatments all establishments in which Cal/OSHA had attempted an inspection. Thus, our estimates measure the causal effect of an attempted inspection and might slightly underestimate the causal effect of the inspections that actually occurred. However, as the vast majority of the attempts were successful, we usually simplify our language by dropping the qualifier "attempted" and referring to our estimates as the causal effect of inspections.

To reduce the effect of very large outliers, we top-coded our measures of injury count (the annual number of workers' compensation claims) and injury cost (the annual value of workers' compensation claims) at their 99th percentiles. We analyzed the logs of our continuous outcome measures: injury cost, sales, employment, and payroll. To reduce the effect of very small outliers, we added roughly the first percentile of nonzero values to our measures ($79 to Injury cost, 10 to Employment, and $100,000 to Payroll and to Sales) before taking logs; our results were not sensitive to these adjustments (*20*). Summary statistics are reported in table S3.

The preinspection characteristics of treatments and controls were very similar on most measures (e.g., employment, payroll, and sales) (table S4). Whereas the treatments averaged 3.7 injuries per year in the 4-year period preceding the randomized inspection and the controls averaged 3.1 over the same period ($t$ test $P$ value = 0.06), their pretrends (14% decline for treatments, 12% decline for controls) were statistically indistinguishable ($t$ test $P$ value = 0.85).

For two reasons, we think that the disparity represents sampling variation rather than conscious selection by Cal/OSHA (*21*). First, we closely replicated Cal/OSHA's random selection procedures to create the pool of establishments at risk of a randomized inspection each year. Second, Cal/OSHA had no information on injury rates for the vast majority of establishments it randomly inspected. In addition, kernel density plots of several key variables the year before the match year (figs. S1 to S3) revealed nearly identical distributions between the treatments and controls, including the variables for which the statistical tests found significant differences.

Even if due solely to sampling error, this imbalance on preinspection injury rates made it important to adjust for preinspection characteristics in our analysis. Thus, we measured the causal effect of inspections via a difference-in-differences analysis. Specifically, we estimated the following model for each outcome $Y_{it}$ at establishment $i$ in year $t$:

$$Y_{it} = \alpha_i + \beta \cdot \textit{Has been randomly inspected}_{it} + \Sigma_k \gamma_k \cdot \mathbf{X}_{ikt} + \Sigma_t \delta_t \cdot \textit{year}_t + \varepsilon_{it}$$

where $\alpha_i$ was a complete set of establishment-specific intercepts (or, in some specifications, conditional fixed effects). *Has been randomly inspected*$_{it}$ was coded "1" the year an establishment was randomly inspected and each year thereafter and was otherwise coded "0." Of primary interest is $\beta$, which represented the estimated effect of a random inspection; that is, the average change in outcome levels pre- versus postinspection. $X_{ikt}$ referred to controls (subscripted $k$), such as average occupational riskiness and log employment, that were included in some specifications. All models included a full set of year dummies ($year_t$). The supplementary materials describe multiple robustness checks for each analysis.

We first analyzed the effects of inspections on injury rates and injury cost and then turned to the possible unintended consequences on firm survival, credit ratings, sales, employment, and payroll. To predict the number of injuries at a workplace, we estimated a negative binomial regression model with establishment-level conditional fixed effects. The point estimate in column 1 of Table 1 indicates that randomized inspections reduce annual injuries by 9.4% [$\beta = -0.099$, $P = 0.013$, incident rate ratio = 0.906, 95% CI = –0.177 to –0.021].

The effects of inspections might attenuate after a few years or might take a few years to emerge. To test for such changes in the effects of inspections over time, we replaced the single posttreatment dummy for inspected establishments with a dummy coded "1" only in the randomized inspection year and a series of dummies for each of the subsequent 4 years. Inspections statistically significantly reduced injuries in the random inspection year and 3 and 4 years later, marginally reduced them 1 year later, but had no significant effects 2 years later (column 2). In short, the reduction in injuries after inspections endured. We found nearly identical annual estimates when we excluded matched groups of which either member (the treatment or control) was inspected 3 or 4 years before the match year (table S5).

To extend our analysis beyond average effects, we also estimated distinct effects of these inspections on the number of minor financial claims (resulting in less than \$2000 in workers' compensation) and the number of major financial claims (at least \$2000). The results of these two regressions were nearly identical: $\beta = -0.107$ for smaller claims and $\beta = -0.136$ for larger claims, with $P < 0.05$ in both instances (table S6). These results imply that inspections reduce the rates of both minor and major injuries.

Turning to the cost of injuries, an ordinary least squares (OLS) regression model with establishment-level fixed effects indicates that randomly inspected establishments exhibited a 26% decline in injury cost (column 3, $\beta = -0.298$, 95% CI = –0.513 to –0.083, $\exp(\beta) = 0.74$, $P < 0.01$). When we permitted the effect of inspections to differ by years since inspection, the negative point estimates suggested that inspections consistently reduced injury cost, and we could not reject the equality of all these coefficients ($P = 0.09$, column 4). The pattern of coefficients resembled the pattern for injury rates, with the year-specific treatment effects statistically significant and larger in magnitude in the year of random inspection and years 3 and 4 after the inspection. Results were nearly identical when we excluded matched groups of which either the treatment or control was inspected 3 or 4 years before the match year (table S5).



**Table 1.** Regressions yield evidence that randomized OSHA inspections reduced workplace injury rate and injury cost (± standard errors). Standard errors clustered by establishment in OLS models (columns 3 and 4). The models in columns 1 and 2 include establishment-level conditional fixed effects. The models in columns 3 and 4 include establishment-level fixed effects. To reduce the effect of very small outliers, we added roughly the first percentile of nonzero values (\$79) to Injury cost before taking the log. To reduce the effect of large outliers, Injury count, and Log Injury cost were top-coded at their 99th percentiles. Sample size in columns 1 and 2 is <409 treatments and <409 controls because the negative binomial specification with conditional fixed effects drops establishments that have no variation in their number of injuries.

| | (1) | (2) | (3) | (4) |
|---|---|---|---|---|
| **Dependent variable** | **Injury count** | | **Log Injury cost** | |
| **Specification** | **Conditional fixed-effects negative binomial regression** | | **Fixed-effects OLS** | |
| Has been randomly inspected (this year or before) | –0.099 ± 0.040* | | –0.298 ± 0.110** | |
| Year of random inspection | | –0.152 ± 0.053** | | –0.379 ± 0.123** |
| One year after random inspection | | –0.023 ± 0.055 | | –0.217 ± 0.145 |
| Two years after random inspection | | –0.033 ± 0.063 | | –0.085 ± 0.172 |
| Three years after random inspection | | –0.135 ± 0.077+ | | –0.558 ± 0.194** |
| Four years after random inspection | | –0.266 ± 0.091** | | –0.455 ± 0.223* |
| Year dummies | Included | Included | Included | Included |
| Observations (establishment-years) | 5593 | 5593 | 5872 | 5872 |
| Number of establishments | 765 | 765 | 818 | 818 |
| Number of treatment establishments | 389 | 389 | 409 | 409 |
| Number of control establishments | 376 | 376 | 409 | 409 |
| Wald tests | | | | |
| Dependent variable sample mean | 3.43 | 3.43 | 7.41 | 7.41 |
| Each treatment coefficient is equal to zero | | $X^2$ = 15.79<br>$P$ = 0.008 | | $F$ = 3.17<br>$P$ = 0.008 |
| Sum of treatment coefficients equals zero | | $\chi^2$ = 7.72<br>$P$ = 0.006 | | $F$ = 7.13<br>$P$ = 0.008 |
| All treatment coefficients equal to each other | | $\chi^2$ = 10.14<br>$P$ = 0.044 | | $F$ = 2.02<br>$P$ = 0.091 |

**$P < 0.01$, *$P < 0.05$, +$P < 0.10$.

**Table 2.** Regressions yielded no evidence that random OSHA inspections influenced employment, payroll, or sales. OLS coefficients ± standard errors clustered by establishment; effects are not statistically significant ($P > 0.10$). To reduce the effect of very small outliers, we added roughly the first percentile of nonzero values (10 to Employment and $100,000 to Payroll and Sales) before taking logs.

| | (1) | (2) | (3) |
|---|---|---|---|
| Dependent variable | Log Employment | Log Payroll | Log Sales |
| Specification | OLS | OLS | OLS |
| Has been randomly inspected (this year or before) | 0.027 ± 0.016 | 0.005 ± 0.013 | 0.002 ± 0.044 |
| Year dummies | Included | Included | Included |
| Establishment-level fixed effects | Included | Included | Included |
| Observations (establishment-years) | 5278 | 5872 | 3190 |
| Number of establishments | 787 | 818 | 640 |
| Number of treatment establishments | 390 | 409 | 329 |
| Number of control establishments | 397 | 409 | 311 |
| Dependent variable sample mean | 3.61 | 14.50 | 14.86 |

To assess the impact of inspections on workplace survival, we defined an establishment to have "died" if it had disappeared from both the NETS and the WCIRB databases. We were unable to observe if any treatment or control establishments died after the sample period ended in 2006. Fortunately, censoring does not lead to bias because our matching of controls to treatments was in the year of the randomized inspection; thus, data on each matched pair of treatments and controls were right-censored after the identical number of years. In our sample, 4.4% of the treatment establishments did not survive until 2006, a rate slightly but not economically or statistically significantly lower than the 5.6% death rate among the control establishments ($P = 0.423$).

Although treatment status was randomized, there were differences between the treatment and control groups' preinspection sales, employment, and payroll. We ran several specifications of survival analyses that condition on these characteristics using a logit, a conditional logit with a fixed effect for each matched pair, and a Cox proportional hazard model with each matched pair its own strata. For all models, survival rates of randomly inspected establishments were not statistically significantly different from those of the controls (see table S7). These results yielded no support to critics of OSHA who claim that inspections harm companies' survival prospects.

Because company death is relatively rare, we also analyzed whether random inspections affected establishments' creditworthiness, using Dun & Bradstreet's Composite Credit Appraisal and PAYDEX scores. We used ordered logit regression models to predict Composite Credit Appraisal, an ordinal dependent variable that ranged from 1 to 4. We used OLS regression with establishment-level fixed effects to predict minimum PAYDEX scores, which ranged from 1 to 100. The point estimates were positive—hinting that inspections, if anything, increased creditworthiness—but very close to zero and nowhere near statistically significant (table S8).

To assess whether random inspections affect firm growth, we estimated fixed-effect OLS models to predict log employment, log payroll, and log sales (Table 2). Randomly inspected establishments did not differ significantly from controls in employment, total earnings, or sales, although each point estimate was positive. The point estimates show that treatment increases employment and payroll by small amounts (2.7% for employment and 0.5% for payroll, neither statistically significant) with fairly narrow 95% CIs (–0.5% to +5.8% for employment and –2.0% to +3.0% for payroll). Thus, we rule out large declines in employment and payroll. The coefficient on sales was also tiny and positive (0.2%), but the confidence interval was much wider (–8.4% to + 8.8%).

In sum, workplaces that Cal/OSHA randomly inspected (or attempted to randomly inspect) subsequently experienced substantially lower injury rates and workers' compensation costs compared with a matched set of workplaces that were eligible for, but did not receive, a random inspection. The lower injury rates were not transient.

With many assumptions (see supplementary materials), our point estimates imply that the reduction in injuries in the 5 years after a workplace inspection reduced medical costs and lost earnings by roughly $355,000 (in 2011 dollars) (*22–24*). This estimated 5-year total is ~14% of the average annual payroll of this sample of employers. Thus, although admittedly imprecise, the estimated benefits of a randomized safety inspection appear to be substantial. These results do not support the hypothesis that OSHA regulations and inspections on average have little value in improving health and safety.

Although this estimated value of improved health is fairly large, it is crucial to know how much employers pay for these improvements in safety, as well as how much employees pay in terms of lower wages or employment. As noted above (and formalized in an illustrative model in the supplementary materials), economists' benchmark model suggests that the increased costs of safety measures that reduce injury rates can also reduce wages, employment, and rates of firm survival. Although we cannot rule out any of these unintended consequences, we found no evidence that inspections lead to worse outcomes for employees or employers. The point estimates on changes in employment, payroll, sales, and credit ratings were all positive, although all coefficients were small, and none approached statistical significance.

The estimates in Table 2 imply that we can be 95% certain that the mean establishment either grows payroll or experiences a decline of less than $221,000 over the 5 years after the inspection (*25*). The lower-bound estimate of lost payroll is in different units than lost earnings and medical costs, and there is substantial uncertainty about our estimated benefits (with a point estimate of $355,000). With that said, these calculations imply that employees almost surely gain from Cal/OSHA inspections.

This result is not consistent with the perfectly competitive model's prediction that Cal/OSHA's mandated increases in safety would reduce employment and/or earnings sufficiently that, on average, employees would be worse off. These results therefore suggest that it is important to test which assumptions of the perfectly competitive model are sufficiently violated to drive this result (e.g., that employees have very good information on hazards or that labor is perfectly mobile).

Our study has several limitations, including its focus on a subset of companies (single-establishment firms in high-hazard industries and with at least 10 employees) in one region (California), a single type of inspection (randomized, not those driven by complaints or by serious accidents), and a single workplace-safety regulator (Cal/OSHA). Our method also ignores any effects of the threat of inspections on as-yet-uninspected workplaces. It is important to replicate this study in other settings and by using additional study designs to examine the generalizability of our results. It is also important to supplement statistical studies such as this one with qualitative research that helps us understand the process by which workplace regulations affect (and sometimes improve) outcomes.


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20. To assess the impact of our handling of outliers, we reestimated our models on variables that were neither top-coded to correct for large outliers nor corrected to account for very small outliers (i.e., we added only 1 before taking the log of Injury count, Injury cost, Sales, Employment, and Payroll). The results, presented in tables S9 and S10 in the supplementary materials, continue to indicate that inspections lead to statistically significant reductions in Injury count and Injury cost. The results also continue to yield no evidence that inspections affected Employment, Payroll, or Sales. The magnitude of these estimated effects on injury rates and injury costs exceeded those yielded by our primary model results. This confirms the conservative nature of our primary estimates and suggests the importance of mitigating the influence of outliers.
21. Cal/OSHA would have had some data on injury rates for workplaces they had recently inspected. Because their procedures were to avoid randomized inspections for workplaces with any inspection in the previous 2 years, we dropped potential treatments and controls that had been inspected within 2 years before the match year. Cal/OSHA only had inspected 7% of treatments in the 4 years before the random inspection year; results were unchanged when we dropped treatments or controls with inspections in the prior 4 years.
22. In the supplementary materials, we show that the cost of reported injuries in medical care and lost wages, not counting pain and suffering, is very roughly \$8400 per employee in high-hazard industries in California. If an inspection reduces all costs by the same 26% that we estimated for workers' compensation costs (Table 1, column 3) and if there is an average of 33 employees per employer in our sample, then a Cal/OSHA inspection leads to roughly \$71,000 in lower medical costs and lost wages per year. If the effect lasts from the inspection year through the next 4 years (as in Table 1, column 4), the total value to society of an inspection is very approximately on the order of \$355,000. This estimate is very rough and ignores the underreporting of injuries (*23*, *24*), safety benefits lasting more than 4 years, the reduction in pain and suffering, and (working in the opposite direction) the discounting of future benefits.
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24. J. Biddle, K. Roberts, K. D. Rosenman, E. M. Welch, *J. Occup. Environ. Med.* **40**, 325 (1998).
25. The figure of \$221,000 is the lower bound of the 95% CI of our estimate on payroll (–0.021) times mean payroll (\$2,101,500) times 5 years.

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**Supplementary Materials**
www.sciencemag.org/cgi/content/full/336/6083/907/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S3
Tables S1 to S12
References (*26*–*33*)

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# Cost-Benefit Tradeoffs in Engineered *lac* Operons

**Matt Eames[1] and Tanja Kortemme[1,2]***

**Cells must balance the cost and benefit of protein expression to optimize organismal fitness. The *lac* operon of the bacterium *Escherichia coli* has been a model for quantifying the physiological impact of costly protein production and for elucidating the resulting regulatory mechanisms. We report quantitative fitness measurements in 27 redesigned operons that suggested that protein production is not the primary origin of fitness costs. Instead, we discovered that the *lac* permease activity, which relates linearly to cost, is the major physiological burden to the cell. These findings explain control points in the *lac* operon that minimize the cost of *lac* permease activity, not protein expression. Characterizing similar relationships in other systems will be important to map the impact of cost/benefit tradeoffs on cell physiology and regulation.**

Expressing proteins uses cellular resources and thus incurs fitness costs (*1*, *2*). To balance these costs and generate a net fitness advantage, cells must couple protein expression to beneficial processes. These cost/benefit tradeoffs (*3*) shape mechanisms that regulate protein expression, such as those in the *lac* operon (*4*). The fitness costs of protein expression have also been hypothesized to govern the speed at which proteins evolve (*5*, *6*) and to influence the operation of regulatory circuits (*7*, *8*). To interpret these effects and derive predictive models of the physiological consequences of protein expression, the underlying sources of both cost and benefit must be identified and quantified. Such models are central to understanding gene regulation, metabolic engineering, and molecular evolution.

Because costs are balanced or even completely masked by coupled benefits under physiological conditions, cost and benefit can be difficult to separate. We used the *lac* operon (*4*, *9*) (Fig. 1A) to separately quantify the cost and benefit of protein expression (*3*); we define cost as the relative reduction in growth rate due to operon expression and benefit as the relative increase in growth rate in the presence of lactose, the substrate of the operon. To dissect the interplay between proposed cost sources and protein benefit, we quantified the effects of genetic changes that modulate three cost/benefit tradeoffs (*5*): protein production efficiency (*10*) (by changing translational optimization and thereby expression level), functional efficiency (by modulating catalysis), and folding efficiency (*6*) (by altering the propensity to misfold).

To determine the growth response, we induced expression of the *lac* operon using the nonmetabolized inducer isopropyl-β-D-thiogalactopyranoside (IPTG) and varied the concentration of lactose. At low lactose concentrations, the change in growth rate relative to that of uninduced cells is assumed to primarily reflect the cost of protein expression, whereas at higher lactose concentrations, growth reflects both the cost and benefit of lactose metabolism. We performed our experiments at full induction to decouple regulatory effects from the cost and benefit of expression and also to avoid complications arising from bistability at low inducer concentrations (*1*). We knocked out the entire *lac* operon and replaced it with engineered versions at the attTn7 locus (*11*). As a control, we confirmed that a knockin (*KIlac*) of the wild-type *lac* operon successfully recaptured native cost/benefit lactose response curves (fig. S1).

[1]Graduate Group in Biophysics, MC 2530, University of California, San Francisco, CA 94158–2330, USA. [2]California Institute for Quantitative Biomedical Research and Department of Bioengineering and Therapeutic Sciences, MC 2530, University of California, San Francisco, CA 94158–2330, USA.

*To whom correspondence should be addressed. E-mail: kortemme@cgl.ucsf.edu