protein-synthesis machinery to translate the TBF1-encoding ORF located downstream in the mRNA. The R-motif adds to this translational control. When plants were treated with elf18, the authors found that this repression of TBF1 synthesis was rapidly and transiently reversed.

In eukaryotic cells (those that contain membrane-bound organelles such as a nucleus), mRNA uORFs are often associated with modulated translation of a downstream ORF in response to changes in certain cell metabolites[11], with the ribosome and uORF-encoded peptide acting as an intracellular metabolite sensor. This translational control can be mediated by ribosome stalling on the uORF for reasons related to the abundance of a specific metabolite. It has been proposed that the uORFs of the *TBF1* mRNA control TBF1 synthesis in response to a decline in the amino acid phenylalanine[10]. Both uORFs encode peptides that contain multiple phenylalanines.

Xu *et al*. used biochemical assays to investigate the role of the R-motif of *TBF1* mRNA and found that it binds members of the polyadenylate-binding protein (PAB) family. Mutational analyses revealed that the presence of the R-motif decreases translation of the downstream ORF and that PAB seems to contribute to this dampening effect. Perhaps relaxation of this translational control involves transient phosphorylation of PAB, which enhances its interaction with factors bound to the 5′ region of an mRNA that promote translation initiation[11].

Plants modulate translation to fine-tune responses to numerous external stimuli[11]. Xu *et al*. used an approach called ribosome footprinting to precisely map the position of individual ribosomes on mRNAs being translated. This revealed that, in response to elf18 treatment, more than 550 transcripts showed rapid and pronounced changes in the number of ribosomes per mRNA. These observed changes in translation did not seem to be associated with changes in mRNA abundance, suggesting that the expression of many mRNAs is under translational control that is affected by the presence of elf18. Many of these mRNAs contained an R-rich region in their 5′ leader sequence. Further investigation will be needed to understand the role of R-motifs and PAB in elf18-mediated translational regulation in plant cells.

The authors tested whether the advances they had made in understanding the regulation of *TBF1* could be used to enable rapid and transient activation of a defence response upon pathogen infection in rice. They used a 'TBF1 cassette' containing the promoter sequence that drives *TBF1* expression and the 5′ leader region located before the start of the ORF encoding *TBF1*. This cassette was effective in regulating the *A. thaliana* master immune-regulator protein NPR1 in engineered rice.

It had previously been observed[5] that high and uncontrolled expression of *NPR1* conferred resistance to various pathogens, but was accompanied by undesirable fitness costs, limiting the potential of this approach in an agricultural setting. When Xu and colleagues engineered rice to constantly express NPR1, the rice were stunted in the presence or absence of pathogens. However, when the authors controlled NPR1 expression with the TBF1 cassette, this resulted in a burst of NPR1 accumulation upon infection with *X. oryzae,* enhancing resistance to bacterial blight without incurring a rice-grain production penalty. Additional tests under various field conditions will be required to determine whether this means of increasing plant innate immunity can result in stable rice production under pressure from a range of pathogens.

These studies highlight the value of using natural regulatory element(s) that provide multiple levels of control to ensure that an engineered gene functions precisely how, when and where it should. Stringent gene control is particularly important for master regulators of stress responses, which often confer fitness costs when expressed globally. The integration of translational-control elements that temper responses on the basis of levels of cellular metabolites or applied small molecules could be combined with cell-specific regulation to express stress-resilience genes more effectively, thereby enhancing crop yields to feed the growing world population. ■

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In Retrospect

Global health estimated over two decades

Reliably measuring global health is a huge challenge. Four papers published in 1997 laid foundations for future global-health estimates, but, despite subsequent advances, better integration of data systems and models is still needed.

PETER BYASS

The Global Burden of Disease Study (GBD), which began in 1992, is an ongoing project that aims to estimate the impact that diseases, injuries and risk factors have on health and mortality worldwide, by country and over time. Twenty years ago, in four papers published in *The Lancet*, Murray and Lopez[1–4] described findings from an early iteration of the GBD. The papers estimated causes of death and disability worldwide in 1990, and projected how patterns were likely to change in subsequent decades. This work formed the basis for the contemporary GBD, which was recently described[5] as a "GPS for global health".

In the early 1990s, reliable cause-of-death data were available for fewer than 30% of deaths worldwide[6], and today's level remains under 50% (ref. 7). The early GBD, which involved input from the World Health Organization (WHO), Harvard School of Public Health and the World Bank, took what data were available and produced estimates about disability and death for 107 diseases and injuries across every region of the world. The estimates were generated using computationally complex models that incorporated epidemiological expertise and known disease information, together with factors such as misdiagnosis levels and data gaps. The work also involved the development of parameters such as disability-adjusted life years — estimated years of life lost to ill health and premature death — that enabled health to be characterized from a more nuanced perspective than had previously been possible.

Murray and Lopez's four papers collated this work, which had previously been published by the WHO to relatively little fanfare. The WHO subsequently distanced itself from the project.

In an editorial[8] that accompanied the papers, *The Lancet* criticized the WHO's timidity, suggesting that the organization should reassess its public-health policies on the basis of the papers' findings. Despite the support of *The Lancet*, however, it would be another ten years before the work of the GBD was continued in a new home — the Institute for Health Metrics and Evaluation in Seattle, Washington.

These early papers were simple and straightforward compared with the sophistication of more-recent work. In the intervening years, the GBD has developed cutting-edge approaches to complex modelling. However, these advances have not been paralleled by major improvements in the quantity and quality of primary data. Good symbioses between models and data are crucial for meaningful outputs. Over-modelling inadequate data or under-analysing copious data are both potential pitfalls in achieving a holistic view of global health. In addition, country-by-country health data remain highly unequal, with availability heavily confounded by socio-economics.

Appetites for reliable health numbers on the national, international and global levels are indisputable. Because actual data are often scarce, particularly for certain regions of Africa and Asia, the GBD has increasingly become regarded as a go-to source for health information. The study is therefore a major factor in much academic research and policy-making. However, not all users understand the distinctions between estimates, results and data, nor the associated uncertainties. As such, there is always a danger that inaccurate interpretations of GBD outputs might misinform research or policy decisions.

Moreover, the contemporary GBD is so complex that outsiders cannot grasp its details or replicate its findings. When models are impenetrable to all but extreme specialists, it is natural to regard health estimates for regions in which few direct data are available with some scepticism. This is particularly true if some outputs from global models are not considered locally plausible. For example, in 2010, the GBD produced estimates of deaths attributable to diabetes, and provided uncertainty bounds that were improbably similar and narrow across world regions, despite huge variations in data availability[6].

As a small window into GBD outputs, consider estimates for the percentages of deaths attributable to nine selected causes in 1990 and 2015 (Fig. 1), from GBD estimates generated in 1997 and 2015 (see go.nature.com/2qvropj). A fundamental principle of GBD modelling is that the whole global time series, from the beginning onwards, should be rerun following methodological tweaks or the addition of new data. Each new set of estimates supersedes previous versions, which can lead to revised estimates for past periods — as seen when the 1997 and 2015 estimates for deaths in 1990 are compared.

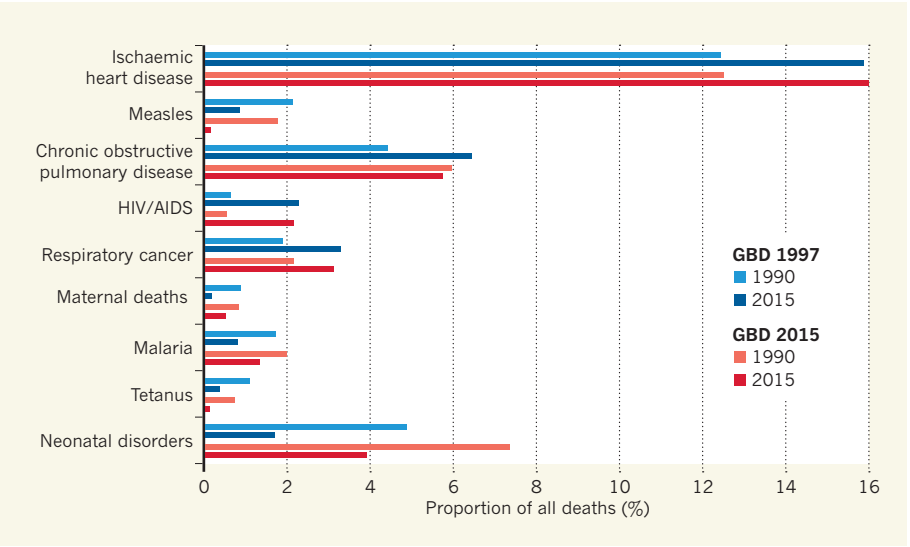

Figure 1 | Proportions for selected causes of death over time, from the Global Burden of Disease Study (GBD). In 1997, Murray and Lopez[1–4] reported results of an early iteration of the GBD, which combined data and complex modelling to calculate, among other things, estimates for the percentage of deaths worldwide attributable to selected causes[1,10]. The authors provided estimates for mortality proportions in 1990, 2010 and 2020. Updated estimates (see go.nature.com/2qvropj) were generated in 2015, covering 1990 and 2015. This bar graph compares the two sets of estimates for nine selected causes of death (GBD 1997 predictions for 2010 and 2020 have been interpolated to provide values for 2015). The estimates generated in 1997 have stood the test of time for some diseases — but for others the updated estimates are very different.

One might expect that estimates for 2015 made in 1997 would be less reliable than the 2015 estimates, which include contemporary data. Nevertheless, the numbers are highly consistent for several major causes of death. However, some differences are apparent — for instance, maternal deaths were not estimated to have decreased nearly as much in the 2015 round as was anticipated in 1997. Conversely, the phenomenal success of vaccination programmes means that deaths from measles and tetanus were estimated to be much lower in 2015 than was anticipated in 1997.

These observations merely scratch the surface of GBD resources. Nonetheless, the comparison is useful when considering how to balance estimation and data-gathering to maximize our understanding of global health. Models such as the GBD are undoubtedly attractive because of their consistent approach across all countries, years, age groups and diseases. Global-health measures that rely more on direct data and less on modelling might be easier to comprehend, but have holes in terms of overall coverage. A study[9] that compared cause-specific mortality estimates from the 2013 round of the GBD with directly captured data from the INDEPTH Network (a network of health and demographic surveillance systems in low- and middle-income countries) found high correspondence between the two sources for the 13 countries in which the network had collected sufficient data. This confirmed the validity of GBD estimates using independent data, and highlighted the current impossibility of using data directly to get a complete overview, particularly in Africa and Asia.

Such comparisons raise the possibility that enhanced synergies between models and data could improve global-health estimates. This would require advances in modelling (which have already been funded) to be complemented by increased resources and greater determination to fill in data gaps around the world, country by country (this remains largely unfunded). Such a convergence would be a win–win scenario for understanding health globally, presumably leading to better policy-making and more-resource-efficient health services. Investment in this nexus between data and estimates will be required for sustainable health development to progress over the next 20 years. ■

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