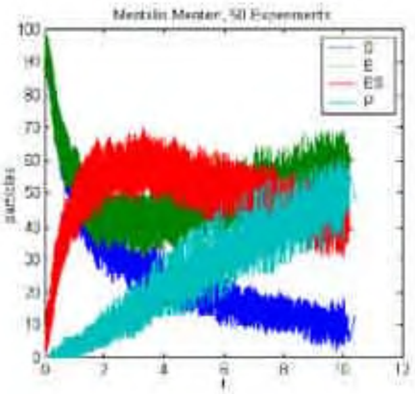

Figure 1. Computer generated stochastic simulation showing how noise accompanies the evolution of an optimal solution.

What is the biological value of building noisome? Among the very first users would be people trying to understand the dynamics of gene regulatory networks *vis-à-vis* the existence of noise *smear* over the network. A number of unsolved questions can be addressed through noisome. For example: Do gene families with a particular noise pattern exist? What mechanisms ensure that genes or a category of genes always function within a specific noise threshold? What happens when the cells cross the optimal noise boundary conditions? Are biological complexity and emergence a function of noise? How do activators and inhibitors impact noise levels in a given network space? Does noise play a role in speciation and phylogenetic evolution of gene networks? The answer to all these questions is: We simply do not know.

Noisome may help genome engineers to make use of noise signatures and design novel genomes finely tuned to specific noise patterns. A less noisy gene would be energetically more favourable to operate and maintain than a noisier gene. The additive/subtractive property of noise can be used to create synthetic networks with a specific noise profile. We do not know if network phenotype is determined by the ratio of low-noise and pure high-noise genes, maintained at a certain equilibrium state. How do pure low-noise and pure high-noise gene families behave in isolation? We have no idea. It would be interesting to investigate the behaviour of low-noise and high-noise genes connected serially and in parallel. This has application in synthetic biology where the sole aim is to create novel and unnatural cell circuits *in-vivo* for biological and clinical applications.

The emergence of noisome may also address a number of questions of fundamental importance. For example, is genome 'compartmentalized' into various noise domains? If yes, are gene communities topologically ordered on the basis of their noise patterns? Do cells use local and/or global noise thresholds as built-in memory primitives? What is the effect of adding noise (strong promoter, gene knock-in) or decreasing noise (weak promoter, gene knock-out) on cell circuits? Is cancer an outcome of mismanaged network noise dynamics? Do chromosomal translocations or deletions push cells beyond an allowable noise threshold? What features and combination of noise patterns make a cell fragile/robust to external conditions? It is obvious that a number of interesting unsolved problems in biology can be addressed through noisome. Transcriptomics and metabolomics only reveal a part of the cell story. Noisomics, the systems biology of noise and a *subspecies* of transcriptomics may turn out to be a *genus* in itself.

1. Elowitz, M. B., Levine, A. J., Siggia, E. D. and Swain, P. S., *Science*, 2002, **297**, 1183–6.
2. Levin, M. D., *FEBS Lett*., 2003, **550**, 135–8.
3. Held, W. and Kunz, B., *Eur. J. Immunol*., 1998, **28**, 2407–2416.
4. Hasty, J., Pradines, J., Dolnik, M. and Collins, J. J., *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 2075–2080.
5. Blake, W. J., Ern, M. K., Cantor, C. R. and Collins, J. J., *Nature*, 2003, **422**, 633–637.
6. Schena, M., Shalon, D., Davis, R. W. and Brown, P. O., *Science*, 1995, **270**, 467–470.
7. McAdams, H. H. and Arkin, A., *Proc. Natl. Acad. Sci. USA*, 1997, **94**, 814–819.
8. Meng, T. C., Somani, S. and Dhar, P. K., *Silico Biol.*, 2004, **4**, 24.

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Ethics in science: On the selective suppression of inconvenient data

In a recent article[1], Narlikar has recounted the circumstances behind Eddington's claim to have provided convincing proof of Einstein's theory of general relativity. This was based on the famous 1919 experiments performed by Eddington and Crommelin during a total solar eclipse. However, recent research by science-historians has given an entirely different perspective on the whole affair[2]. It transpires that Eddington had resorted to unethical means to substantiate his claim. The details of the 1919 experiments have now been fully exposed in a book by John Waller[2].

When light from a distant star passes close to the sun, it gets deviated by a minute fraction of a degree because of the gravitational warp of space. This deviation should be about 1.7 arcsec if Einstein's theory was correct. On the other hand, if the light ray followed the existing Newtonian laws, the deviation should be only around 0.8 arcsec. In 1919, Eddington planned to set out on an expedition to regions where the solar eclipse would be clearly visible, and to set up experiments to measure the deviation of the stellar light in the vicinity of the sun. This was certainly an ambitious aim. The problem of accurately measuring such minute displacements with the available instruments was further compounded by several others: if the light rays did not pass almost along the edge of the sun during the eclipse, but farther away, the gravitational effect would be smaller and so the deviation would be still less; atmospheric turbulence as well as variations in temperature during the measurements would contribute to the distortion and would have to be adjusted for. Such adjustments could only be carried out if proper statistical techniques were employed, and this required a minimum of six stars in each photographic frame, whose locations were not displaced during the course of the determinations.

The situation was further worsened by the poor visibility on that particular day. Two separate teams were conducting the experiments, one led by Eddington at Principe, and the other under Crommelin at Sobral. Eddington was the overall leader by virtue of his standing in the scientific community. Neither team produced measurements that could definitely confirm either the Newtonian or Einsteinian theory. But even before he set out, Eddington was convinced that Einstein's general theory of relativity was correct. On the basis of his conviction, Eddington evaluated the results according to whether they conformed or not to his preferred theoretical predictions. He judiciously selected only those readings that could be presented as unequivocally supporting the Einstein theory, discarding all those photographic plates where the value of the deviation fell close to what Newtonian theory predicted. In all, he suppressed almost two-thirds of the photographs from the Sobral and Principe expeditions!

Eddington's contemporaries accepted this blatant falsification uncritically. In this, they were also swayed by the strong support extended by the Royal Society of London to Eddington. J. J. Thomson, President of the Royal Society, threw his personal weight behind Eddington's interpretation. The Astronomer Royal too joined this unholy alliance, leaving the rest of the scientific community no choice but to accept meekly the carefully edited results and the interpretation thereof.

Clearly, what Eddington did was unethical. The suppression of data that refused to fit into the pre-determined pattern could have had disastrous consequences. However, Eddington was lucky; he was vindicated later on the basis of much better experimental results. But for this, his posthumous reputation would have been severely tarnished.

Selective suppression of – or ignoring – 'inconvenient' data is not a rare phenomenon. It is probably the most commonly practised form of unethical behaviour among scientists. Such falsification of data is most often trivial; usually it is the students' way of responding to the rigid standards insisted on by referees of theses or editors of science journals. How often have graduate students in organic chemistry sent the *same sample* of their synthetic product for microanalysis, until the values come within the acceptable range? And then all the earlier results are conveniently consigned to the dustbin and only the best values mentioned in the thesis! The slightly more enterprising among them would even try to 'nudge' the values to fall within the limits! Similarly, the practice of ascribing inexplicable peaks in the NMR spectrum to 'junk' and omitting mention of such aberrant spectral features must also be fairly universal among budding organic chemists. Actually, this is rather a silly thing to do, since the detailed exploration of an unexpected by-product can sometimes lead to discovery of a totally new reaction.

One shudders to think how disastrous the consequences could be if clinical research scientists too were to indulge in such discreet 'editing' of the toxic profile of a new chemical entity under trial. Suppose, while conducting the early phase clinical trial, they came across an adverse drug reaction (ADR) in a very small percentage (say, 0.1 to 1.0%) of the patients and decided to ignore this. Since such trials are usually carried out in patients numbering just a few thousands, such an ADR would be seen, at the most, in a handful of patients. If the compound is marketed subsequently, and a million patients are prescribed this drug, then the same ADR will manifest in hundreds of patients. The consequences could be terrible if the ADR were of a serious nature.

Luckily, clinical research scientists are always scrupulous in recording all ADRs and such a calamity, due to suppression of data, has not occurred so far. What can happen though, is a faulty interpretation of the significance of the ADR, or the emergence of the ADR only after prolonged use of the drug. This seems to have been the case with the recent highly publicized voluntary withdrawal from the market of drugs such as Vioxx and Lotronex. [Here we are not concerned with the ethics of *marketing* a drug that has been proved to have an unacceptable risk–benefit ratio].

Returning to the Eddington story, it is worth analysing why the people at large, and the scientific community in particular, were so eager to accept his findings uncritically. First, there was the drama associated with the event: an innovative theory is proposed, that challenges the existing paradigm; the complexity of the new theory is explained to the public in simple terms by a brilliant mind; and then the theory is tested and vindicated by means of an easily understandable, but difficult to execute experiment, set in an exotic locale! Secondly, and this was especially relevant to the scientific community, the entire process seemed to exemplify the 'scientific method' at its best; the strictly objective interpretation of the collected data proving the superiority of the new theory over the old.

It is unfortunate that in retrospect, it symbolized the exact opposite – the unabashed manipulation of the data to fit into a pre-conceived notion! Needless to say, this misguided attempt of Eddington does in no way diminish the brilliance of Einstein's insights. As Waller concludes, Einstein's ideas did not require the kind of boost that Eddington sought to provide.

1. Narlikar, J. V., *Times of India*, 1 January 2005.
2. Waller, J., *Fabulous Science*, Oxford Univ. Press, 2002.

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