a more favourable alignment for reaction? For example, friction and confinement offer a versatile way to align molecules[7], and tribologists, who earn their bread from the study of these things, have known for a long time that friction promotes chemical reactions[8]. The tribological question[7,8] is not directly addressed in Sheiko and colleagues' experiments, but will be an interesting motivation for further work.

And what about using the heat released to accomplish useful chemical change? Carbon–carbon bonds, by dint of their strength, release a lot of energy when they are broken — just as, in a bout of tug of war, energy is lost when the rope fails and competing teams fall to the ground. Although Sheiko *et al.* did not set out to capture energy from breaking carbon–carbon bonds, there is no reason that molecules could not be designed that use this energy for productive chemical means. In this area, too, Sheiko *et al.*[1] have presented a fundamental proof-of-principle on which further efforts can be built and go beyond the more obvious, unwanted consequences of mechanical degradation. ■

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COMPARATIVE GENOMICS

Difference of expression

Rasmus Nielsen

Evolutionary studies tend to focus on alterations in proteins. But evolutionary change can often occur through modified gene expression, a process that is now under investigation with species-specific microarrays.

Gene expression, the major determining factor of protein abundance in the cell, is regulated by various mechanisms, such as protein binding to the DNA sequence and interference by small RNA molecules. On page 242 of this issue[1], Gilad *et al.* describe their study of gene expression in four primates. Their work is aimed at identifying similarities and differences in gene expression between humans and their nearest relatives.

As we elucidate the complex molecular machinery that controls gene expression, our ignorance of its role in evolution is becoming increasingly alarming. In most cases, we know little about the way in which gene expression is involved in how organisms adapt to new environments or otherwise evolve. It has long been hypothesized that adaptation over short evolutionary time may often proceed by modifications in the regulation and interaction of genes rather than in the protein gene-products themselves[2]. Proteins tend to interact in complex networks, and so small changes in the abundance of one protein may have profound consequences. At the DNA level there may be many different mutations that affect gene-expression levels, but very few potentially beneficial mutations that directly affect protein function. Nonetheless, for convenience, most evolutionary studies have focused on protein evolution, leaving gene expression as one of the great unknowns in evolutionary biology.

Gilad *et al.*[1] make new strides in this field of research. They compare gene-expression data in humans, chimpanzees, orangutans and rhesus monkeys to identify genes that have changed their level of expression in the human lineage. This research differs from earlier studies[3,4] in using microarrays designed specifically for each species. Microarrays consist of a number of probes that bind messenger RNA from specific genes (mRNA is the linking molecule between a gene and the protein it encodes). By determining how much mRNA binds to each probe, the relative abundance of mRNA from each gene can be assessed. However, if the same microarray is used for all species, results may differ between species because of species-specific mutations that affect the binding affinity of the probes. Although this problem can be partially circumvented by removing genes that have such mutations, species-specific microarrays are the only known way to obtain a fair comparison among several divergent species without the loss of any genes.

Using this technology, Gilad and colleagues demonstrate that most genes are under natural selection to maintain a constant level of expression, but that a few genes show evidence of species-specific changes. The fact that selection in most cases is working to maintain expression levels near some optimum is not surprising — levels of expression of a gene that are too high or too low would presumably often be detrimental to an organism. Gilad *et al.* also observe no systematic increase or decrease in the regulation of gene expression in either humans or chimpanzees, contrary to previous claims to this effect[3–5]. But the authors do find that some groups of genes, particularly those encoding gene-transcription factors, tend to include greater numbers of upregulated genes in humans. Transcription factors are proteins that themselves play a role in regulating expression levels. So this observation is further support for the view that many evolutionary changes that are specific to humans may be related to gene expression.

Gilad *et al.*[1] also find that genes that are significantly up- or downregulated in humans, compared with other species, are often genes that have changed rapidly at the DNA-sequence level[6]. So there seems to be a correspondence between genes with altered expression and genes that have been targeted by positive darwinian selection in their protein-coding regions. This makes sense — we would expect changes in the function of a protein to be followed by changes in its distribution and abundance. Likewise, we may expect genes that have suffered a loss or reduction in functionality to subsequently experience an increased rate of evolution in both the sequence of the protein it encodes and its expression level, because selective constraints on it will have been relaxed.

What factors might be causing differences in gene expression between species? Such factors could include changes in the DNA close to the gene, for example changes in transcription-factor binding sites, or in distantly located elements such as gene enhancers, RNA genes or genes encoding transcription factors. Quantifying the relative importance of the evolution of these various elements will not be easy, but large-scale studies comparing many different organisms should reveal correlations between evolutionary changes at the DNA level and changes in expression level or pattern. The comparative analysis of expression data may thereby serve to detect functional correlations between DNA and expression levels in organisms in which it is difficult to carry out direct studies using standard genetic techniques. The result, I predict, will be a new perception of the mechanisms underlying evolutionary change — one in which the emphasis is on changes in regulatory elements, in RNA genes and in segments of DNA other than protein-coding genes. ■

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