One size does not fit all

High-throughput RNA interference (RNAi) screens offer a tantalizing amount of data, but with these data comes the challenge of applying an appropriate statistical interpretation. It is tempting to look to the well-developed statistics used in large-scale small-molecule screens and simply apply these to RNAi screens. In a Review, Birmingham and colleagues point out that there are pitfalls in doing so. Small-molecule screens are often optimized for low false positive rate, whereas RNAi screens produce a much broader range of relevant hits. Birmingham and colleagues compare data characteristics of both screen types and present a workflow for the statistical analysis of RNAi screens going from data triage to normalization, quality control and hit identification. For each step, they discuss the appropriate statistical tools.

Review p569

ADAM investigates evolution

Over the course of evolution, organisms acquire a large number of mutations, some of which enable them to survive in challenging environments. The long time scale of evolution makes it impossible to recapitulate the process and to pinpoint adaptive mutations in a sea of neutral ones. Enter Escherichia coli and Tavazoie and colleagues. The former grows at a pace that allows evolution on a laboratory time scale, within days rather than millions of years, and the latter developed array-based discovery of adaptive mutations (ADAM) for bacteria. This screen finds mutations that underlie the adaptation of E. coli to environmental challenges with high sensitivity and specificity.

Brief Communication p581, News and Views p565

Sequencing NRPs

The classical pathway of translating mRNA on a ribosome is not the only way for a cell to make a protein. Nonribosomal peptide (NRP) synthetases generate NRPs, among which are many pharmacologically important substances such as antibiotics. As most NRPs contain nonstandard amino acids, efforts to sequence them have been very time-consuming. Pevzner and colleagues now present an algorithm based on dereplication, the comparison of new NRP spectra to those of similar compounds, which reduces the time for cyclic NRP sequencing from weeks to minutes. In cases for which no related spectrum is available, the authors introduce an algorithmic solution for de novo sequencing.

Brief Communication p596

Digital allelotyping

Heterozygous single-nucleotide polymorphisms (SNPs) that cause allele-specific gene expression (ASE) are likely to point to cis-regulatory regions that are good candidates in the search for genetic determinants of human diseases. To comprehensively interrogate the transcriptome for SNPs associated with ASE, Zhang, Church and colleagues combine their padlock-based genome capture technique with RNA-Seq. The improved design and synthesis of the padlock probes allows them to efficiently capture 27,000 SNPs on genomic DNA and cDNA in two single reactions and to identify the 10–20% of SNPs that map to genes with ASE in the cell lines tested.

Article p613

SAXS and the structure

Though structural genomics initiatives have greatly increased the number of solved protein structures, a substantial amount of time is required to obtain atomic-resolution structural information by X-ray crystallography or nuclear magnetic resonance spectroscopy. Tainer, Adams and colleagues now demonstrate a small angle X-ray scattering (SAXS)-based pipeline, which could greatly increase the throughput. Though the structural resolution of SAXS is approximately 15 Å, this is high enough to discern molecular shape and oligomeric state, which provides clues as to the biological function of a protein. Sample preparation for SAXS (which is performed in solution) is minimal compared to that for X-ray crystallography, data can be rapidly collected and analyzed, and the success rate is much higher because it is not dependent on obtaining a high-quality protein crystal. The researchers show that a throughput of 20 proteins per week is possible with a largely automated SAXS pipeline.

Article p606