Geneticist seeks engineer: must like flies and worms

Phenotyping is rapidly becoming the limiting step in genetic studies of model organisms. Increasing throughput is a technological challenge that calls for engineers.

The past two months have seen an outburst of reports on genome-wide association studies linking human gene variants with diseases. These discoveries are the fruits of the knowledge and technology gained with the sequencing of the human genome. With more genomes being sequenced, similar studies are also becoming feasible in model organisms, where the larger range of accessible phenotypes will permit exquisite dissection of complex traits, like those related to behavior and development.

The field of genetics, however, is facing a historical reversal in terms of experimental limitations. What was once considered the major bottleneck—interrogating an entire genome in many samples—is becoming feasible thanks to microarrays and other tools for measuring genetic polymorphisms. Instead, the bottleneck now is phenotyping. Establishing patients' clinical characteristics will always require intensive one-on-one interaction with clinicians. But for model organisms, it should be possible to develop technologies that allow high-throughput phenotyping. What exactly these enabling technologies should be is yet unclear, but one thing is certain: they represent a technological challenge that requires the expertise of engineers and the support of funding agencies.

On the wish list are technologies that reduce experimental time and human intervention while allowing parallel analysis of multiple individuals. This would not only accelerate research but also improve data quality, by increasing the number of individuals that can be examined—thus increasing statistical power—and decreasing the effect of environmental noise. The ability to measure small quantitative phenotypic changes should underlie any advances.

Developments involving automation and new instrumentation naturally fall into the realm of engineering challenges, but one of the difficulties in enlisting engineers' help has been the lack of clearly defined objectives. As opposed to genetic material, there is no universal phenotype. Rather, every researcher studies their favorite traits in their favorite model organism. As a consequence, no top-priority challenges have been identified that are likely to inspire academics and ensure funding. As for the commercial developments, the market size for each specific phenotype assay is often too small to attract business interest.

This could change if a handful of broadly applicable technologies were identified. Would it not be possible for geneticists working on different problems to define common needs? …to agree on a list of bottlenecks that universally plague different assays? Such an exercise would at least help define the framework to engage engineers in translating these needs into technologies. Realistically, no technology may directly be applicable to diverse organisms and experimental designs, but some will be adaptable.

Take sample handling. Automated in yeast genetics, sample handling remains a bottleneck in many experiments in which the sample is not a liquid. Technologies facilitating manipulation of diverse organisms deserve more attention. In that area, the 'worm cytometer' has been a milestone. Originally developed to sort *Caenorhabditis elegans* based on size and fluorescence, the instrument has now been commercialized with adaptations capable of dealing with objects as diverse as plant seeds, mosquito larvae and fish embryos.

Imaging is another example of broadly enabling technology. In general, progress in high-content, automated imaging is desirable because it permits quantitative measurement, as opposed to gross qualitative observation—a paradigm change with repercussions beyond model organism genetics, for example, in mammalian cell–based assays. Digitized image analysis can facilitate difficult phenotype assessments, like those requiring inspection of whole organs. For example, the 'wingmachine', conceived at Florida State University, can measure the position of veins and edges in fly wings. Improvements in automated recognition of landmark features, ability to follow the same object over time and adaptations to recognize various shapes and sizes as well as three dimensions would likely benefit a wide range of applications.

Other phenotypes intrinsically challenging to measure are those related to behavior, but many of them come down to locomotion and movement. Some investigators have started using video monitoring, and the potential market seems large enough to have justified a few commercial developments, which could be improved and expanded.

Which of these or other technologies will be broadly useful and deserve the most attention remains an open question that will be best answered by the main stakeholders—geneticists and engineers. Regardless of the outcome, there is an opportunity for engineers to tackle projects likely to influence the future of genetic research. The engagement of engineering departments in solving this challenge of genetics should be supported by academic infrastructures and by funding agencies. Without such investment, the lack of high-throughput phenotyping of model organisms will soon be a limitation to progress.

Erratum: Geneticist seeks engineer: must like flies and worms

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In the version of this Editorial initially published, the development of the 'wingmachine' was improperly attributed to the University of Florida. The instrument was developed at Florida State University. The error has been corrected in the HTML and PDF versions of the article.