EDITORIAL

Apples, oranges and unknown fruit

For many microbiologists their ultimate goal is to understand microbial life at the whole-cell level. Here, Fred Neidhardt gives his view that attention must be paid to the growth conditions for this goal to be realized.

For over a century microorganisms have attracted the attention of a wide variety of scientists. Among the myriad reasons for this is the usefulness of microorganisms in exploring the fundamental processes of life at the cellular level. For some of us, the muse has been the goal of 'solving' a living cell; for others the vision has been more modest, but the lure equally strong. It is the thousands of microbiologists who contribute directly or indirectly, consciously or unconsciously, to 'cell solving' that I address.

'Solving' a cell means gaining sufficient understanding to represent its components and processes mathematically in a model that accurately predicts behaviour — especially growth — in various conditions. This dream is no longer far fetched. For paradigmatic cells such as *Escherichia coli*, annotation to give meaning to the extensive sequence information that is now available is being improved. Profiling the activity of the total genome through transcriptional and translational monitoring is fairly accurate and commonplace. Monitoring metabolite flux through cellular pathways is less developed, but improving. The myriad of macromolecular interactions in the cell are beginning to be known. The vectorial processes that import and export small molecules and macromolecules, cell division, the metamorphosis between growing and non-growing states, and the interactions with other cells and the environment are all now yielding to molecular analysis. Importantly, the necessity of systems analysis for modelling a cell has become recognized by microbial physiologists.

But here is the rub: modelling needs data — tonnes of data, including the numbers of molecules of each chemical species in each particular cellular location, the rates of reactions and quantitative accounts of molecular interactions, and data on how all these change with time under different environmental conditions. Much of the needed numerical information is being gathered today, but most of it is inappropriate for serious modelling. The results of molecular-genetic, biochemical and ultrastructural analysis are largely independent of the physiological state of the cell culture and can be readily applied to the general corpus of knowledge about the cell. But microbial metabolism and physiology are different. Whether the goal is modelling or simply any worthwhile quantitative study of microbial metabolism or physiology, the brutal fact is that all the numbers depend on the growth condition of the cells being measured. Reproducibility demands attention to the microbial strain, the growth medium, control of aeration and pH, and the use, wherever possible, of populations in steady state (balanced) growth. Measuring and publishing the growth rate is the best way to define and authenticate the physiological state of the cells. Check your favourite journals. How many papers describe the growth conditions and record the growth rate? The shameful fact is that studies are still being conducted with insufficient attention to growth conditions, and without mention of growth rate — 'early log', 'mid-log' and 'late log' are phrases that should be banned. However painstakingly acquired, the quantitative data from one laboratory can rarely be combined with those from another, and the databases for microbial metabolism and physiology consist of apples, oranges and unknown fruit.

To be honest, more than simply specifying the growth conditions is needed. Serious modelling demands the use of reference conditions. Some guidance and suggestions for reference conditions have been made for enteric bacteria[1], but these are incomplete and are rarely heeded anyway. As a result, most of the expensive monitoring of genome expression (to cite only one experimental approach) in recent years has come from experiments that have only themselves as referent, rather than also functioning as part of a universe of information that can be integrated with other data. Perhaps some of you cell mavens will take up this cause, organize a workshop or two and develop reference conditions for your organism.

Another force compels us to mend our ways. Support of microbial research must cover many vital subjects[2]. Microbial cell research is more costly today than in the era of sterile toothpicks and reusable Petri plates, M9 minimal medium and Klett colourimeters, inexpensive radioactive isotopes and Geiger counters. To conduct today's expensive research without heeding the need for the integration of data from different laboratories is well-nigh unconscionable. We cell zealots must give assurance that the data we gather at great expense is usable by others — that's just good science.

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1. Neidhardt, F. C., Bloch, P. L. & Smith, D. F. *J. Bacteriol.* **119**, 736–747 (1974).
2. Curtis, T. P. *Nature Rev. Microbiol.* **4**, 488 (2006).