Cell-cycle regulation by numbers

A mathematical model of the cell cycle, of great interest in itself, may be a first step towards the much more ambitious models people will be building in the decades ahead.

ONE of the deepest pits into which journalists can fall is that of what may be called prescriptive conceit. That is the tendency of people who have been observers of some scene for many years to believe that they know better than the actors currently on stage what lines should next be said. The result is pompous and hortatory prose littered with verb-qualifiers such as 'should' and even 'must'. The tendency is a pitfall because experience also shows that the only people who read that kind of prose are those who recognize at the outset that they will agree with the prescriptions; other people's beliefs will be unaffected.

That is by way of half an apology (some may even consider it to be a negative one) for this part of *Nature*'s campaign for a better regard among molecular biologists for the quantitative aspects of their exciting work. OK, these guys are indeed telling the rest of us how the cell works — which molecules do what to which other molecules. From time to time, there are even a few scraps of structural information that lend conviction to hand-waving accounts of 'mechanism'. But they are still naming the parts of the machine, without explaining to the rest of us why it works like that.

Specifically, there are two dangers in the current cult of the qualitative in molecular biology. One is that it gives the impression that everything is cut and dried. Replication of DNA is faithful to the template, the translation of mRNA into protein similarly reflects what is written in the genome (give or take a modicum of ambiguity in nuclear splicing) and the question of how external influences may modulate the genomic autonomy of the cell must await the naming of the parts concerned.

The second danger is more serious: the practitioners are at risk of missing important truths about the systems they are studying. Two years ago, an article in this series singled out cell division as a phenomenon likely to be determined by 'quantitative triggers', not qualitative ones (*Nature* **355**, 201; 1992). The same piece concluded with a plea that molecular biologists should resurrect the Law of Mass Action.

Independently of these urgings from the sidelines, Bela Novak and John J. Tyson from the Virginia Polytechnic Institute at Blacksburg now appear to have done just that (*J. Cell Science* **106**, 1153–1168; 1993). (Novak really belongs to the Technical University of Budapest.) What they have done is to construct a mathematical model of the regulation of the cell cycle by the biochemicals now known to be involved.

The still emerging tale of how the cell cycle is regulated is one of the most enthralling of the past few years, involving the interplay between experiments with amphibian oocytes and studies of the genetics of yeast strains defective in some aspect of cell-cycle regulation.

In essence, nevertheless, the story is straightforward. (The third edition of *The Molecular Biology of the Cell*, published earlier this year, has an excellent up-to-date account.) The key event in the life-history of a cell is its division into two replicas of itself, accomplished during 'M-phase' (where 'M' stands for mitosis). The rest of the cell cycle, called 'interphase', is from one point of view merely a preparation for mitosis, but cells such as neurons spend their whole time in that condition. Otherwise, interphase is when the cell's complement of DNA is replicated and the organelles required to send two daughter cells successfully on their way are manufactured.

What controls the oscillation of cells between interphase and mitosis? What else but a 'factor'? That was originally called MPF (for maturation promoting factor), but has now been identified as a dimer of two distinct protein molecules, a cyclin and a protein kinase related to that originally identified in fission yeast and known as cdc2. The activity of MPF as a kinase (or phosphorylating enzyme) depends on the manner in which its cdc2 component is itself phosphorylated, but some of the enzymes controlling that process have also now been identified.

Novak and Tyson are above all concerned that their model should allow for the two feedback loops recognized in experiments. First, active MPF stimulates its own production, which is positive feedback. But active MPF also stimulates the destruction of cyclin (by what is called 'ubiquitin-conjugated enzyme'), which is a negative feedback.

The result, inevitably, is a set of linear differential equations (in which the only differential coefficients are the rates of change of concentrations with time). In reality, there are 13 of them, but only 9 are independent (because of the assumption that the total concentration of cdc2 is constant throughout the cycle). Altogether, there are 18 rate constants for the chemical reactions involved, while it is possible to look for solutions of the equations only by saying something about the initial values of the 13 concentrations of the materials involved in regulating the cell cycle.

The equations can be solved only numerically, but that is no great handicap. Moreover, the agreement with experiment seems remarkably good. For example, it is possible to extract from the equations a curve describing the conditions for equilibrium between total (bound or otherwise) cyclin concentration and that of active MPF. And that turns out to be unstable. There is some point at which a small increase of cyclin concentrations brings about a jump in active MPF concentration of nearly an order of magnitude — just the kind of trigger cell-cycle regulation needs.

Perhaps the most remarkable illustration of the fidelity of the equations to real life is their use in the simulation of the oscillation of the cell-cycle regulators in cell-free extracts from *Xenopus* eggs. That is the most remarkable phenomenon in itself. Like other amphibia, *Xenopus* embryos must grow into tadpoles autonomously, with no external support, so that mature oocytes must contain the biochemical machinery required for many successive cell divisions. So even if the nuclei are removed, so that there is no DNA to replicate, cytoplasm on its own will go through the motions of cell division. What Novak and Tyson find is precisely what they expected — an oscillation of their system with a period of about 80 minutes.

Where this will lead is easily imagined. Novak and Tyson's parameters have been chosen to match the *Xenopus* case. No doubt they are busily applying the equations to other systems. It will be interesting to learn how the rate constants vary from one system to another, but careful matching of the numerical results with experimental data should also help to identify the many points at which understanding is incomplete.

And that is only a beginning. The coupling of this model to the external environment of the cell is at present only rudimentary, for example, but putting that right will entail the addition of further equations. Indeed, some model of this kind is likely eventually to be the core of a mathematical model of the cell as such. Eventually, that will be a project exceeding in complexity the Human Genome Projects in their various forms, with some thousands of coupled equations. But cell biologists should not be disheartened by the prospect. Those who model the chemistry of the Earth's atmosphere or even that of interstellar molecular clouds are well used to systems that are at once as mathematically simple and almost as complex.

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