The lac repressor and a feeling of *déjà vu*

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The lac repressor has passed into the folklore of molecular biology. Introduced in 1961 as a theoretical construct by Francois Jacob and Jacques Monod[1] in their classic paper entitled 'Genetic regulatory mechanisms in the synthesis of proteins', the lac repressor was a key element in the control of genes (*lac* operon), which dictate the synthesis of proteins responsible for the metabolism of lactose in *E. coli*. Repressors were conceived as elements which bound to specific regions of DNA called operators and in their complexed form, inhibited transcription (i.e. mRNA synthesis). Inducers were the other element in the Jacob–Monod scenario, which when added displaced the repressor and thus 'turned on' genes, leading to enhanced protein synthesis. In the early 1960s the molecular identity of the lac repressor was unknown, until the remarkable success of Benno Müller-Hill and Walter Gilbert[2] in isolating a protein that was indeed the repressor. This achievement is all the more spectacular in retrospect, when one realizes that a typical *E. coli* cell probably contains only 10 to 20 molecules of the repressor[3]. The context in which the hunt for the repressor began is described by Müller-Hill[4]: '... we read Monod's *Comptes Rendus* paper[5] right after it came out. I remember well the discussion that followed in the group. Some of us loved the impeccable logic of it, while others thought it was detached from any reality. Wallenfels invited Monod to give two lectures in Freiburg at this time, providing the chance to see and hear the impressive man. "Nature works in a Cartesian and not in a Hegelian manner", he began his lecture. I doubted that, but was not the repressor a wonderful problem?'

Over the years the playing fields of gene regulation have shifted from prokaryotes to eukaryotes and the lac repressor has taken its rightful place in textbooks of molecular biology. A fall out of recombinant DNA research has been the use of the '*lac* promoter' (and variants) as a switch in front of cloned genes in bacterial plasmids. Addition of inducers, pre-eminent among these is isopropylthio-β-D-galactoside (IPTG), leads to enhanced gene expression and synthesis of proteins of interest. Inducers and promoters (and by implication, repressors) are thus central to the controlled expression of foreign genes in bacteria. Now, several years after its isolation and canonization in molecular biology's hall of fame, comes a report on the crystallization of the lac repressor[6]. Most appropriately, single crystals of a complex with a 16-base pair operator nucleotide have been obtained. While the repressor crystals diffract to better than 3.5 Å, the crystals of the complex do so only to 6.5 Å. But what is really intriguing is that Pace *et al.* observe that soaking the crystals of the repressor-operator complex in a solution containing the inducer IPTG, results in cracking. This leads inexorably to the speculation, so beloved by all biochemists, biophysicists and molecular biologists, of a 'conformational or structural change' on interaction of the inducer with the repressor–operator complex. The lac repressor is a tetrameric protein with four identical subunits, each consisting of 360 amino acids. Over a quarter century ago Monod *et al.*[7] anticipated allostery in the repressor, by analogy with haemoglobin. Pace *et al.* in their recent paper[6] draw attention to the observations of Perutz[8] that the cracking of deoxyhaemoglobin crystals on introduction of oxygen was due to a structural difference between the two forms of the molecule. Soon we will undoubtedly learn about the molecular details of the complex and in the not too distant future, further details on the effects of the inducer. Where does all this molecular reductionism lead us? For an interesting view we must turn again to Benno Müller-Hill (and Monod): 'One day, late in the afternoon, I saw Monod standing in the door. "Hello" he said. "Hello" I answered. And then he simply said "Benno, after all it was pedestrian", bowed and disappeared, leaving me baffled for a long time. Now, many years later, I like to interpret his comment as "slow, down to earth, with only a few technical crutches" and think it was, after all, a compliment.'

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