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# Regulation of Gene Expression

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## Abstract

Genomics is like cryptography; how can we understand a text written in an unknown language? Champollion managed to decipher hieroglyphics thanks to simultaneous inscription of the same text on the Rosetta Stone. The studies undertaken by our Unit are based on this approach, comparing the texts of pairs of genomes. Exploitation of the mine of information represented by the complete sequence of genomes led to the concretisation of a precise aim, developed during the sequencing programme: to elucidate the link between genome architecture and cell structure.

## Annual Report

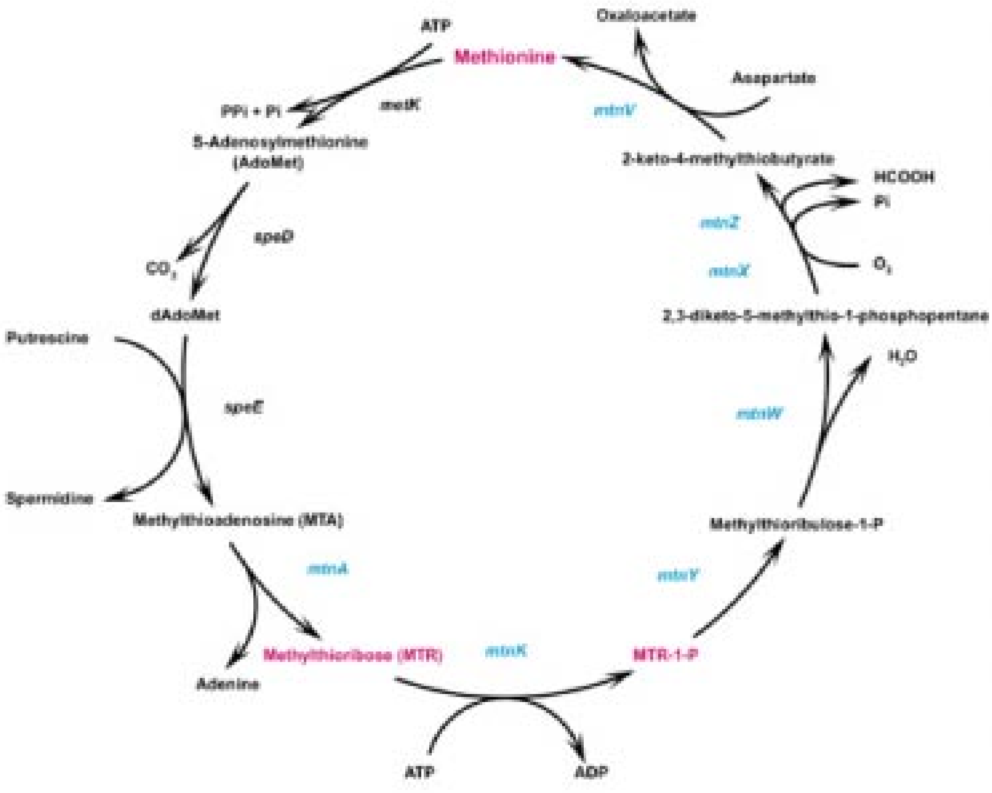
The work of the Genetics of Bacterial Genomes Unit (GBG, member of CNRS URA 2171) is based on the long-term aim of determining the way in which bacterial genes work together. Exploitation of the mine of information represented by complete genome sequences led to the concretisation of a precise aim, progressively developed during the sequencing programme: to elucidate the link between genomic architecture and cell structure. This link is based on a simple supposition, leading to the hypothesis that cells may be considered to organise assembly procedures and therefore to serve effectively as "Turing machines", the conceptual ancestors of computers. However, as these "machines" produce similar "machines", they are faced with the paradox described by the mathematician John von Neumann: they must have an image of the machine somewhere. It is thus a natural progression to try to determine whether this image is actually found in the genome itself. The aim of the work of this Unit is to explore this hypothesis by systematically combining *in vivo* experiments and *in silico* experiments, new techniques made possible by the advent of computers.

1. How does the model bacterium *Bacillus subtilis* use sulphur?

The aim of sequencing the genome of *Bacillus subtilis* was to investigate the role, if indeed there is one, of the distribution of genes on the chromosome in determining the temporal and structural expression of those genes. After much reflection, we chose to study polyamine metabolism, and the metabolism of sulphur in particular, as particularly sensitive probes for studying the possible links between genomic structure, cell structure and gene expression. Sulphur is a particularly important element in this field because it is highly reactive, which makes it particularly sensitive to all forms of selection pressure and subject to compartmentalisation in the cell.

Although sulphur is ubiquitous (all proteins start with a sulphur-containing amino-acid residue), this element has not been studied in detail (due to intrinsic experimental difficulties). However, the sequencing of all the genes in a genome, in parallel with efficient techniques for modifying genes *in situ* , should make it possible to investigate sulphur metabolism. The Unit's first task was to define the problem and to identify the main pathways for the anabolism and catabolism of sulphur-containing molecules in *B. subtilis* . The first regulatory elements were then detected. The systematic use of new "large-scale" biological techniques (proteome and transcriptome analyses) made it possible to study global regulation in response to the availability of sulphur in the medium and to identify novel genes involved in sulphur metabolism. All the stages of polyamine synthesis have been identified, in particular, those linked to sulphur metabolism. This led researchers from the Unit (and from HKU Pasteur Research Centre, created at the same time by the Head of the Unit) to characterise the entire pathway for the recuperation of methionine. This pathway begins with S-adenosylmethionine, and regenerates methionine by recycling S-methylthioribose without oxidation. This pathway is highly original and one of the enzymes involved, which is very similar to ribulose bisphosphate carboxylase (RuBisCo) – the most abundant enzyme on Earth, responsible for the fixation of carbon dioxide by plants – raises questions about the way in which enzymatic activities were recruited to metabolic pathways during the course of evolution and about the origins of RuBisCo itself.

The conclusion of these studies is that bacteria from the same class as *B. subtilis* (which contains many pathogenic bacteria, including the causal agent of anthrax) behave differently from enterobacteria, not only in the regulation of the corresponding pathways (which is normal as regulatory systems are not well conserved during evolution), but also in the metabolic reactions themselves. This renders the study of these bacteria particularly interesting, opening up new avenues for the identification of totally new antibiotic targets (patent pending). The resemblance of these bacteria to archebacteria is quite remarkable. This is an important observation in the current debate concerning the origin of cells lacking nuclei.




2. Chromosomal organisation and control of gene expression (Enterobacteria)

Although numerous studies have been carried out by laboratories worldwide, the structure of the bacterial chromosome is very poorly understood, as is its link with gene expression and cell structure. The main model other than *B. subtilis* is *Escherichia coli* (due to the enormous amount of information available concerning this bacterium worldwide) However, to put experiments into an integrated biological context, the results are compared with those obtained for other related bacteria, in particular *Photorhabdus luminescens*, which was chosen because it lives in pure cultures in the natural environment and interacts with specific well-identified hosts (a nematode and insect larvae).

The H-NS protein, the function of which is still unknown despite the large number of studies carried out over the last thirty years, has been studied in more detail. This protein interacts with DNA or RNA (or both), but its direct or indirect role in controlling the structure of the chromosome is not understood. A detailed phylogenetic study investigating the possible function of this protein in organisms living in very different environments (cold in particular, as it is a "cold-shock" protein) and the role of this protein within cells (using large-scale transcriptomic and proteomic techniques, in particular) was associated with analysis of acid shock or growth in an acidic environment. These studies revealed that the protein is probably involved in proton management in the cell. It seems to interact preferentially with RNA, in as yet undetermined conditions. We have shown that, in addition to acting as a negative regulator, this protein also plays a positive role, which we also analysed by comparative genomic methods.

3. *In silico* genomic analysis

An essential element of the Unit's activity is the integration of *in silico* predictive studies (genomic analysis) and experimental investigations. New databases have been constructed, making it possible both to annotate genomic sequences in more detail systematically, and to link genomic annotations with large-scale biological data (transcriptome analysis). This organisation of information has made it possible to study genomic sequences in detail and to discover a number of new properties, concerning evolution in particular. One important and unexpected observation concerns the major role played by metabolism in shaping the genomic sequence itself. It seems like we are dealing with a finished game, limited to objects that represent the alphabet in the four-letter genomic language, and this restricts what can be written. However, *in silico* approaches can also be used to study the organisation of the chromosome itself and to put forward hypotheses about the distribution of genes with respect to cell structure. This has made it possible to draw up hypotheses, which we are now going to test experimentally.

**Figure 1**: A novel metabolic pathway for the recycling of methionine

**Figure 2**: The larvae of the mosquito *Anopheles gambiae* are sensitive to a *Photorhabdus luminescens* toxin that has been characterised in the laboratory

**Keywords**:

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