# Bacterial gene regulation: an overview

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Bacteria are highly efficient and metabolically flexible organisms, with their genomes providing them with the ability to adapt to many different environmental conditions. For example, pathogens like *Escherichia coli* and *Clostridium perfringens* grow and survive very well in water and soil, respectively, but are also highly adapted to growth in the human body.

It is clear that these microorganisms, and most other bacteria, have the ability to control or regulate their gene expression so that only the gene products required at any one particular time are expressed. This issue of *Microbiology Australia* describes the many different process that bacteria use to regulate gene expression.

In bacteria, regulation of gene expression occurs primarily at the transcriptional level, and specifically targets the process by which transcription is initiated. Initiation of transcription involves an interaction between a multi-subunit enzyme complex, the DNA-dependent RNA polymerase, and a nucleotide sequence in DNA, termed a promoter [1].

## RNA polymerase

The active site of RNA polymerase is formed from the two large beta and beta prime subunits (Figure 1). The core enzyme also contains two identical alpha subunits and an omega subunit. The alpha subunits consist of two independent domains joined by a flexible linker. The amino terminal domain dimerises and assists in the assembly of the beta and beta prime subunits. The carboxy terminal domain can interact with proteins or DNA sequences upstream of certain promoters (see below). The omega subunit has a role in a process, termed the stringent response, which is also discussed in more detail below.

To begin transcription, the core enzyme must first associate with the sigma subunit to form the holoenzyme (Figure 1). It is the sigma subunit that specifically recognises the nucleotide sequences that make up the promoter. It correctly orientates the RNA polymerase on the promoter, and facilitates unwinding of the DNA duplex ahead of initiation. Most bacterial species contain one main sigma factor and several alternative sigma factors that specifically recognise subsets of promoters.

## Promoter structure

The two main sequence elements in a bacterial promoter are the –10 box and –35 box (Figure 1). As their names suggest, these sequence elements are located 10 and 35 base pairs upstream of the transcription start point. In *E. coli,* the consensus sequence for the –10 box is TATAAT, while that for the –35 box is TTGACA. The closer the sequence of a particular promoter is to these consensus sequences, the more strongly it binds RNA polymerase, and the higher the level of transcription.

Some promoters contain additional sequence elements. One of these, often termed an extended –10 sequence, is located just upstream of the –10 box and is bound by a specific domain of the sigma subunit (Figure 1). Other promoters have an AT-rich sequence, located upstream of the –35 box; that is termed an UP element. UP elements act as binding sites for the carboxy terminal domains of the alpha subunits (Figure 1).

In both cases, the presence of these additional elements results in higher levels of transcription. No known promoter contains all four of these sequence elements, with each element containing the exact consensus sequence. Indeed, variation from the consensus sequence has been used to set the basal level of transcription from different promoters.

The amount of RNA polymerase within the cell is limiting, and there is competition between different promoters to bind the little that is available. A 'strong' promoter (one that closely matches the consensus), will bind RNA polymerase more efficiently, which will result in a higher basal level of transcription. Alternatively, the cell may require only low levels of some gene products, and the relevant genes are therefore equipped with 'weak' promoters that vary significantly from the consensus, compete poorly for RNA polymerase and, as a result, have a low basal level of transcription.

## Stages in the initiation of transcription

RNA polymerase binding to the promoter is followed by open complex formation where the two DNA strands are separated around the transcription start point and the template strand is moved into the active site of the enzyme. The RNA polymerase then moves into the initiation phase where the first few nucleotides of the mRNA are covalently coupled. Finally, the RNA polymerase moves into the elongation phase, transcribing the complete mRNA strand. The sigma factor dissociates from the core enzyme during this last phase.

Each of these steps in the process of transcription offers the opportunity for 'fine tuning', where the efficiency of the process can be varied from basal levels in response to a cellular or environmental signal.

## Modes of bacterial gene regulation

In many bacterial species, the activity of alternative sigma factors can increase in response to specific stresses. Control over alternative sigma factor activity can be very complicated, involving systems that operate at the transcriptional, translational and post-translational level. However, the end result is an increase in the intracellular concentration of an active alternative sigma factor that competes with the main sigma factor for the core enzyme. This process in turn results in increased binding to, and transcription from, a set of promoters carrying specific sequence elements (see the article in this issue by Lyndal Thompson and Liz Harry).

The intracellular concentration of specific small intracellular molecules can also influence transcription of particular genes. The best example involves what has been termed the stringent response, where amino acid starvation results in decreased transcription of a set of genes encoding components of the translational machinery. These conditions result in an accumulation of a small molecule, ppGpp, which binds to RNA polymerase in a manner that is dependent on the omega subunit. Binding of this ligand has the effect of destabilising open complexes, but specifically at promoters that contain a GC-rich sequence around the transcription start point. This additional sequence element is largely confined to the genes involved in translation.

The most widespread means of regulating transcription involves sequence-specific DNA binding proteins. Proteins that act positively to boost transcription are termed activators, and are covered in more detail by Rachel Schubert and Keith Shearwin in their article, while those that act negatively to decrease transcription are termed repressors; these are covered in the article by Charlene Kahler.

Some regulatory proteins can act as either an activator or a repressor depending on the position of their specific binding site within the promoters they control. Regulation of transcription by this means depends, in turn, on regulating the DNA binding activity of the regulatory protein.

DNA binding can be influenced by ligands that reflect a certain nutritional status in the cell. The best known example of this is the binding of allolactose to the Lac repressor protein. DNA binding can also be affected by modification of the regulatory protein. Two-component regulatory systems contain a membrane-bound sensor that, in response to a specific environmental signal, acts to enable phosphorylation of a partner regulatory protein. The phosphorylation of the regulatory protein influences its DNA binding activity as can been seen in Jackie Cheung and Julian Rood's article in this issue.

Non-specific DNA binding proteins can also influence transcription. The DNA inside the cell is heavily compacted into a structure called the nucleoid. This dynamic structure is controlled by a series of small DNA binding proteins. The binding of these proteins can influence the access of RNA polymerase to specific promoters, and therefore the level of transcription, in both a positive and negative fashion; more detail can be found in John Davies' article.

It is common for a specific gene to be subject to regulation by more than one system, especially in bacteria that are adapted for growth in a series of radically different environments. It is also common for a single regulator to control expression of multiple genes. These more complex regulatory systems are explored in articles by Cynthia Whitchurch, Alastair McEwan and Michael Jennings.

Finally, two new fields of importance to the regulation of bacterial gene expression have emerged in recent years. The widespread nature of quorum sensing systems, and their dramatic effect on gene expression in a variety of bacterial species, has only recently become appreciated. These systems are explored in an article by Staffan Kjelleberg and colleagues. Likewise, the role of small RNA molecules in regulating gene expression is an area of intense investigation and is described in an article by Neville Firth.

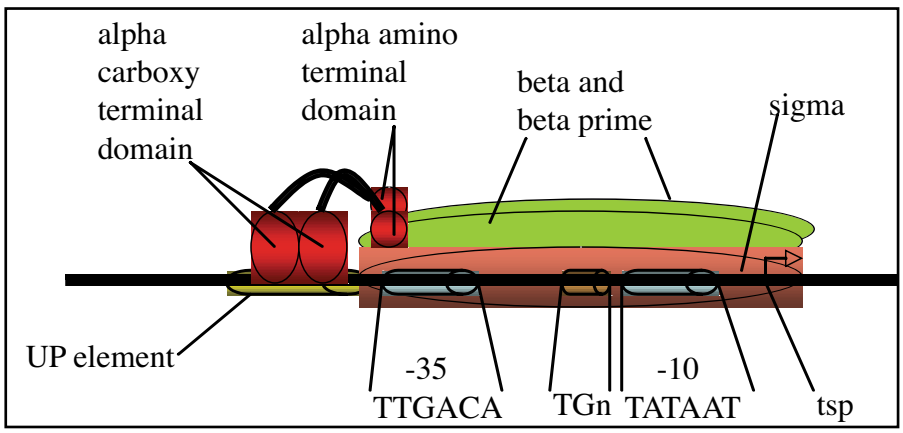


**Figure 1. Schematic diagram showing the interaction between RNA polymerase and the various sequence elements within a bacterial promoter. TSP represents the transcription start point.**

## References

1. Browning DF & Busby SJW. The regulation of bacterial transcription initiation. *Nat Rev Microbiol* 2004; 2:1-9.

**MICRO-FACT**

*About 500 different species of bacteria inhabit the human gut.*