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Bacterial Regulatory Networks

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Preface

Higher eukaryotic organisms, including humans, use vision, hearing, smell, touch or taste to promptly analyse the surrounding environment and react appropriately to avoid danger or take benefit of a favourable situation. In humans, perception of a danger or stress may result in adrenaline being released in the blood. Adrenaline contributes to increase speed and strength or to decrease pain sensitivity, thus making your body and brain ready to take quick decisions such as running away or fighting. Similarly, when you smell or see something that is likely to be good food, you will start to salivate and prepare your digestive organs to process the food that you will inevitably be tempted to swallow.

One may think that prokaryotic organisms do not have such sensory sophistication, but a closer look at their molecular equipment indicates that they have this capacity. In bacteria, the decision-making process is all about a quick change in gene expression. Such change starts with the synthesis of new determinants/molecules/proteins that will be more appropriate to cope with the newly encountered environment. This is combined with the arrest in synthesis of other molecules that became useless in the new context, since carrying on with their production will be nothing else than a waste of precious time and energy. For example, in an iron-limiting environment, and iron is an essential element of many key biological processes, bacteria will switch on the expression of genes that will allow synthesis and release of siderophores (Chapter 10). These molecules are scavengers that will actively hunt and trap iron wherever available in order to bring it back into the cells. This internalization procedure will also involve receptors and transporters, the expression of which is also induced upon perception of low iron levels in the environment. The production of all the components involved in active iron capture is not required in other conditions than iron limitation and therefore a tight control in expression of dozens of genes prevents unnecessary waste of energy.

Iron limitation is only one of many other examples that are described in this book. The multitude and complexity of control events happening in one bacterial cell over its lifetime are tied into a hugely sophisticated 'bacterial regulatory network', which within seconds drastically change the transcription profile in the cell. The control events may involve master regulatory elements that sit on top of a hierarchical cascade, and which control global responses by affecting expression of hundreds of genes. These are for example alternative sigma factors that come into play to influence selectivity of the RNA polymerase in response to general stress situation (Chapters 1–3). Another example is the global regulator H-NS, a DNA-binding protein that keeps hundreds of genes silent (Chapter 7). These factors may in turn control expression of other regulators whose role will be more specific and that will induce change in expression of very few or even only one gene. A notorious regulatory system involved in responding to very specific changes in the environment is the two-component system (Chapter 8). This system involves a sensor protein whose role is to identify precisely what the environmental conditions are and in many cases it will be responsible for monitoring the presence/absence of only one specific stimulus. It is also important to highlight that in many cases the bacterium would like to respond to environmental changes not only at a single cell level but would like to organize a coordinate change in the whole bacterial population. One such phenomenon has been known for years as quorum sensing (Chapter 4). This system is pinpointing to the fact that bacteria might not behave in a selfish manner but thanks to appropriate regulatory mechanisms and to the production of diffusible molecules have established their own communication/language skills. Quorum sensing has given a new vision of the microbiological world, and the Science behind this social behaviour was fancily quoted by Peter Greenberg (University of Washington) as 'sociomicrobiology'.

It is remarkable that in many cases some of the changes induce by bacterial regulatory network are hardly visible to the human eyes. However, in several cases these changes in bacterial behaviour are striking. One example is the series of regulatory events, in response to harsh nutritional stress, which leads to sporulation of bacteria such as *Bacillus subtilis*. Such drastically different state of the bacteria may cause the emergence of two distinct subpopulations, and has been linked to so-called bistable regulatory networks (Chapter 12). In other cases, bacteria may switch from a single cell and motility behaviour to a sessile lifestyle within a compact but organized and active bacterial population called biofilm. Sometimes, the morphotype of a bacterial colony primed to form a biofilm is clearly identifiable on agar plates. Such a colony may display a remarkable wrinkly aspect often associated with the production of an exopolysaccharide whose aim is to glue bacterial cells together. The switch between motile and sessile lifestyles is also the result of sophisticated regulatory networks, and in some cases these regulatory cascades result in the production of a simple secondary messenger, such as the c-di-GMP (Chapter 5), whose mechanism of action and impact on cell behaviour is yet far to be clearly understood. Finally, chemotactic networks sensing gradient of attractive nutrients or repelling toxic compounds guide mobility and directional movement of a single bacterium (Chapter 9). Observing bacteria swimming and tumbling is something that was earlier catch by the human eye looking through rudimentary microscopes and whose mechanism and control are now understood with exquisite molecular details.

The regulatory networks are not necessarily linear and could be seen as trees or microchips with integrated circuits involving multiple routes and ramifications. Signalling into one branch will spread into many other routes that in a way or another have a connection with the initial input. Moreover, the signalling does not necessarily go exclusively into one direction but involves feedback loops control for example once the initial stimulus or signal is gone. These multiconnections and ramifications very often encourage scientists to present highly sophisticated diagram in which stimuli, regulators and effectors are connected by a multitude of arrows that challenge our analytical capacity. It is also important to realize that regulatory controls may not only be exerted at transcriptional levels and the importance of small regulatory RNA in post-transcriptional control of gene expression is nowadays a very fashionable field of investigation (Chapter 6).

The book that has been assembled here is far to be comprehensive but is meant to cover a wide array of examples, which hopefully will reflect this complexity while providing a useful tool to gain better grasp in understanding bacterial regulatory networks, how they have evolved (Chapter 13) and how they could further be studied and understood. One should be aware that there is probably a gap in between how these regulatory networks work and are inter-connected under circumstances that have been created in our laboratories, and how they really behave when the bacteria are thriving in their natural environment or host. This is certainly a challenge for further research to understand adaptive behaviour of bacteria in their natural niches, which may be of fairly higher complexity than our test tubes, not only in terms of nutrient or oxygen availabilities (Chapter 11) but also in terms of promiscuity with a multitude of other organisms.

I would like to thank the authors that have contributed to the writing of this book. They are all leaders in their field and their commitment to this task has been greatly appreciated. I also would like to thank all the colleagues, whose names are listed here below, that have helped to review the chapters and provided insightful suggestions to

the authors. Finally, I wish the owner of this book an enjoyable time reading it and hope he/she will recommend it to many colleagues in the field be it a microbiologist or any curious neophyte eager to broaden his/her vision of a microscopic but rich and sophisticated world.

Alain Filloux (pictured)

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