SUMMARY

All living systems have to respond to changes in their environment — this capacity could even be phrased as a defining property of a living system. In order to respond to a change in the environment, the first step is to register that a change has occurred. We humans have developed five senses, seeing, hearing, feeling, smelling, tasting, that allow us to actively register the environment and note changes within it. Not only for humans is this capacity important, but also for more simple forms of life, including unicellular organisms like bacteria. And indeed, also unicellular organisms have developed “tools” that allow them to measure changes in their environment.

However, monitoring the environment by itself is not sufficient. Cells also actively have to process the information from the environment and, possibly, change their current behavior. If for example E. coli, initially surrounded by an excess of glucose, observes that the glucose concentration decreases in favor of lactose, in order to survive, it has to change its behavior. The bacterium for example could change its internal metabolic circuit from glucose-powered to lactose-powered by expressing different enzymes, or decide to move to different places with possible higher concentrations of glucose. In both scenarios, the change in the environment leads to an active response of the bacterium.

The connection between the change in the environment, the signal, and the response of the cell is facilitated by networks of interacting proteins, which jointly form a signaling cascade. Cells have many different signaling cascades, since there are many different signals and signals can lead to a variety of responses. Arguably, the most important property of a signaling cascade is the transfer of information from the signal to the response as reliably as possible. To study the reliability quantitatively I use information theory, since this provides us with an excellent measure, the mutual information between signal and response. Using information theory it can be shown that the reliability of the information transfer depends upon the ratio of two quantities, the amplification of the signal, or the gain, and the inherent noise of any biochemical cascade. In this thesis we will study these quantities, the gain and the noise, in more detail, especially in Chapters 2, 3, 4 and 6.

Increasing the reliability of a cascade in general requires more energy, for example for the production of more proteins or additional phosphorylations. Since energy resources are limited for every cell, a large reliability therefore should be obtained while keeping the cost low. One possible solution for cost reduction is the simultaneous use of a single protein for multiple functions or in multiple cascades, a process called multiplexing. In Chapters 5, 7 and 8 this idea is worked out in more detail.

Reliability of signaling cascades

In Chapters 2 and 3 I look at the reliability of signaling cascades for time-varying signals. Recent studies have shown that some small network structures are overrepresented within signaling cascades, so-called network motifs, and for these motifs I study the reliability. The reliability is quantified using the mutual information between signal and response. For time-varying continuous signals, the mutual information is replaced by the mutual information rate, which i) is frequency dependent, and ii) is directly proportional to the gain-to-noise ratio of the cascade, which now is frequency dependent as well. By studying both the gain (amplification) and the noise simultaneously, we observe that positive feedback or positive autoregulation increases the gain-to-noise ratio at small frequencies, showing
that slowly varying signals can be transmitted more reliably if positive regulation is present in the
cascade. Negative feedback enhances the reliability of signaling at high frequencies, but only if the
feedback is within the cascade, upstream of the final response. Then negative feedback can even lead
to a peak in the gain-to-noise ratio as a function of the signal frequency.

For cascades with feed-forward properties (either coherent, incoherent or diamond) I observe
that the gain-to-noise ratio is enhanced if the signal is split in two separate intermediate proteins,
which then later recombine at the response. However, to observe this, coincidence detection at the
response is required, meaning that for activation of the response both intermediates should be present
simultaneously. This form of activation can be obtained both through homo- or heterodimerization
of the intermediate proteins. Next, in this chapter, we observe that for a feed-forward motif the gain-
to-noise function can have high-pass or low-pass characteristics as a function of frequency which,
surprisingly, does not depend on the type of feed-forward motif, either coherent or incoherent. By
actively changing the different coupling strengths between the two pathways in a feed-forward motif,
the gain-to-noise ratio can be switched from a low-pass to a high-pass filter and vice-versa.

Diffusion noise

Many signaling cascades have as their natural starting point a receptor, although this is not always
ture. These receptors sense a specific ligand concentration which diffuses in the medium surrounding
the receptor and stochastically binds and unbinds to the receptor. Over 35 years ago, an interesting
study by Berg and Purcell has provided an answer to the question what the minimal limit in the uncer-
tainty is of a concentration measurement if such a single receptor would measure the concentration
over some time interval. This limit has been disputed in later papers, creating an open question. In
Chapter 4, using a different analytical derivation and computer simulations, we confirm the findings
of Berg and Purcell of 35 years ago, establishing, again, the fundamental limit on noise in a concentra-
tion measurement. The limit consists of two terms, one originating from the stochastic dynamics of the re-
cipient and one from the diffusive behavior of the ligand particles. Importantly, the fundamental limit
depends on the fractional occupancy of the receptor. This reflects the fact that a receptor that is bound,
can not measure "new" ligand molecules, thereby increasing the uncertainty in the measurement of
the outside concentration. Moreover, in this chapter we present a simple model which provides the
correct correlation time, and therefore the correct measurement uncertainty, and the parameter range
for which the simple model is accurate.

Signal integration

Focussing on the receptors in Chapter 5 I study signal integration by receptors. Recent experiments
have shown that receptors, or in general proteins, can act as logic gates, meaning that the response
depends on the combined information of two signals. We wondered how versatile this mechanism is.
Using a simple statistical mechanics model we show that indeed receptors are capable of performing
any gate by tuning kinetic parameters. On evolutionary timescales, this would be a mechanism for
cells to obtain receptors which function as any specific logic gate. As interesting, we show that on
much shorter timescales, that of protein signaling, all logic gates can be formed from a limited set of
receptor monomers that dimerize.
Oscillatory signals

It is increasingly recognized that cells often use oscillatory signals to transmit information. Intuitively, one would expect an oscillatory signal to increase the variability in the output compared to a constant signal. Since this increase in variability makes the signaling cascades less reliable, the use of oscillatory signals seems, from this point of view, disadvantageous. However, in Chapter 6 we show that, counter-intuitively, oscillatory signals not necessarily lead to lower variability in the output of a gene regulatory network. This effect relies on the fact that a switch driven by an oscillatory signal, becomes more periodic, than when driven by a constant signal. The oscillatory input signal then leads to a more constant output level than the constant input signal.

Multiplexing

Multiplexing, the art of transmitting multiple different signals simultaneously through a shared pathway, is the topic of the final two chapters of this thesis. In Chapter 7 the problem of multiplexing constant signals is studied. Here we show that two signals can indeed be encoded into a shared cascade and decoded into two responses, where each response is sensitive to a single signal only, with absolute reliability. Since the input signals are constant in time, we refer to this type of multiplexing as AM multiplexing.

In Chapter 8 we extend the problem as posed in Chapter 7, by asking the question if oscillatory signals and constant signals jointly can be multiplexed. Here one response is sensitive to the properties of the oscillatory signal (like the oscillation period and the amplitude, but not the mean level), while the other response is sensitive to the concentration of the constant signal. We show that indeed networks can be constructed that multiplex these signals, and as expected, we find that, next to the intrinsic biochemical noise, also the cross-talk between the two signals acts as a bottleneck for information. However, the total amount of information through the network can be increased enormously with respect to the AM multiplexing strategy.