Response dynamics of perfect adaptation in cells

Author: Anggie Rizo Zambrano
Facultat de Física, Universitat de Barcelona, Diagonal 645, 08028 Barcelona, Spain.

Advisor: Marta Ibañes Miguez

Abstract: Cells are capable of responding to external stimuli manifesting different dynamical behaviors. An interesting case is the perfect adaptation response, which means that when the amount of stimulus is changed abruptly and permanently, the response is only transient and returns to its previous levels of activity. The aim of this work is to analyse three different models, two of them previously reported, and study if they show perfect adaptation and in what conditions. Using numerical methods and through mathematical analysis, we reproduce known results and characterize new scenarios.

I. INTRODUCTION

Response mechanisms of cells are an open problem due to the complexity of the interactions of proteins within signaling pathways. However, recent studies have been successful in coming up with mathematical models that gets us closer to solutions that can be contrasted experimentally. We have to take into account that we have to solve a 4D problem with the intervention of the spatial and temporal coordinates but here we will only focus on the temporal dynamics because this is what has been studied most, although new experimental techniques allows the exploration of the complete problem [1].

In this work we study perfect adaptation in three different models. Perfect adaptation is interesting because we can find it in human senses, i.e smell, this is why perfect adaptation is also known as *"sniffer"* [2]. Mathematically, perfect adaptation requires the steady state of the response element to be independent of the stimulus and for a change in stimulus to cause a change in response: these will be the main conditions that we will demand our systems to fulfill. We will do that by describing the dynamics of the models through the law of mass action.

The structure of this work is as follows. In the first model we study a system that will not be able to exhibit perfect adaptation. In the second one we add a new variable, *"x"*, that regulates the response levels when a change in stimulus is applied, therefore exhibiting perfect adaptation. The model obtained has been presented in [2]. At last, we adapt the work made in [3]. We simplify the model in [3] by making some assumptions that will be commented further on in the text. This model is based on TGF-β pathway that contains receptors and ligands. These ligands are present in the extracellular space but they can bind a receptor and form a ligand-receptor complex. Then, they ultimately drive a transcriptional response in the cell nucleus. As there are many types of ligands and receptors, this gives a variety of possible combinations that can trigger different cell processes such as, cell proliferation, cell growth, cell differentiation etc. [3]. The study of biological processes that are possible is beyond the aim of this work and our only focus is on the dynamics of the ligand-receptor complex that leads to a perfectly-adapted response.

II. SINGLE VARIABLE MODEL

We start with a simple case, purely theoretical, that does not correspond to a known biologic element. Our system receives a stimulus concentration, $[S]$, and the velocity of the change in concentration of the response element, $[R]$, is given by the next rate equation:

$$\frac{d[R]}{dt} = k_1[S] - k_2[S][R] \tag{1}$$

where k_1 and k_2 correspond to rate constants. The stimulus is creating a response at the same time that it destroys it. An stationary state solution is easily obtainable by equating Eq. (1) to 0 which results in

$$[R_{ss}] \equiv R_{ss} = \frac{k_1}{k_2} \tag{2}$$

From Fig. 1 we can see that perfect adaptation is not achieved, although the steady state is independent of the signal input. A mathematical demonstration as to why this model is not perfectly adapted is herein proposed. Consider the system in the stationary state with stimulus concentration $[S]$ and an instantaneous change in the stimulus $[\Delta S]$ that causes a change $[\Delta R]$ in the response $[R]$. Introducing these terms in Eq. (1), and by eliminating some equal terms of the stationary initial state, we obtain:

$$\frac{d[\Delta R]}{dt} = (k_1 - k_2[R_{ss}])[\Delta S] - k_2\left([S] + [\Delta S]\right)[\Delta R] \tag{3}$$

The first term cancels by substituting Eq. (2) in Eq. (3) and finally:

$$\frac{d[\Delta R]}{dt} = -k_2\left([S] + [\Delta S]\right)[\Delta R] \tag{4}$$

This model cannot exhibit perfect adaptation because even if we have found a steady state independent of the stimulus, there is nothing that produces $[\Delta R]$ (Eq. (4)).

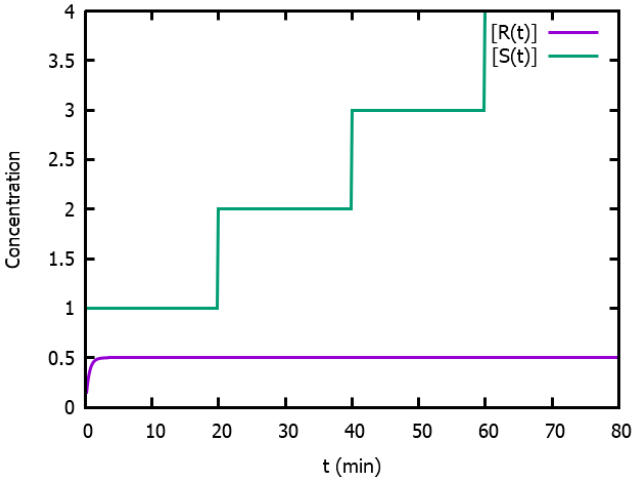

FIG. 1: Evolution of the response ($[R]$, violet) when the concentration of stimulus ($[S]$, green) changes abruptly every 20 minutes. Results from the single variable model. Parameter values are $k_1 = 1\,\mathrm{min}^{-1}$ and $k_2 = 2\,\mathrm{min}^{-1}$. Adimensional concentrations are used.

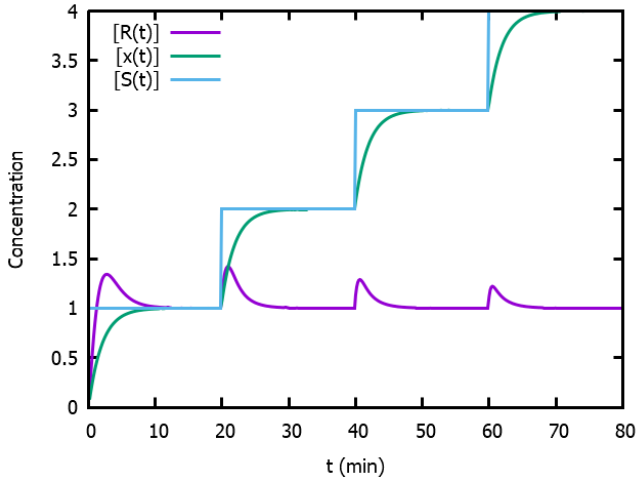

FIG. 2: Evolution of the response ($[R]$, violet) and species x ($[x]$, green) when the concentration of the stimulus ($[S]$, blue) increases an amount $[\Delta S] = 1$ every 20 minutes. Results from the sniffer model. Parameter values: $k_1 = 1\,\mathrm{min}^{-1}$, $k_2 = 1\,\mathrm{min}^{-1}$, $k_3 = 0.5\,\mathrm{min}^{-1}$, $k_4 = 0.5\,\mathrm{min}^{-1}$.

III. SNIFFER MODEL

An extension of the first model is analysed here by adding a new species, x, which evolves according to a new equation. The model used here has been presented in [2]. We assume that $[R]$ and $[x]$ are being synthesized and degraded [2, 4]:

$$\frac{d[R]}{dt} = k_1[S] - k_2[x][R] \tag{5}$$

$$\frac{d[x]}{dt} = k_3[S] - k_4[x] \tag{6}$$

Once again, the steady state solution is independent of $[S]$, as seen by equating Eq. (5) and Eq. (6) to 0:

$$[R_{ss}] \equiv R_{ss} = \frac{k_1 k_4}{k_2 k_3} \tag{7}$$

Fig. 2 shows that an abrupt increase of the stimulus causes an abrupt increase in the response that decays in time to previous levels: it exhibits perfect adaptation. Every time the stimulus increases, there is a transient and weaker response (Fig. 2).

Valuable information of the model dynamics is obtained by plotting the phase space $([R], [x])$.

The phase portrait is understood in the following way: each nullcline represents Eq. (5) or Eq. (6) equal to 0, its intersection describes the stationary solution [5]. The vector field is simply the time derivative for each variable. With these notions, it is easy to see that a change in stimulus concentration will cause a trajectory

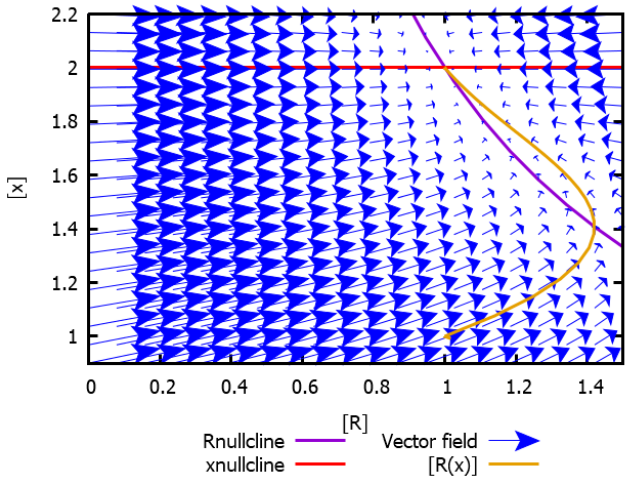

FIG. 3: Phase portrait for the sniffer model. Arrows correspond to the vector field when $[S] = 2$. Nullclines of each variable and trajectory for $[S] = 2$ (from the stationary state of $[S] = 1$) are also shown. Parameters are those of Fig. 2.

to the stationary point. This is another way of describing perfect adaptation.

To explain why this model becomes perfectly-adapted, we make a similar approach as the one made in the single variable model, and additionally consider changes in $[x]$ to be slow, so in small time scales $[x] \approx [x_{ss}]$ and only a change in $[R]$, $[\Delta R]$, is noticeable, yielding:

$$\frac{d[\Delta R]}{dt} = k_1[\Delta S] - k_2[x_{ss}][\Delta R] \tag{8}$$

By replacing the value of $[x_{ss}]$ (Eq. (6) equal to 0) in Eq. (8), we obtain:

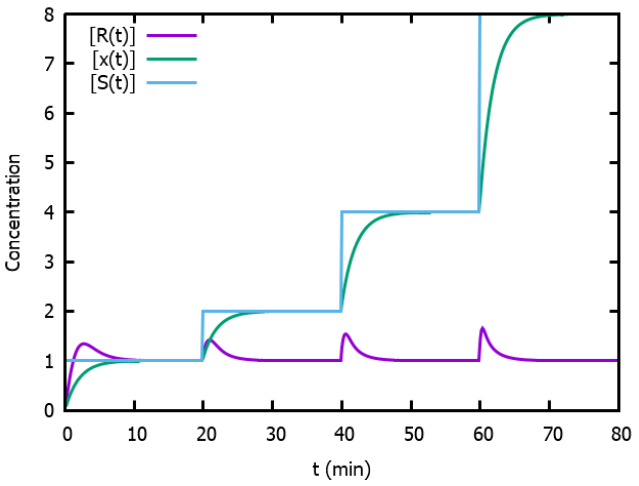

FIG. 4: Evolution of the response ($[R]$, violet), species x ($[x]$, green) when the concentration of the stimulus ($[S]$, blue) changes a constant relative amount $[\Delta S]/[S] = 2$ every 20 minutes. Results from the sniffer model. Parameter values: $k_1 = 1\,\mathrm{min}^{-1}$, $k_2 = 1\,\mathrm{min}^{-1}$, $k_3 = 0.5\,\mathrm{min}^{-1}$, $k_4 = 0.5\,\mathrm{min}^{-1}$. The amplitude of response is nearly constant, in contrast with Fig. 3.

$$\frac{d[\Delta R]}{dt} = k_1[\Delta S] - \frac{k_2 k_3}{k_4}[S][\Delta R] \tag{9}$$

Therefore, we can see that in the sniffer model, both conditions for perfect adaptation are satisfied. The steady state response is independent of the signal (Eq. (7)), and there is a change of response when a stimulus change is applied. Moreover, if we consider the response element to be sufficiently fast ($d[R]/dt \approx 0$, that means Eq. (8) equal to 0), the result is $[\Delta R] = \frac{k_1 k_4}{k_2 k_3}\frac{[\Delta S]}{[S]}$. Thus, the amplitude in response depends on $[\Delta S]/[S]$. We have checked through simulations that this prediction holds (see Fig. 4).

IV. TWO-COMPARTMENT MODEL

At last, we explore the signaling mechanism for the TGF-β pathway. The model proposed in [3] is simplified, such that we consider only one type of receptor (whether it is type I or II will be irrelevant for the final results), while all the other considerations are mantained, i.e receptor-ligand complexes can traffick between the plasma membrane and the endosomes: receptors and ligand-receptor complexes are internalized into the endosome and recycled to the plasma membrane continuously; receptor degradation has a constitutive and ligand-induced contribution and internalized ligand-receptor complexes concentration determine the concentration of the response [3]:

$$\frac{d[ST]}{dt} = k_a[S][T] - (k_{cd} + k_{lid} + k_i)[ST] \tag{10}$$

$$\frac{d[T]}{dt} = P_T - k_a[S][T] - (k_{cd}+k_i)[T] + k_r[\bar{T}] + \alpha k_r[R] \tag{11}$$

$$\frac{d[R]}{dt} = k_i[ST] - k_r[R] \tag{12}$$

$$\frac{d[\bar{T}]}{dt} = k_i[T] - k_r[\bar{T}] \tag{13}$$

$[S]$ corresponds to the ligand (i.e stimulus) concentration, $[T]$ is the TGF-β receptor and it can bind to form the ligand-receptor complex $[ST]$. The variables $[\bar{T}]$ and $[\bar{ST}]$ are the receptor and ligand-receptor complex once they are internalized. k_a characterizes the ligand-receptor complex formation, k_{cd} is the rate of constitutive degradation, k_{lid} is the ligand-induced degradation rate constant, k_i is the internalization rate constant, P_T is the rate of receptor production. Both sound (active) and unsound receptors are recycled with rate k_r, however, only the active ones do so with an efficiency $\alpha \leq 1$. The model is dominated by the competition between two rate constants: k_{cd} and k_{lid} which are combined in the CIR ratio $\left(CIR = \frac{k_{cd}}{k_{lid}}\right)$ [3]. The constitutive degradation constant, k_{cd}, affects receptors and ligand-receptor complexes that have not been internalized, therefore it will eliminate them. The ligand-induced degradation constant, k_{lid}, affects the active receptors (i.e those that are bound to a ligand), also eliminating them.

Fig. 5 shows perfect adaptation. We are in the limit of low CIR ($k_{lid} \gg k_{cd}$) [3]: ligand-receptor complexes are degraded continuously, causing the attenuation of the activity and the return to previous activity levels.

The opposite case is when the CIR ratio is high ($k_{cd} \gg k_{lid}$) [3], we expect the transient response to disappear (Fig. 6) because although the constitutive degradation induces the elimination of receptors and plasma membrane ligand-receptors, this does not affect the internalized complexes, which are already producing activity.

It is interesting to change other parameter values, from which we have obtained the following cases.

If the recycling mechanism from the active receptors is suppressed (i.e $\alpha = 0$), active receptors that have bound and are internalized cannot return to the plasma membrane and repeat the binding and trafficking processes, but because they are strongly degraded (low CIR limit) we would expect the same result as in Fig. 5 (see Fig. 7).

Fig. 8 shows that the response is capable of exhibiting perfect adaptation within the high CIR limit [3]. This happens when not all receptors bound to the ligand (stimulus) are recycled back (i.e $\alpha < 1$).

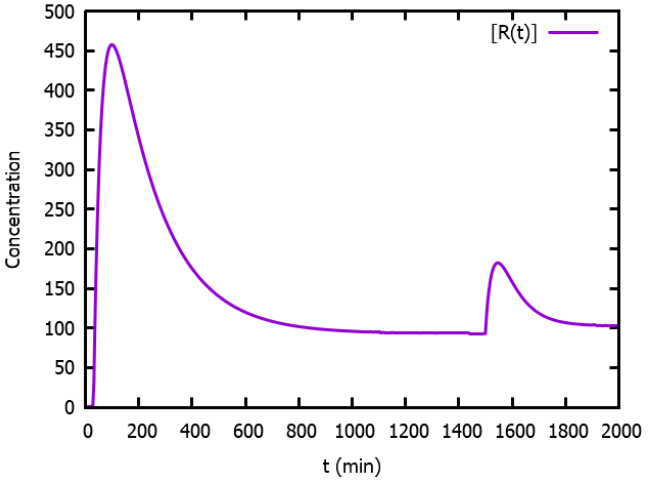

FIG. 5: Response concentration, $[R]$, as a function of time for low CIR. Results from the two-compartment model. Parameter values: $k_a = 10\,\mathrm{min}^{-1}$, $k_{cd} = \frac{1}{36\times3}\,\mathrm{min}^{-1}$, $k_{lid} = 3/4\,\mathrm{min}^{-1}$, $k_i = 1/3\,\mathrm{min}^{-1}$, $P_R = 8\,\mathrm{min}^{-1}$, $\alpha = 1$, $k_r = 1/30\,\mathrm{min}^{-1}$, $[S] = 3\times10^{-5}$. A change in signal concentration, $[S] = 0.01$, is applied at $t = 30\,\mathrm{min}$ and $[S] = 0.05$ at $t = 1500\,\mathrm{min}$.

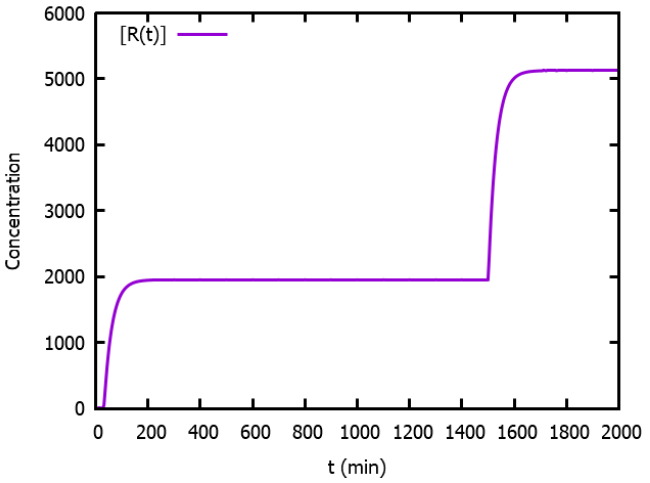

FIG. 6: Response concentration, $[R]$, as a function of time for high CIR. Results from the two-compartment model. Parameter values: same as in Fig. 5 with the same stimulus changes but $k_{lid} = 0\,\mathrm{min}^{-1}$.

In Fig. 9, by eliminating the terms associated with the recycling mechanism but working within the low CIR limit, we obtain a transient response and adaptation. Nevertheless, the activity is very low due to the ligand-receptor complexes not being able to return to the plasma membrane. Receptors will run low in the plasma membrane and ligands will not be able to bind them and internalize, so the perturbations of the system will decrease in time until they will not be detected anymore.

Ultimately, we find the stationary state of the two-compartment model by equating to 0 all the equations of

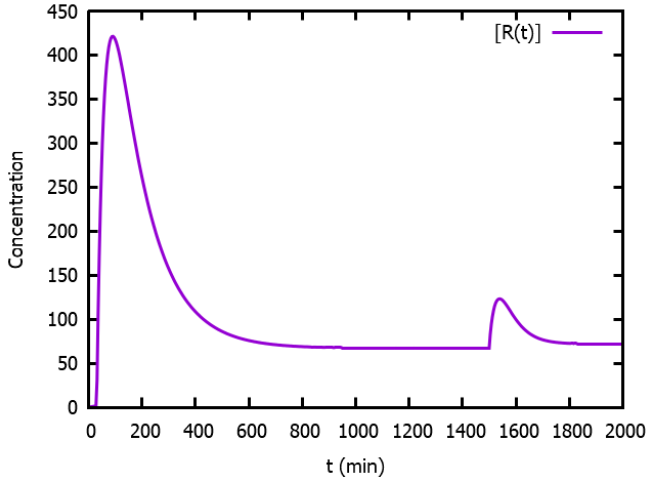

FIG. 7: Response concentration, $[R]$, as a function of time for low CIR. Results from the two-compartment model. Parameter values: same as in Fig. 5 with the same stimulus changes but with $\alpha = 0$.

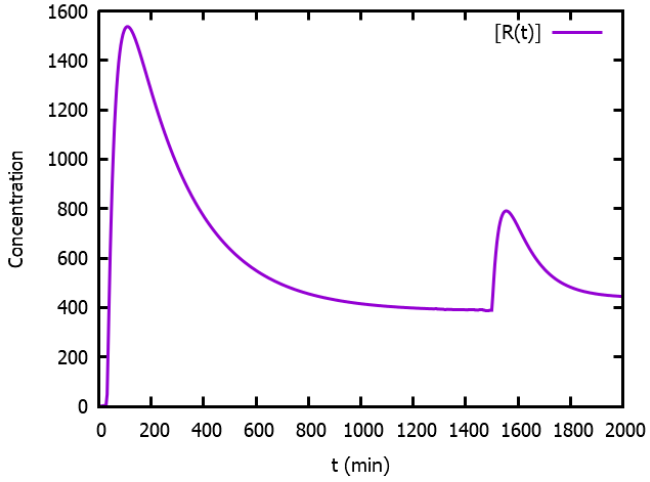

FIG. 8: Response concentration, $[R]$, as a function of time. Results from the two-compartment model. Parameter values: same as in Fig. 5 with the same stimulus changes but with $k_{lid} = 0\,\mathrm{min}^{-1}$, $\alpha = 0.5$. (i.e as in Fig. 6 but with $\alpha = 0.5$).

the model [3]:

$$[R_{ss}] = \frac{k_i}{k_r}\frac{P_R}{k_{cd}+k_{lid}+(1-\alpha)\,k_i k_a}\frac{c[S]}{1+c[S]} \tag{14}$$

where the variable $c[S]$ carries all the dependence on the stimulus and will dictate the system's behavior. It takes the following form

$$c[S] = \frac{k_{cd}+k_{lid}\,(1-\alpha)}{k_{cd}+k_{lid}+k_i}\frac{k_i k_a}{k_{cd}}[S] \tag{15}$$

From Eq. (15), we can see that the only way to have a stationary state independent of the stimulus, is for high

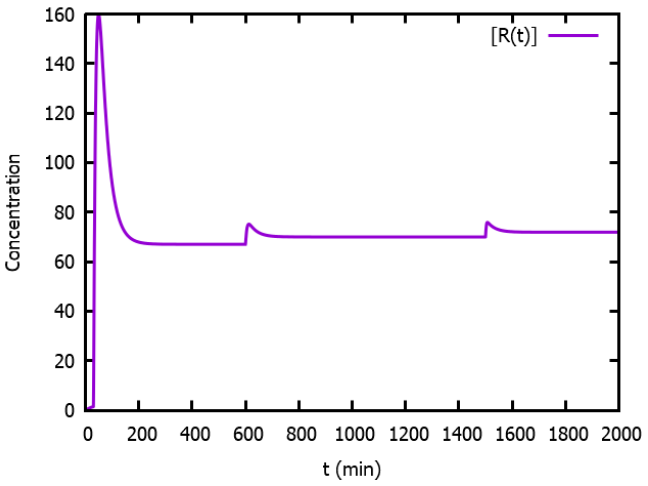

FIG. 9: Response concentration, $[R]$, as a function of time. Results from the two-compartment model when the recycling mechanism is totally suppressed. Parameter values: same as in Fig. 5, but with a stimulus change of $[S] = 0.01$ at $t = 30$ min, another one of $[S] = 0.02$ at $t = 60$ min and a last one of $[S] = 0.05$ at $t = 1500$ min.

values of $c[S]$. This happens for low values of k_{cd} and therefore, within the low CIR limit. Also, to produce a change in $[R_{ss}]$ when a stimulus change ($[\Delta S]$) is applied, we must assume that $[ST]$ is a fastly changing variable and that $T + [ST]$ changes slowly [3]. After some algebra we arrive to [3]:

$$\frac{d[\Delta ST]}{dt} = k_a[\Delta S]T_{ss} - (k_a[S] + k_{cd} + k_{lid} + k_i)[\Delta ST] \tag{16}$$

Taking into account the previous assumptions, we conclude that the system is able to respond to a stimulus change in the steady state, satisfying both requirements for perfect adaptation.

V. CONCLUSIONS

Firstly, we have been able to reproduce some of the work done in [2] and [3] (with a simplified model) and we have extended them to wider scenarios.

- For the single variable model, we have been able to conclude that even though it accomplishes the requirement of having a steady state independent of the stimulus, it cannot show perfect adaptation because there is not a mechanism to lead it there.

- In the sniffer model, Fig. 2 reproduces the results made in [2]. Perfect adaptation is reached because the steady state response is independent of the stimulus and the system is able to answer to a change in stimulus. In addition, we have found that the amplitude of the change in response is dependent on the relative change in stimulus.

- For the two compartment model, we have verified the results in [3], although in a much simpler way. Perfect adaptation is reached when we are working within the LOW CIR limit ($k_{lid} \gg k_{cd}$) or within the HIGH CIR limit ($k_{cd} \gg k_{lid}$) but reducing the effectiveness of recycling [3]. We also extend the study to a system with no recycling mechanism and the model exhibits adaptation. We see how the ability to recycle receptors for rebinding is an important feature for the TGF-β pathway to exhibit perfect adaptation.

Acknowledgments

I want to thank my advisor Marta Ibañes, for taking her time to help me in everything and for solving my doubts. I have cherished my time working and learning from her. To my mum and her family, from whom I have received nothing but support and to my friends, Cristian and Karolina, for giving me the best years of my life.

[1] Kholodenko, B., Hancock, J., Kolch, W. Signalling ballet in space and time. *Nature Reviews Molecular Cell Biology*, vol 11., pp 414-426, 2010.
[2] Tyson, J. J., Chen, K. C., Novak, B. Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. *Current Opinion in Cell Biology*, vol 15., pp. 221-231, 2003.
[3] Vilar, Jose M. G., Jansen, R., Sander, C. Signal Processing in the TFG-β Superfamily Ligand-Receptor Network. *PLOS Computational Biology*, vol 2., p e3., 2006.
[4] Ferrell, James E. Perfect and Near-Perfect Adaptation in Cell Signaling. *Cell systems*, vol 2., pp. 62-67, 2016.
[5] Strogatz, Steven H. Non-linear Dynamics and Chaos with Applications to Physics, Biology, Chemistry and Engineering. *Addison-Wesley*, 1995.