IBMS1 Tutorial 2.7.2

FDG: Negative feedback and rhythms in the HPA axis

Wed 12.4.2017 13:00/14:00

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Aim

The aim of this tutorial is to explore the concepts of negative feedback and how it can affect pulsatile hormone release. Although we will use the stress (hypothalamic-pituitary-adrenal, or HPA) axis as an example in this tutorial, the same principles can be applied to the other hypothalamic-pituitary axes.

Learning outcomes

1. To describe the temporal relationships between the various hormones of the HPA axis

2. To describe how pulses of hormone release are generated by these interactions (especially negative feedback).

3. To outline how an acute stress can change the temporal relationship between different stress hormones.

Before the class

No specific preparation is required for this class, although thinking back of what we have discussed in lecture 2.7.2 about pulsatility and about feedback will be helpful.

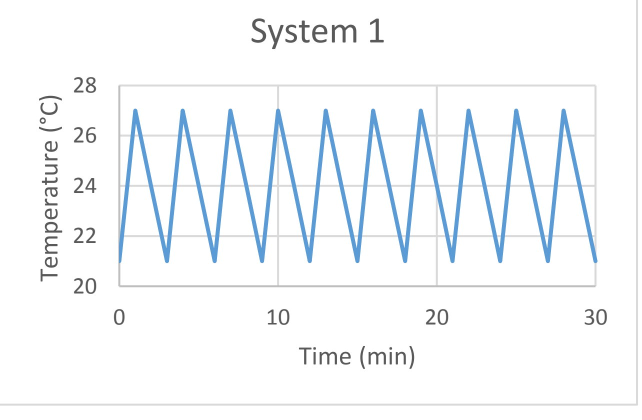
In the class

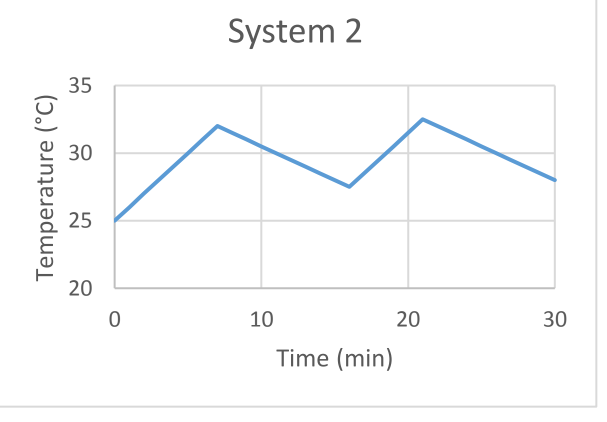
1. We will use house heating system as an example of negative feedback. It may sound strange, but the basic principles that allow a heater to correctly heat your house are the same as those regulating hormone release!

You will be divided in two group, and each group will be given a different set of "rules" through which the system works. You will have to work together to produce a (rough) graph of how the temperature in the house will change over time. It should take about 10 minutes to prepare the graph, and 5 minutes to discuss it.

Each group will then describe their results to the other group, and we will discuss and try to understand the differences between them.

Below you will find the graphs for the two systems





Both systems oscillate around their set-point.

System 1 should allow only a small temperature excursion of 2°C, from 24 to 26 °C, however, because the heating/cooling process is so fast, it generates larger oscillations. After the first cycle, it oscillates between 21 and 27 °C, which is much larger than what is requested.

System 2 is less tightly regulated, and should allow an excursion on 4°C, between 28 and 32°C. However, it heats and cools slower so the oscillations are slower and it stays in range. When at regime, it oscillates between 27.5 and 32.5, which is very similar to what requested.

System 1 takes approx. 3 min per oscillation, while system 2 takes approx. 15 min.

Which does the job better? Number 2. Although slower and less precise, it gives temperature in the desired range, while number 1 strongly deviates from that.

Faster heating/cooling rates produce faster oscillations but they are not as easy to control. If the heater sampled the temperature more frequently it could correct the problem

2. We will then use a computer model of the HPA axis to show how changing equivalent parameter in the biological system will produce similar results. This is a bit more complex because we will consider two outputs: the amount of ACTH and the amount of cortisol produced.

Do not worry about the exact functions of these hormones at this stage, we are interested in **basic principles** in this tutorial. Lecture 2.7.3 will outline the functions of ACTH and cortisol in more detail.

You will be able to change some of the parameters in the system and see the response.

Some points you may want to consider:

- What is the temporal relationship between the two hormones?

ACHT and CORT oscillate in a parallel manner, with some delay between the two

- What aspect of pulsatility is modified when the amount of CRH in the system increases too much? What if it is too low? (try decreasing it to 5 or increasing to 80)

Low CRH will not be enough to drive pulsatility. After a first brief response, the system will stay at a steady low level of hormone.

High CRH will generate a very big ACTH pulse; this will be followed by a strong CORT pulse, which eventually will shut down the system. Some small pulsatile behaviour is seen here

What happens if the adrenal gland takes too long to respond to ACTH? What if it is too fast? (after resetting CRH to 20, set the adrenal delay to 0.5 min, 20 min or 60 min)

Delay 0.5 min -> the adrenal gland responds too quickly, so the system recovers immediately and we get no pulsatility

Delay 20 min -> normal pulsatility (note that 10-20 min is what is experimentally measured in rats)

Delay 60 min ->still pulsatile, but the adrenal takes more to “catch up”. Pulses go from 1 per h to 1 every 2.5h

3. Finally, we will see what happens if we impose a stressor.

The model assumes a constant level of CRH input, we will simulate an acute stressor by giving a large CRH stimulus for a short time.

a) Let's start by giving a 30 min "stressor" at time 2.8h, when CORT is rising. What happens?

b) Now let's give a stressor of the same length at time 1.6h, when CORT is falling. What happens now? What is the difference?

c) What happens if you give a very long stressor (for example at 2h give a 600 min stressor, and increase simulation length to 10h to see long-term effects)?

Some points you may want to consider:

- The strength of the response to stress depends on the phase of CORT (that means if it's in the rising or the falling part of the pulse). Can you think of a biological reason for that?
- What real-life situation is c) similar to?

TIP: when imposing a stressor, the model shows the "unstressed" output of CORT as a grey line. Use that to compare the "stressed" and "unstressed" profiles.

In a) we see a large increase in ACTH (up to about 12 AU), followed by a peak in CORT (about 7 AU), then the pulsatility is back to normal. (AU = arbitrary units, the model does not use real-world concentrations in this case, because we are just interested in **relative changes rather than absolute values**)

In b) we see similar dynamics as before, but this time the amplitude of the peaks is lower (about 7 for ACTH, 3.5 for CORT)

Although the biological reason for this behaviour is not known, there are a few important considerations to be made:

1. Pulsatility and rhythmicity of CORT and ACTH are changed in many pathologies such as depression or arthritis. This may result in modified responses to stress. If you are interested you can look at this review "The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration", Lightman and Conway-Campbell, Nature Reviews Neuroscience 2010

2. CORT levels vary not only hourly; they also have a daily rhythm (so-called circadian rhythm). Just as we saw on a short time scale here, the responses of the axis vary during the day.

3. There is a recent study that shows that having pulsatility associated with a variable response is less energetically demanding on the system than it would be having a constant level of CORT, which would be associated with less variability in acute stress responses. In this case the organism favours saving energy rather than increasing accuracy.

4. Finally, this example shows how dynamic interactions between different molecules can generate complex responses.

Situation c) resembles "chronic stress" (although in a simplified manner). In this case pulsatility disappears, and the set-point of the system is increased. An increase in the set-point of the axis is seen in people with chronic stress.

NOTE: the model is also available online at the following address:

https://nicolaromano.shinyapps.io/hpamodel/

Task 1 – Group 1

Rules for house heating system #1

1. Start temperature = **21°C**
2. Set-point = **25°C**
3. If the temperature goes **>1°C** below the set-point the heater will start
4. The heater increases temperature of **6°C** per minute
5. If the temperature goes **>1°C** above the set-point the heater will stop
6. When the heater is off, the temperature goes down **3°C** per minute

Draw a graph with time on the x-axis and temperature on the y-axis.

Calculate the temperature at 1 minute intervals, from 0 to 30 minutes

Example of how to proceed:

We start at 0 min, with a temperature of 21°C

We are >1°C below the set-point, so the heater starts, and in a minute it will heat 6°C

At 1 min the temperature will then be 27°C

We are now >1°C above the set-point…

Task 1 – Group 2

Rules for house heating system #2

1. Start temperature = **25°C**
2. Set-point = **30°C**
3. If the temperature goes >**2°C** below the set-point the heater will start
4. The heater increases temperature of **1°C** per minute
5. If the temperature goes >**2°C** above the set-point the heater will stop
6. When the heater is off, the temperature goes down **0.5°C** per minute

Draw a graph with time on the x-axis and temperature on the y-axis.

Calculate the temperature at 1 minute intervals, from 0 to 30 minutes

Example of how to proceed:

We start at 0 min, with a temperature of 25°C

We are >2°C below the set-point, so the heater starts, and in a minute it will heat 1°C

At 1 min the temperature will then be 26°C

We are still below the set-point, so we will continue to heat

At 2 min the temperature will be …