

Systems medicine Lecture notes

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Lecture 4

Two-gland feedback in the stress-hormone axis generates seasonal clocks and explains clinical phenomena with a timescale of months

Introduction

So far, we discussed a single endocrine gland controlling its own size, with beta-cells as our main example. We now explore what happens when *two* glands control each other's sizes. We will see that this creates a feedback loop with a timescale of months, which can produce damped oscillations. We will explore such feedback in the HPA axis, a stress-response pathway whose output is the hormone **cortisol**. The HPA pathway is clinically important: it is involved in problems of chronic stress like high blood pressure, and in mood disorders such as major depression and bipolar disorder. It is commonly employed in medicine to suppress the immune system using cortisol-analogous called **glucocorticoids**, often simply called **steroids**.

We will see how the two-gland feedback loop

- Creates seasonal hormone oscillations that provide a proper hormonal set-point for each season.
- Explains clinical phenomena with month's timescale, such as the side-effects of steroid treatment.
- Finally, we will explore a possible origin of mood fluctuations that last months in bipolar disorder.

The HPA axis controls responses to physical and psychological stress

When we wake up we get a surge of energy (for some of us, including the author, this takes a bit of time), thanks to a morning surge in the blood concentration of the hormone **cortisol**. We get a similar surge of cortisol if we suddenly see a threat, such as a large bear coming at us. The surge focuses the mind and gets us ready to run or fight. We get a cortisol surge even if we *predict* that a threat is coming, such as a serious psychological stress. The hormone cortisol takes minutes to act, and a surge lasts for about 90 min. Additional stress responses within seconds occur through the sympathetic nervous system and secretion of adrenalin that makes our hearts beat fast and the liver secrete glucose (which we won't discuss). Without cortisol and adrenaline, we wouldn't have the energy to stand up.

The hormone system that controls cortisol is composed of a series of three glands, which we will denote H, P and A, It is thus called **the HPA axis** (Fig 4.1). H stands for the hypothalamus, a brain region between our ears that receives neural inputs from many other brain regions, and converts

this information to hormones that act on the rest of the body. H is activated by various emergencies and stresses, including low glucose, low blood pressure, inflammation, and psychological stresses. It is activated by alcohol and other addictive substances, which will play a role in the next chapter on addiction. It is also regulated by the brain's circadian clock which keeps track of the time of day.

All of these inputs are processed in H, and combined¹ into the output of H: an increase the rate of secretion of the hormone CRH, which we will call x_1 . This hormone is secreted into a private blood vessel, called the portal system, which flows into the next gland P, a pea-sized gland called the pituitary, which lies at the bottom of the skull.

In P, the hormone x_1 stimulates cells to secrete the hormone x_2 (ACTH) into the blood stream. Together with x_2 , P also secretes beta-endorphin, which is a pain-killer and causes euphoria (similar to morphine).

The messenger hormone x_2 flows with the blood and reaches the third gland of the axis, A, the adrenal cortex. The word 'cortex' refers to the outer layer of the adrenal gland that lies on top of the kidneys². The cells in A secrete the final hormone, cortisol, denoted x_3 . Cortisol closes a negative feedback loop by inhibiting the rate of production and secretion of its two upstream hormones, x_1 and x_2 (Fig 4.1).

Cortisol is a small fat-like hormone (steroid hormone). Because it is fatty, it can penetrate the membranes of all of the cells in the body. It is sensed by special receptors inside the cells. When these receptors bind cortisol, they go into the cell nucleus, bind the DNA at specific sites, and cause the expression of genes that respond to the stress. Cortisol has many effects, including increasing the production of glucose, increasing blood pressure and suppressing inflammation. It also has effects on attention and memory. It thus gets the body ready to respond to the stress, and to prepare for more stress.

Sudden stresses cause an **acute** response, in which cortisol levels rise from their normal range of 100-300 nM to close to 1000nM. These pulses last about 90 min, the half-life of cortisol. If the stress lasts for weeks or more, as in psychological worries, cortisol causes the symptoms of **chronic stress**: weight gain, high blood pressure, risk of heart problems and diabetes, bone loss and depression. Chronic high cortisol also causes cognitive changes, including increased sensitivity to negative stimuli and heightened anxiety, as well as decreased learning (technically, decreased inhibition of the amygdala by the prefrontal cortex, and damage to the hippocampus). That is one reason we take nice deep sighs of relief in our class (deep breaths work to relax the fast adrenaline

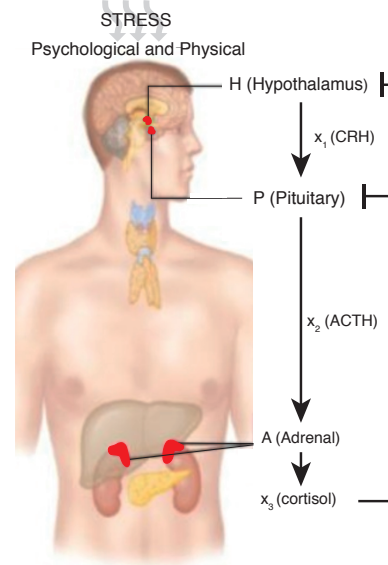


Figure 4.1

¹ How the inputs are combined is an open question: is it a product or a sum of the inputs? It is likely to be a product.

² Incidentally, the middle of the adrenal gland secretes (and gives its name to) adrenaline. It is not part of the HPA axis.

system, and also cause a nice perception of the class as a pleasant place, which reduces stress). The HPA axis is in fact implicated in mood disorders, as we will discuss later in this chapter.

Cortisol for optimal functioning thus needs to be in a middle range. Insufficient levels result in low energy, and excessive levels over time cause the symptoms of chronic stress. The middle range of inputs to the HPA axis can be thought of as stimulations that is healthy, as in sports and challenging activities that interest us. The lower range is boredom and the higher range stress.

The classic model for the HPA axis explains responses on the fast timescale of hours, but not on the slow timescale scale of months

The classic description of the HPA axis discussed so far is what you will find in textbooks. It's the "HPA version" of the minimal model we saw for glucose and insulin. Let's write it down mathematically so we can explore its properties. Our main conclusion will be that the model shows the expected response to acute stress, but cannot explain phenomena on the scale of weeks-months. We will later expand the model by adding control of gland sizes, and open up a world of phenomena on the month's timescale.

We package together all of the inputs to H into a single quantity $u(t)$. This input u causes H to secrete the hormone x_1 , which is degraded with a timescale of minutes at rate α_1 . This can be described as follows, using the same logic as we did for the glucose minimal model of lecture 1:

$$\frac{dx_1}{dt} = q_1 \frac{H u}{x_3} - \alpha_1 x_1.$$

the inhibitory effect of x_3 on the secretion of x_1 is described³ by the term $1/x_3$, so that the more x_3 , the less production of x_1 .

The hormone x_1 acts on P cells (called corticotrophs) to induce secretion of the second hormone x_2 . Secretion is inhibited by x_3 . The hormone x_2 has a half-life of $1/\alpha_2 = 10$ minutes, and so

$$\frac{dx_2}{dt} = q_2 \frac{P x_1}{x_3} - \alpha_2 x_2$$

The hormone x_2 in turn induces the cells of the adrenal cortex A to secrete x_3 , whose half-life is $1/\alpha_3=90\text{min}$

$$\frac{dx_3}{dt} = q_3 A x_2 - \alpha_3 x_3$$

To solving for the steady-state, we set $d/dt=0$, as in the previous chapters, and do the algebra. The cortisol steady-state depends on all of the model parameters, and rises with the input u and the sizes of the two glands A and P

$$(1) x_3^{st} = \left(\frac{q_1 q_2 q_3}{a_1 a_2 a_3} u HPA \right)^{\frac{1}{3}} \sim u^{\frac{1}{3}} P^{\frac{1}{3}} A^{\frac{1}{3}}$$

³ Binding of cortisol affects production as $1/(K+x_3)$ where K is the binding affinity to the receptor- called the Michalis-Menten equation explained in Appendix A. The $1/x_3$ term is a good approximation when x_3 concentration exceeds K , as it does for cortisol whose blood levels are on the order of 100nM and K is on the order of 10nM.

Similarly, the steady states of the other two hormones also depend on all parameters. x_2 rises with the size of P but drops with the size of A, because A inhibits its upstream hormone x_1

$$(2) \quad x_2^{st} \sim \sim A^{-\frac{2}{3}} P^{\frac{1}{3}}$$

$$(2) \quad x_1^{st} \sim u^{\frac{2}{3}} P^{-\frac{1}{3}} A^{-\frac{1}{3}}$$

These equations correctly show that the hormone levels rise when stress input u occurs, with a timescale of minutes-hours.

These equations, however, do not explain phenomena on the scale of weeks-months:

- (i) Effect of taking steroids to suppress inflammation – if taken for weeks or more, these drugs shouldn't be stopped at once. Steroids need to be gradually tapered down, to avoid risk of dangerously low levels of cortisol.
- (ii) HPA hormone imbalances that occur for months after pregnancy.
- (iii) The month-timescales of depression and bipolar disorder.

Moreover, the glands A and P are made of cells that divide and are removed (the H gland is in the brain and, like most brain neuronal tissues does not show sizable turnover of cells. Most neurons don't divide, with some exceptions such as in the hippocampus). To maintain proper size, the A and P glands must have feedback control as discussed in lecture 2. Since the glands act in a series of hormone secretions, it turns out that they control each other's growth. This situation is described next.

The HPA axis shows a feedback loop in which two glands control each other's size

The cells of the A and P glands proliferate and are removed with a typical turnover time of about 1-2 months. They have feedback loops that balance cell proliferation and removal. The inputs to these loops are the HPA hormones themselves. The hormone x_1 acts not only to induce secretion of x_2 by P cells, it also increases the cells proliferation rate. Similarly, x_2 acts to induce x_3 secretion and also to induce adrenal cortex cell proliferation (Fig 4.2).

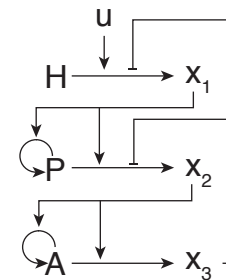


Figure 4.2

Thus, **the HPA axis shows two occurrences of the motif we saw for insulin-glucose**, in which a signal controls both secretion and proliferation. In the HPA axis, the two motifs are stacked on top of each other.

The equations for P and A total cell mass are the difference between proliferation and removal

$$(4) \quad \frac{dP}{dt} = P(b_P x_1 - a_P)$$

$$(5) \quad \frac{dA}{dt} = A(b_A x_2 - a_A)$$

Here a_P, a_A are the cell removal rates ($1/a_A, 1/a_P \sim 1 - 2$ months), and b_P, b_A are the hormone-dependent proliferation rates.

These two equations have important consequences for the system on the scale of months. Here we come to the concept of **separation of timescales**. There are two very different timescales in the system, a fast timescale of hours for the hormone production and removal, and a much slower timescale of months for changes in gland masses. Therefore, the steady-states from Eq (1-3)

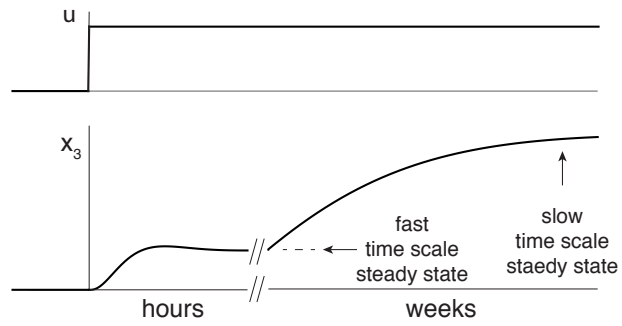


Figure 4.3

correctly describe what happens if input u is presented for a few hours. But if u is present for weeks, A and P sizes change gradually, and the system finds its full steady-state with changed gland masses (Fig 4.3). Thus, Eq 1-3 are more accurately described as '**quasi-steady-states**'.

When we solve the steady-states of the 'slow equations' Eq 4-5, we find that the steady-state hormone levels become much less sensitive to the physiological parameters of the HPA axis. In particular, the only way to get steady state is $x_{1,st} = a_P/b_P$, $x_{2,st} = a_A/b_A$.

These hormone levels thus do not depend at all on production per cell q_1, q_2, q_3 , removal rates etc. Cortisol similarly turns out to have a simple steady state level robust to almost all model parameters (by plugging in x_1^{st} to Eq 1):

$$(6) x_3^{st} = \frac{q_1 b_P}{\alpha_1 a_P} u$$

Nicely, cortisol rises linearly with the input u , as it should. It provides a measured response to stress inputs. Cortisol steady-state concentration does not, however, depend on production parameters q_2, q_3 , which vary, for example, with blood volume and metabolism. It also does not depend on the hormone removal parameters α_2, α_3 . As in the case of glucose, the circuit protects cortisol baseline levels from variations in many physiological parameters, compensating these changes by means of slow growth and shrinkage of the glands.

The gland changes protect also the dynamics. Cortisol dynamics after an acute stress input are independent on q_2, q_3 , an example of dynamical compensation that we saw in the previous chapter.

We can derive equations for the gland masses on the timescale of months by using the quasi-steady state approximation for the hormones. This means using the fact that on the timescale of months, hormones can be assumed to be at their fast-steady state levels, Eq 1-3. Plugging x_1 and x_2 into Eq 4-5, shows a **negative feedback loop between P and A**:

$$(7) \frac{dP}{dt} = P(c_P u^{\frac{2}{3}} P^{-\frac{1}{3}} A^{-\frac{1}{3}} - a_P)$$

$$(8) \frac{dA}{dt} = A(c_A u^{\frac{1}{3}} P^{\frac{1}{3}} A^{-\frac{2}{3}} - a_A)$$

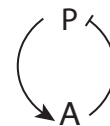


Figure 4.4

P acts to increase the size of A, by the action of x_2 (Fig 4.4). In contrast A acts to shrink P, because the hormone it secretes, cortisol, reduces x_1 which is the growth factor for P.

The P and A glands form a negative feedback loop that can oscillate with a seasonal timescale

For the remainder of this lecture, we focus on the timescale of months. This is the timescale of the negative feedback loop between the two glands. Like many negative feedback loops, it can show damped oscillations. To see this, follow Fig 4.5 from the top and go with the arrows, clockwise. A starts large, and this reduces P (first arrow). Smaller P reduces A. Smaller A makes P grow back. Large P makes A grow, closing the repeating cycle (Fig 4.5). Each of these steps has a delay due to the tissue turnover time, about 2 months. The overall time for a full cycle is **on the order of a year**.

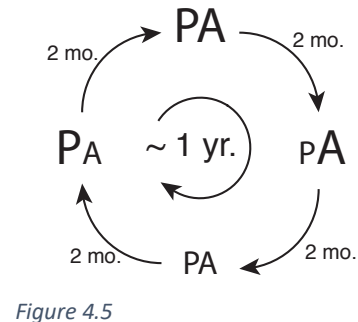


Figure 4.5

When Avichai Tendler in his PhD with me found this year timescale, we got goosebumps. A year is important for organisms because of the changes in seasons. It is useful to have **an internal clock that can keep track of seasons**, as we will discuss below.

To understand this clock, it helps me to make an analogy of the A-P feedback loop to a mass on a spring. Suppose the mass is at rest at its equilibrium point (Fig 4.6). If you pull the mass down, the spring will stretch and cause a force pointing back to the equilibrium point. If you let go of the mass it will return, but at equilibrium will have high velocity v , so it will overshoot and compress the spring. The compressed spring pushes the mass back down, and so on, to obtain sustained oscillations (Fig 4.6).

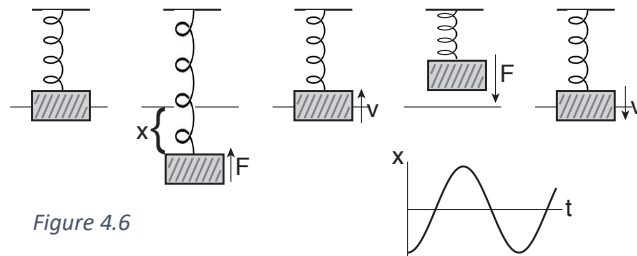


Figure 4.6

To describe this motion, we can use Hooke's law of the spring: the force grows with the extension of the spring, $F = -kx$. This force, according to Newton's law, $F=ma$, changes the acceleration a , which is the rate of change of velocity $a = dv/dt$. Thus $dv/dt = -\frac{k}{m} x$. Velocity is the rate of change of position x , so that $dx/dt = v$. This is like a negative feedback loop in which v increases x but x decreases v (Fig 4.7). Thus, x and v are like A and P, and the negative feedback can act as an oscillator.

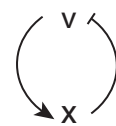


Figure 4.7

When you simulate the slow equations for A and P you don't get sustained oscillations, but instead damped oscillations that decay away. To get damped oscillations in the spring analogy, we can put the spring in a container with a viscous fluid like honey. The honey causes a drag force which is proportional to velocity: $dv/dt = -kx - b v$ (Fig 4.8). The spring does not oscillate forever but instead settles down to its equilibrium point.

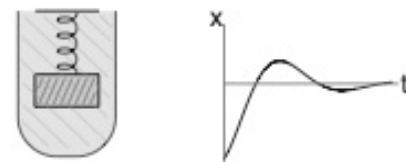


Figure 4.8

There is also a “drag”-like force in the equations for A and P. For example, large A makes more cortisol, which inhibits x_2 , the growth factor of A. Thus large A mass acts to reduce itself, similar to large velocity v which causes more drag and slows itself (thanks to Z. Tan in the lecture for this comment).

Model for steroid withdrawal explains overshoot and recovery over months

When you pull the damped spring and let it go, it oscillates and relaxes to steady state. This provides a way to study the HPA oscillator, by seeing what happens when you pull it away from equilibrium and watch it recover. Let us therefore consider situations that perturb the HPA axis, reasoning that the two-gland feedback loop should show months-scale recovery dynamics from perturbations.

One common situation occurs when cortisol levels are high for weeks or more, and then are suddenly lowered. This occurs in the medical situation in which people take glucocorticoids (long-lasting cortisol analogues such as dexamethasone or prednisone) for extended periods and then go off the drugs (Koch-Weser and Byyny, 1976; Dixon and Christy, 1980). Glucocorticoid steroids are given to reduce inflammation or suppress immune responses, as in asthma and autoimmune diseases, and after transplants.

Giving high doses of steroids for a few days usually causes no problems. But if they are given for two weeks or more, it is important not to stop steroid treatment all at once. If you do, the patient will show dangerously low cortisol. They can't make enough cortisol by themselves, causing serious symptoms: blood pressure drops to potentially fatal levels. This is called **steroid withdrawal**. Thus, one must gradually reduce doses over months.

Steroid treatment can be modelled by external (exogenous) cortisol D added to the equations (by replacing x_3 by $x_3 + D$ in Eq 1 and 2). In this case, both pituitary and adrenal gland sizes shrink, due to inhibition of their growth factors x_1 and x_2 by D . It's as if the glands 'think' there is too much cortisol and shrink to return it to baseline. This causes the atrophied and involuted adrenal gland observed in extended glucocorticoid treatment (Nicolaidis *et al.*, 2000).

Thus, simulations of steroid withdrawal begin with small gland sizes A and P , after a long period of high exogenous cortisol D , and then setting D to zero. This is like pulling the spring hard, and then letting it go. You can see this in Fig 4.5, starting at the bottom (small A and P), and following the arrows. The dynamics show that P recovers first and A follows it. As a result, x_2 overshoots after 3 months and goes back to normal after 9 months, whereas cortisol is abnormally low and recovers more slowly after 9 months (Fig 4.9). The overshoot of x_2 is due to the release of x_1 inhibition, which causes P to grow. Only when P returns to normal size is x_2 sufficient to allow A to grow and recover.

Such overshoot dynamics were found by Graber et al, in an example of a “small-data” study which followed $n=14$ patients who went off prolonged steroid treatment or had a cortisol-secreting tumor in their adrenal removed (GRABER *et al.*, 1965). Patients showed a large (10-fold) overshoot in x_2 and a slower recovery of cortisol over 10 months (Fig 4.9), in agreement with the model.

Seasonality in hormones

With the mass-on-a spring-spring analogy we can also understand what happens to the HPA axis when it gets inputs that change over a year, like the length of the day. The seasons entrain the oscillator to a period of one year. It’s like putting the honey container on a platform that oscillates up and down: the spring picks up the platform’s frequency (one year) and begins to oscillate with the same frequency. Even if its natural frequency (perhaps 10 months) is a bit different, it can still entrain effectively to a yearly input.

Due to this year-scale frequency, the two-gland feedback loop can be **entrained** (driven) effectively by signals that vary over the year. This includes daylight, day-length and other environmental factors.

Indeed, animals have seasonal behaviors and physiological changes across the year. Birds and mammals migrate, change their feathers/fur, hibernate and mate in certain seasons. The signals for this seasonal cycle have to do with day length variation. Days are shortest in December 21 and longest in June 21 (Fig 4.10). Day length affects a hormone secreted in the brain, called melatonin, which feeds into the P gland.

But animals do not rely only on external signals such as day-length to figure out which season it is. **Animals have an internal clock that keeps track of seasons.** Such an internal clock is crucial, for example, to avoid mistaking a series of cloudy days in summer as winter. Evidence for such a

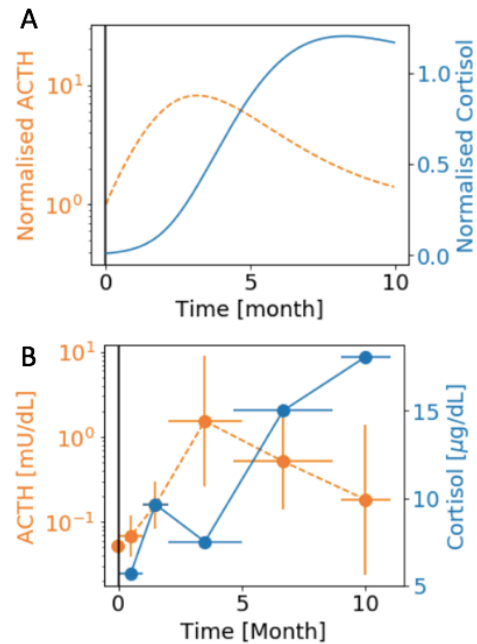


Figure 4.9

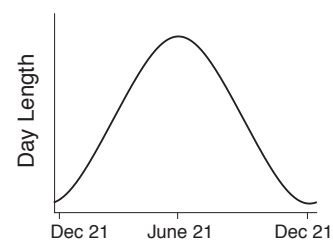


Figure 4.10

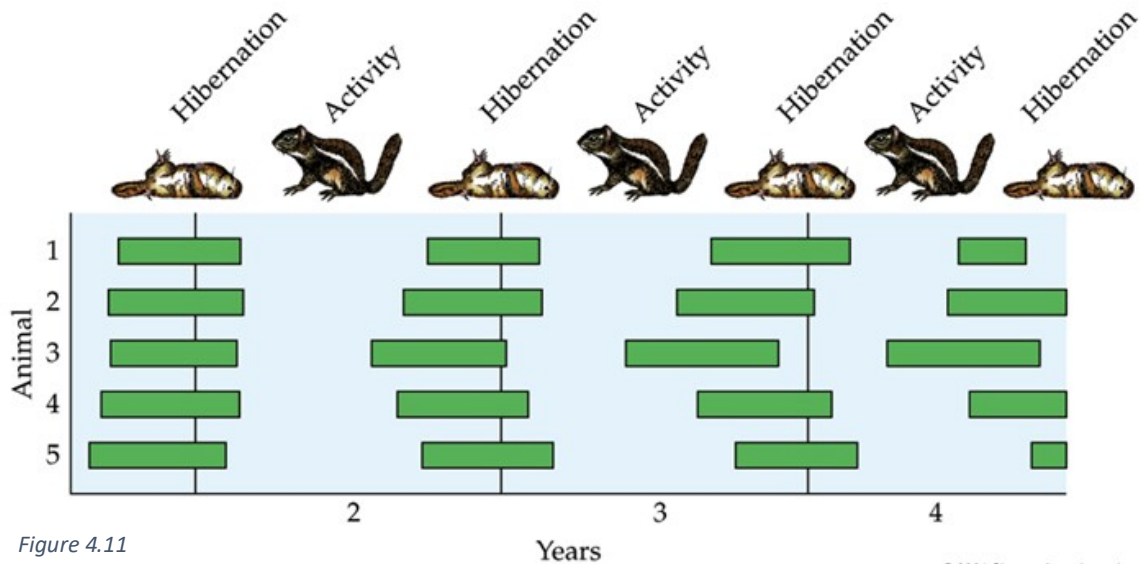


Figure 4.11 © 2001 Sinauer Associates, Inc.

clock was found when various animals were kept in constant day-length conditions for years. They still showed the seasonal changes, although not with a 12-month period, but with a 10 month period (Fig 4.11). This inner clock is thus called a **circa-annual clock** (circa=about, annual=year). The mechanism for this seasonal clock is not well-characterized, but the pituitary is thought to be involved, due to its response to a day-length dependent melatonin signal (Wood and Loudon, 2018).

The long timescale of the $A - P$ oscillator may provide some of the inertia of this internal clock. Since the A-P circuit is a damped oscillator, it cannot, by itself, explain how the seasonal clock runs also in animals kept under constant conditions for years. But a yearly oscillating input can drive the oscillator to show sizable seasonal oscillations.

To study the effects of entrainment by yearly cycles of day-length, we can study the HPA axis with inputs that vary with a period of one year, $u(t) = 1 + u_0 \cos(\omega t)$. The peak input occurs at the shortest day of the year, December 21. It is worth noting that the seasonal input depends on geography: The amplitude u_0 increases with latitude. It is about 2 times larger in London than in Tel Aviv (Teets, 2003). It can be computed by the daylength equation of astronomy.

A model with no gland mass changes would predict that hormones follow the day length input. When input is highest (midwinter for cortisol), all hormones are highest. Adding gland mass changes, however, changes this picture and provides specific predictions: (Fig 4.12):

- (i) Peak cortisol should not occur at the time of peak input (December 21) *but rather be delayed by about two months*. This delay is due to the delay in the feedback loop, and is determined by only two parameters: the P and A tissue

turnover times a_A and a_P . The model therefore predicts a cortisol peak at late winter/spring. The shift and amplitude can be derived analytically from linearized equations.

- (ii) Cortisol and x_2 (ACTH) are in approximate **anti-phase**, with x_2 peaking in late summer/fall. This antiphase cannot occur in a model without gland size changes, because in such models the two hormones vary together within minutes-hours of each other.

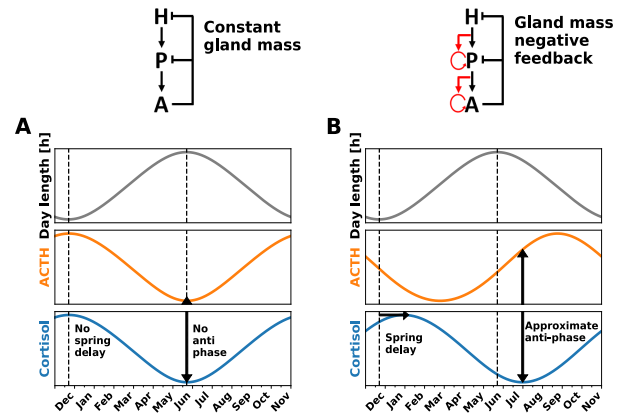


Figure 4.12

Large scale electronic medical record (EMR) datasets show the predicted oscillation phases

To test such predictions requires data on cortisol and x_2 collected in different months. Here we can see two types of data sources in systems medicine- hypothesis-driven 'small-data' and exploratory 'big-data'.

A small-data study is usually done with a focused research question and scope. An example is the UK Whitehall study on cortisol levels of thousands of British civil servants. One striking finding is that the lower the civil service rank, the higher the cortisol level. Indeed, socioeconomic status is a strong predictor of health and longevity across cultures: the lowest decile has about ten years shorter mean lifespan than the top decile.

When tested for seasonality, saliva cortisol levels (meta-analysis with $n=18,698$ subjects) was maximal in winter-spring and minimal in fall (Miller *et al.*, 2016). There was a 17% peak to trough amplitude between spring and fall saliva cortisol. A Swedish study of a dozen people found a saliva cortisol maximum in spring with a larger amplitude of 30% (Persson *et al.*, 2008), as predicted by the northern latitude of Sweden. A study in Australia found similar phases with a maximum is Australian winter-spring, which is 6 months different from the northern hemisphere, as expected.

In addition to these specific studies on cortisol, one can utilize 'big-data'. An exciting advance in systems medicine is the increased availability of large, searchable medical datasets. These are called **electronic medical records (EMR)**. For example, Israel's largest health insurer (Clalit) includes data about half of the Israeli population over 15 years (2002-2017) totaling about 50 million life-years, with broad socioeconomic and ethnic representation. The data includes disease codes, drugs purchased, and blood tests. Thus, one can explore many hypotheses or look for patterns. For seasonality, you can compare hormone tests according to the month of the year they were taken.

A major issue with EMR datasets is **ascertainment bias**. The medical tests were done for a clinical reason, as opposed to a uniform sample of the population as attempted in many 'small-data'

experiments. To address this bias requires ways to filter-out data from people with medical conditions that can confound the results. For the purpose of detecting seasonality, for example, one can remove all people with chronic disease according to international disease codes. One can also filter out, for each blood test, data from individuals that took a drug that affects that specific test. Finding such drugs can be done from the ERM data itself, by finding drugs that significantly affect test results on average. Finally, one can remove tests which include indications for infection to avoid effects of yearly infection cycles.

A second major issue for hormone tests is the circadian rhythm- tests done at different times of day give different answers. Thus, it is important to consider only tests done at a certain time of day, or even at a certain time after dawn, to avoid the effects of circadian oscillations in the hormones.

We can now plot hormone levels as a function of the month of the year. A picture emerges (Fig 4.13). In both males and females, blood cortisol ($n=104,255$ blood tests) shows a peak in spring and a minimum in fall, as predicted. The timing of the peak and trough correspond to tissue turnover parameters of about two months. There are fewer x_2 (ACTH) tests in the dataset (a few thousand after filtering), and hence more noise. Yet it appears that x_2 peaks in summer as predicted at least in females which have more tests and hence more statistical power (Fig 4.13, orange line).

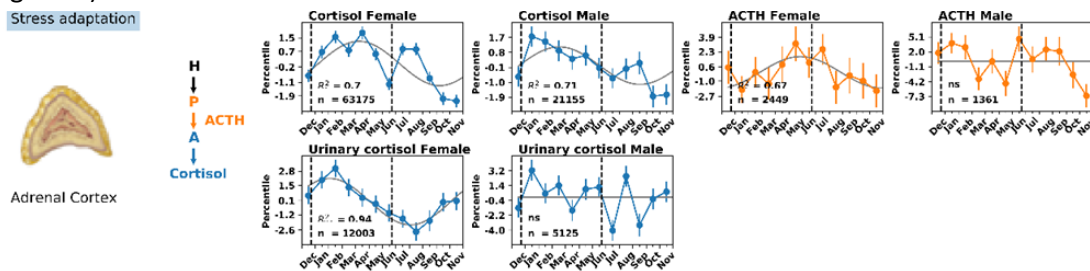


Figure 4.13

The oscillation amplitude of a few percent matches the predicted amplitude at the 31° latitude of Israel. The model predicts larger amplitudes at higher latitudes (Fig 3b), where daylength changes more strongly with seasons, reaching about 20% and 30% peak-to-trough in London and Stockholm respectively. Tests of saliva cortisol in other countries show the expected rise with latitude (Fig 4.14). Tests in Australia show the right seasonal dependence, but shifted by 6 months (Australian winter is in May-August).

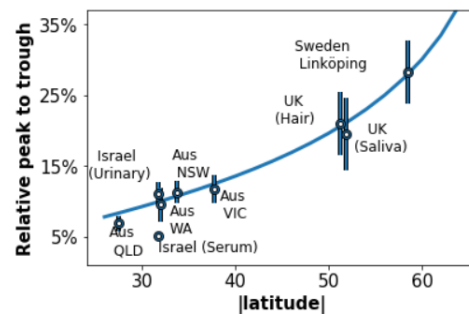


Figure 4.14

Since the HPA axis is implicated in mood disorders (Watson and Mackin, 2006; Herbert, 2013), the seasonal variation in the HPA axis may contribute to **seasonal component of affective disorder (SAD)** (Rosen *et al.*, 1990; Mersch *et al.*, 1999; Avery *et al.*, 2001), also known as ‘winter blues’. This is a relatively common disorder at high latitudes (1% prevalence in Florida and 10% in Alaska). The spring cortisol peak might explain why the SAD symptoms peak in spring. For example, suicide

rates peak in April (Bridges, Yip and Yang, 2005). Likewise, seasonal HPA oscillations can contribute to the seasonal component of major depression and other mood disorders.

Other HP axes control reproduction, growth and metabolism, and show similar seasonal oscillations

The HPA axis is one of four axes that together control major fitness components of living organisms: reproduction, metabolism, growth and stress. The hypothalamus H and pituitary P participate in all four. That is why P is sometimes called “the master gland”. Each axis has its own x_1, x_2 and x_3 hormones (Fig 4.15). The hypothalamus H secretes x_1 hormones to induce the pituitary cells to secrete x_2 hormones that activate an effector organ for each axis to secrete x_3 .

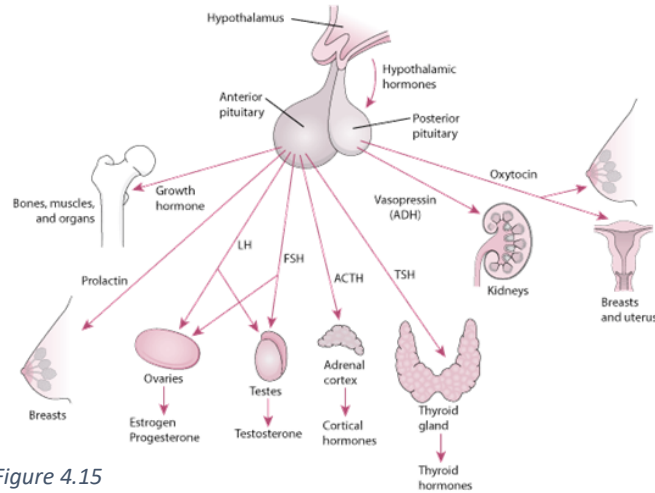


Figure 4.15

In the reproduction axis, for example, the x_2 -hormones are FSH and LH, and the x_3 hormones are estrogen (from the ovaries in females) and testosterone (from the testes in males). For metabolism, the x_2 hormone is TSH, and x_3 is thyroid hormones secreted from the thyroid gland. For growth, x_2 is growth hormone, given as therapy for short stature as in the case of the young football player Messi, and x_3 is IGF1. (Fig 4.16)



Figure 4.16

As in the HPA axis, all of these axes show a combination of two mass-control motifs stacked on top of each other (Fig 4.17). In all of them, there is a fast feedback loop in which x_3 inhibits secretion of x_1 and x_2 . There is also a slow organ-size control feedback in which as in the HPA axis, growth control feedback are at play. The hormones act as growth factors for the glands, with slight variations between the circuits in the configuration of the arrows. For example, thyroid gland growth is regulated by its upstream hormone $x_2 = TSH$ (Fig 4.17).

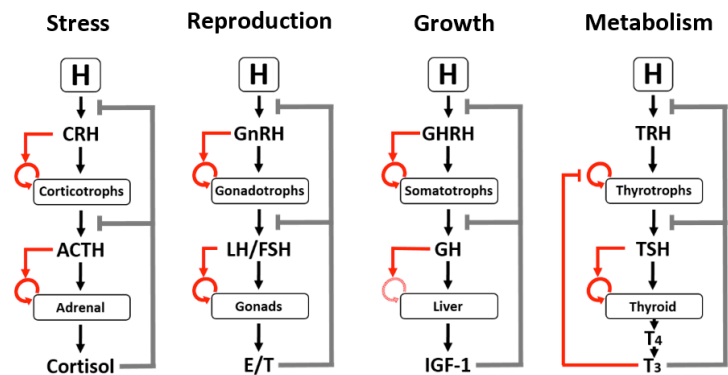


Figure 4.17

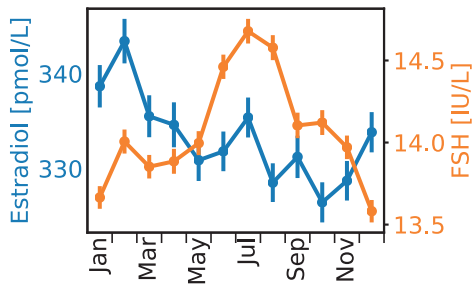


Figure 4.19

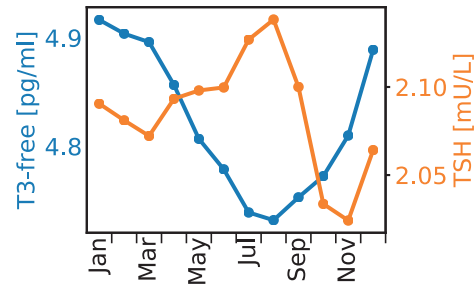


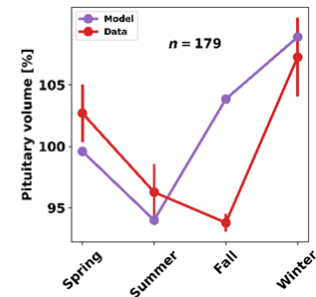
Figure 4.20

This leads to the prediction that the x_2 -hormones should peak in summer/fall and the x_3 hormones in winter-spring. Indeed, Clalit EMR data shows that in both the thyroid axis and the reproduction axis, x_2 -hormone blood test levels (TSH, LH, FSH) show a peak in late summer, about 1-2 months after June 21 (Fig 4.19/4.20). The x_3 hormones (free thyroid hormone T3, estradiol, testosterone) show a late-winter/spring peak (Fig 4.19/4.20), as predicted. Oscillation amplitudes for most hormones are in the range of 4-10%. Some of these tests exceed 6 million data points(!), such as TSH tests, with error bars smaller than the dots in Fig 4.19. For all hormones see Fig 4.21.

In all of the axes, pituitary cells are predicted to be at maximal total mass in winter. The pituitary volume seems to change seasonally as predicted, based on MRI images (Fig 4.20)



Figure 4.20



In contrast to the spring delay of the hormone oscillations, blood tests for key metabolites such as glucose, calcium and other important compounds and ions, show smaller seasonal oscillations, which peak around the shortest or longest days of the year with no delays. Thus, hormones work hard to keep essential metabolites relatively constant.

Intriguingly, the late-winter peak of the different axes suggests that humans have a peak season for reproduction, growth and stress response (or more precisely, cortisol stimulation). This is supported by data collected in numerous studies that shows peak child growth, peak sperm quality in winter. Similarly, conceptions peak in winter in countries with temperate climate. Conception peak shifts to summer in northern clines. Cultural and regional effects complicate the interpretation of conception seasonality. But overall, there is a case for a biological basis of human seasonality. Although modernity makes seasons less impactful, in previous centuries there has been a season for every purpose.

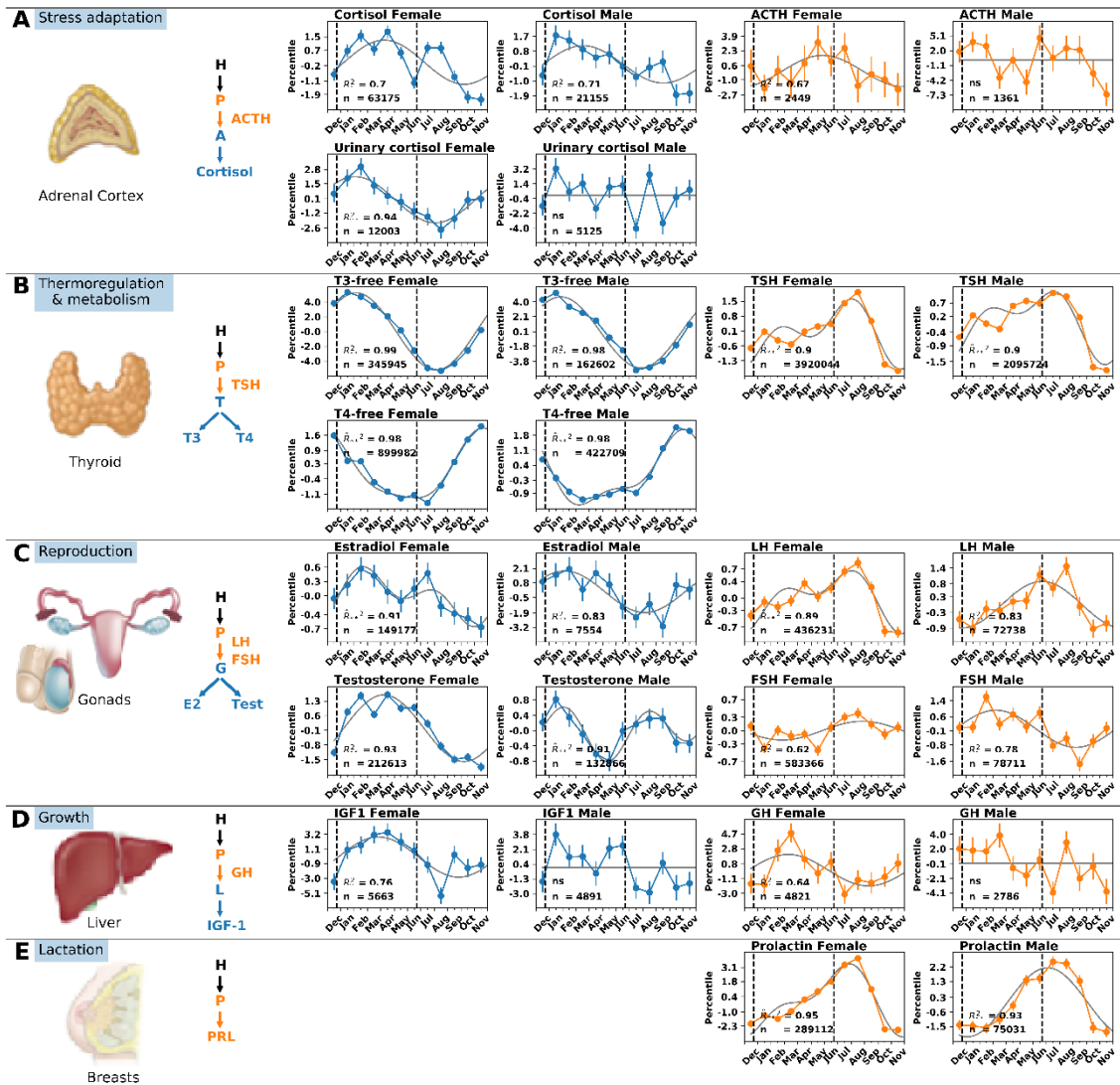


Figure 4.21

Bipolar disorder has a timescale of weeks-months, and this timescale can be generated by tissue size fluctuations

To end this lecture, let's use these concepts to explore a mystery in psychiatry. We consider a major mood disorder called **bipolar disorder (BD)**. BD was formerly called manic-depression. It is characterized by periods of months of depression with negative thoughts and low energy, and periods of mania for days to weeks with excessive high energy, irritability and poorly-thought-out decisions. This is unlike the mood swings we all have: depression seriously interferes with the ability to feel joy, to function, eat and get out of bed; mania has delusions that can seriously damages relationships and work relations. BD is a leading cause of suicide and self-damage, and causes suffering to about 1-2% of the worlds' population.

As in most psychiatric conditions, the biological understanding of BP is still lacking. It has a genetic component, but no genes of large effect have been identified. Medication such as lithium can stabilize moods for some people, but the mechanism is not clear. There is no blood test for depression or bipolar, unlike diabetes where a simple blood glucose test is the basis for diagnosis. Diagnosis is done by interviews with trained psychiatrists. Since the mystery is so great, we can afford to speculate using the concepts of this lecture.

We focus on the timescale of BD: what sets a weeks-months timescale for mood swings? Neurons work in seconds, hormones in hours, and gene expression changes take a day or less. Few processes can supply such a month's timescale.

We can explore the hypothesis that the month's timescale is due to tissue size variations. The glands of the HPA axis are natural candidates. The HPA axis is known to be dysregulated in major depression (MD) and BD: people with MD and BD have high cortisol and enlarged adrenal cortex. Conversely, high cortisol and enlarged adrenal causes depression (as in Cushing's syndrome mentioned above). High doses of glucocorticoids cause mania-like symptoms and/or depression in a fraction of patients. Historically, the one of the first clues for the existence of a stress pathway came from Selye's work on autopsies of stressed animals and suicide victims which showed enlarged adrenals. This was before anyone knew of hormones.

Often, BP episodes are preceded by stressful or joyous life events. To make a conceptual model for BP, we therefore need to schematically conceptualize psychological stresses. To do so, we simply note that life events lead to perceptions in the brain (Fig 4.22). Perceptions are person-specific and depend on experience and narratives. For example, a life event such as the victory of a political candidate in an election causes different perceptions in different people: some grieve, others rejoice, and others don't care. Perceptions affect our behavior which in turn affects life events. The HPA axis output, cortisol, also affects perceptions as discussed above.

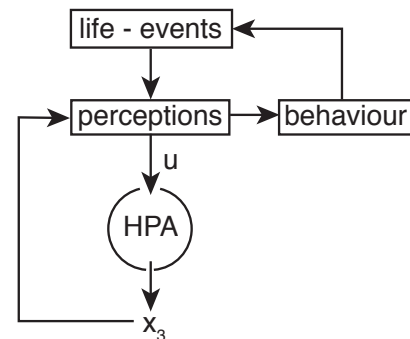


Figure 4.22

Let's suppose that people with BD tend to perceive life events in ways that create larger input signals to H, a kind of psychological excitability. We can model these inputs, based on fluctuating perceptions, as a noisy input signal $u(t)$ with a standard deviation σ . In people with BD, let's assume that σ is larger than in people without BD.

Such a noisy input to the HPA two-gland feedback loop causes a fascinating phenomenon: the loop shows noisy oscillations in gland sizes and in hormones, with a typical timescale of months. The larger the variations in the noisy input amplitude σ , the larger the amplitude of these oscillations. To see this, we can use the spring analogy: put the spring in its honey container on the back of a flatbed truck driving on a rough gravel road (Fig 4.23). The spring picks up vibrational frequencies close to its natural (resonance) frequency and starts making noisy, erratic oscillations (Fig 4.24).



Figure 4.23

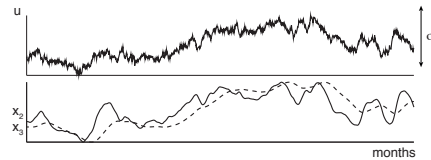


Figure 4.24

Note that these oscillations are due to stresses, and are different from the seasonal oscillations discussed above. Seasonal oscillations are small, and ride on top of the day-day stress responses. To see seasonal oscillations, you need to average over many people, in order to average out the stress-signals of different people. The noisy oscillations we are talking about now are larger, and don't have a seasonal phase which is the same for everyone in a given region- they have a different phase in each person.

Thus, the noisy oscillations of the HPA axis might account for some of the inertia and timescale of mood swings in BD (Fig 4.24). Similar oscillations in the HP-thyroid axis may cause energy ups and downs typical of BD. A question for current research is how (and whether) the hormones and gland sizes exactly map to mania and depression.

If such HPA oscillations indeed turn out to be important for BD, it points at a way to consider treatment. One can build a controller- an algorithm that administers cortisol at the right phase of the oscillations, in a way that tends to dampen the oscillations out (Fig 4.25). This is similar to an effect known to anyone who ever rode on a swing: if you kick at the right time you can gradually stop a swing from swinging. Indeed, simulations suggest that such a controller can reduce oscillation amplitudes by a large factor (Fig 4.25). These directions are a current research project in our group.

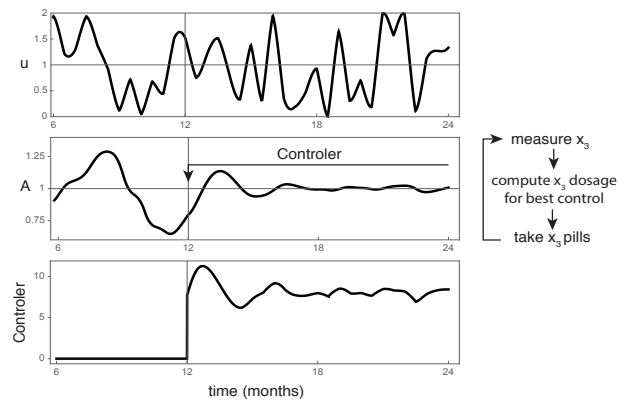


Figure 4.25

We might ask what purpose do moods serve in healthy physiology? A leading hypothesis is that moods evolved as a mechanism to allocate effort in proportion to reward (Medzhitov and Stearns, 2016, quoting Nesse, 2015). "When payoffs are high, positive mood increases initiative and risk taking. When risks are substantial or effort is likely to be wasted, low mood blocks investment." There is thus evolutionary benefit to a system that can slowly change moods according to integrated information on risks and rewards. The system learns about risks and rewards over the time-frame of weeks. The inertia of HPA gland sizes can help provide such an integrated swinging

pendulum for moods. This creates a tradeoff, however, towards fragility to mood disorders including depression and bipolar disorder. Since genes affect many aspects of behavior, and gene effects add up, there will be a distribution of set points between people. Some people draw genes at the extremes of the distribution, with increased fragility to disorders. The fragility can be exposed due to stressful life events.

To sum up, when two tissues control each other's sizes, an oscillatory phenomenon on the timescale of months can occur. The two-gland oscillator allows the HPA stress pathway to synchronize with the seasons, making different hormonal set-points for different times of the year. The cost of this ability is hormone imbalance after delivery and possibly noisy mood swing oscillations in a small percentage of people prone to BP. More generally, the body can be considered as an ensemble of interacting organs that constantly adjust their size and activity to changing conditions and to the states of other organs.