

Hormone Circuits Lecture notes

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Lecture 7

Major depression and the slow timescale of treatment

Major depressive disorder (MDD or depression) is the most common psychiatric disorder, with lifetime prevalence of about 20% in women and 12% in men. Depression severely impairs quality of life, preventing the basic feeling of joy and making standard daily activity including sleeping, eating and working very difficult.

Depression can have an early age of onset (first episode) in teenage years, and sometimes a late onset (Fig 7.1). It can happen again and again over life, with an incidence that rises with age, making it also an age-related disease.

Despite its prevalence and severity, the biological understanding of MDD is limited. The causes of depression are a combination of genetic, biological and environmental factors (the usual mantra when the precise cause is unknown).

As in virtually all areas of psychiatry, diagnosing depression is done by interview with a clinician. There are no blood tests or other objective markers. Currently it based on subjective categories listed in Fig 7.2, taken from the diagnostic and statistical manual edition V (DSM-V, the bible of psychiatric diagnosis). MDD is thus composed of many different disorders and severity levels. It is as diverse as humanity is diverse. Advances in markers for MDD or quantitative measures for its nature and severity would be very important.

One of the known causes of depression is stressful life events, such as death of a close person or sexual or physical abuse. A stressor can lead to a depressive episode, which can continue for months or years after the stressful events.

Indeed, the stress response pathway, the HPA axis of lecture 4, is deregulated in many cases of MDD. Recall that in the HPA axis, stress inputs u cause the hypothalamus H to secrete the hormone x_1 , causing

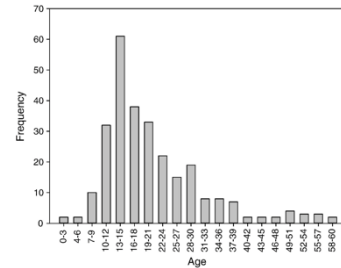


Figure 7.1

Criteria for Major Depressive Episode

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
 - (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
 - (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
 - (4) insomnia or hypersomnia nearly every day
 - (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
 - (6) fatigue or loss of energy nearly every day
 - (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
 - (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
 - (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- B. The symptoms do not meet criteria for a Mixed Episode (see p. 365).
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Figure 7.2

secretion of x_2 by the pituitary P , which causes the secretion of **cortisol**, x_3 , by A , the adrenal cortex (Fig. 7.3).

The adrenal A is enlarged and cortisol is high in about 50% of people with depression. We will focus on this type of high-cortisol depression in this lecture.

High cortisol is not only a side-effect of depression, it also seems to cause depression: for example, depression is a common symptom of Cushing's syndrome, the excess secretion of cortisol due to a tumor in P or A . Depression is also a common side-effect of cortisol-analogue drugs, called glucocorticoid steroids, when taken for periods of weeks or more. Very high levels of cortisol have profound effects on cognition that can contribute to depression, by making negative stimuli more salient, and reducing the ability to explore behavioral options (eg trying repeatedly to open a stuck door when there is a fire, instead of seeking other ways out).

One way that clinicians describe the state of depression is that once it begins, it is usually hard to exit. In an attempt to move closer to a quantitative description, we can make a theoretical plot that describes this "hard-to-exit" feature. We plot stress input u averaged over weeks on the x-axis, and adrenal mass A on the y-axis (remember that enlarged A is found in depression) (Fig 7.4). If we start at low stress and normal (low) A , and increase stress, the adrenal A grows moderately. This is the non-depressed state, called the **euthymic** state, which means a state which is as tranquil and neurotic as most of us most of the time.

Then, at a critical stress level, the adrenal grows by much and enters a new state of high- A , namely depression. Now lowering u again doesn't make A return to its previous levels. One needs to dial down u to very low levels in order to reach a threshold for A to return to normal (Fig 7.4). This phenomenon is called "**hysteresis**", and we would like to see how it might arise from physiological circuits.

The HPA axis by itself cannot provide hysteresis to stress input as far as we know. We need to add an additional slow-timescale gland or organ. The logical candidates are brain regions involved in depression. One of the best-studied brain regions is the **hippocampus**, which we will denote h . We use lower case h , because uppercase H is already taken for the hypothalamus, which lies anatomically close to h in lower-middle part of the brain. The hippocampus, h , has important functions in forming long-term memories and in learning. In people with long-term depression, the volume of h is about 20% smaller, and h progressively atrophies over years of untreated depression, causing memory and learning problems. Thus, depression is linked with a state of small h and large A .

Other brain regions important for depression include the amygdala which helps detect threatening stimuli, and the prefrontal cortex, important in meaning making.

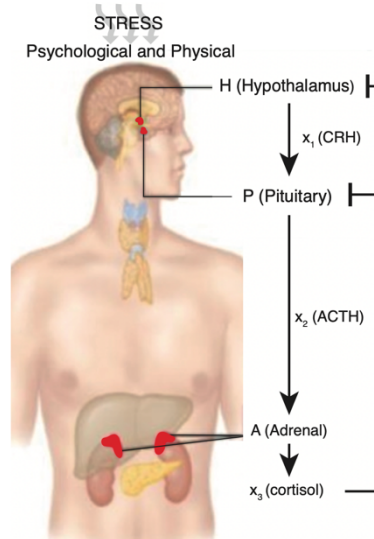


Figure 7.3

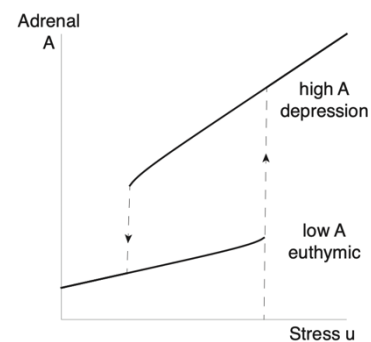


Figure 7.4

Treatments including SSRIs take weeks to have an effect

Despite the lack of understanding, effective treatments exist for depression.

One class of treatment is non-pharmacological, that is without drugs. This includes exercise (at least 20min x 3 times per week), healthy nutrition, and psychological therapy. Effective therapy includes cognitive behavioral therapy (CBT) and interpersonal therapy. Its success depends on the relationship and alliance formed with the therapist.

Effective drugs also exist for MDD. Many anti-depressant drugs work well in ~30-50% of patients. The right drug is chosen after some experimentation to minimize side-effects for each particular patient.

The current first line of treatment is **selective serotonin reuptake inhibitors (SSRI)**, which increase the availability of the neurotransmitter serotonin in the synaptic cleft (Fig 7.5). Serotonin has many brain functions (I think of it like the function of 220V electricity in the kitchen, powering many useful devices). SSRIs work by inhibiting reuptake pumps that drink up serotonin from the cleft, thus increasing its levels. Other antidepressants increase serotonin levels by different mechanisms, but typically they are not used as a first line of treatment due to more severe side-effects. Other drugs affect other neurotransmitters such as dopamine and norepinephrine.

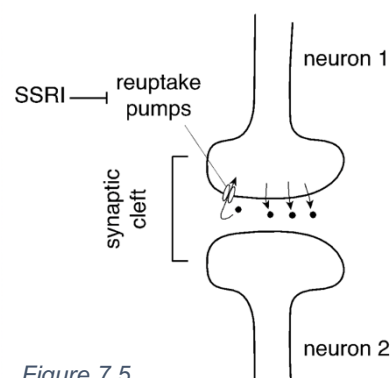


Figure 7.5

A more extreme form of treatment, that is effective in about 50% of the cases, is ECT. After written consent, electric current is passed through the brain under complete anesthesia, causing an epileptic seizure.

Interestingly, although serotonin is increased within hours of treatment with SSRIs, and many side-effects start as early, virtually all antidepressants *take 4-6 weeks to have clinical effect*. Similarly, ECT requires repeats over several weeks.

We therefore see that it is not the direct effect of serotonin or ECT which causes clinical improvement, but rather an indirect, longer-term effect of treatment.

Hypotheses about this delay include changes in gene expression and in DNA methylation. In this lecture we will explore an explanation based on the sizes (functional masses) of glands like A and brain regions like h . The rationale is based on the fact that among their many effects, SSRIs, ECT and other treatments for MDD all act to enhance the growth and activity of h .

Thus, our goals in this lecture are to make a simple model as a testable theory for the dynamics of depression. We want to understand why it takes weeks to see a clinical improvement in MDD? Also, we want to understand why some people are more prone to depression than others? How does stress cause depression and why depression stays long after the stress input is over?

A model for depression based on a toggle switch between HPA and brain regions

Our approach will be based on the separation of timescales in depression: hormones and SSRIs work in hours, and glands grow over weeks to years. We will therefore use the model

of the slow and fast timescales of the HPA axis, and add to it known interactions with the hippocampus h to provide a circuit that can show hysteresis (Fig 7.6).

We will see that, in a range of parameters, the model has two stable fixed points. The biology of one fixed point corresponds to what is known about the healthy condition. The second fixed point is characterized by higher HPA activity, enlarged adrenal and atrophied hippocampus, as found in the depressed state. Prolonged, but not acute, stress leads to a transition from the healthy to the depressed fixed point. Antidepressant treatment can cause the reverse transition, from depressed to healthy state, after weeks of treatment but not within hours.

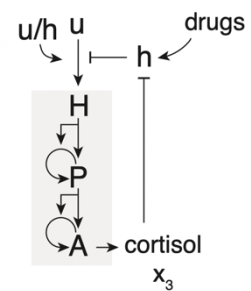


Figure 7.6

The model in this lecture is more tentative than in other lectures due to the preliminary state of biological knowledge about depression. We use the hippocampus h as a concrete example, well-studied and relatively clear, but we keep in mind that this can represent additional brain areas, like the prefrontal cortex and amygdala, which are important in anxiety and depression. A huge simplification is that we chunk the complex activity, mass, composition and richness of a brain region into a single variable, $h(t)$ (Fig 7.7).

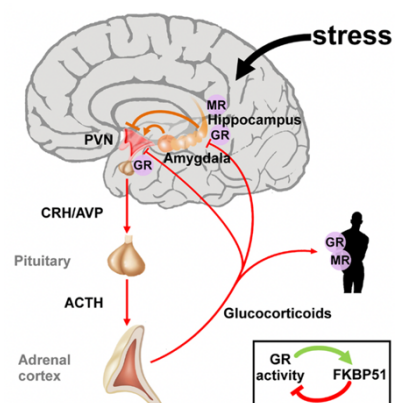


Figure 7.7

The hippocampus is modelled as *inhibiting stress input* u . We will model this by replacing u in the HPA model by u/h . We can use other functions $f(u, h)$ and get similar results. Biologically this inhibition of stress inputs is caused by inhibitory neurons from h to H . The hippocampus seems to help H not respond to inputs if we remember that they are not really stressful.

The interpretation of stimuli as stressful is extremely context- and memory-dependent. For example, in 1895, the film by the Lumiere brothers called "The coming of the train" according to some reports "caused fear, terror, even panic" (Fig 7.8). If you saw the film today, with your knowledge of movies, your brain would stop the danger signal to the HPA axis, because we learned that movies are safe.



Figure 7.8

The second important interaction in the circuit is that cortisol x_3 inhibits h functional mass. There are three well characterized ways that x_3 shrinks h : (i) neurotoxicity- the killing of neurons at high cortisol levels, (ii) the shrinking of the synapses in the neuronal arbor, which is a reversible process once cortisol is lowered, and (iii) the slowing of neurogenesis. Neurogenesis means the formation of new neurons from stem cells. The hippocampus is one of the few brain regions where neurogenesis is known to occur. Neuron replacement is slow at the rate of a few percent per year.

These negative influences are relevant at high levels of x_3 ; at lower levels, x_3 has invigorating effects on h and its activity. Thus, x_3 has an inverse-u shaped (biphasic) effect, positive at low levels and negative at high levels (Fig 7.9).

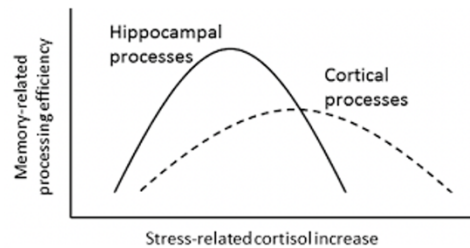


Figure 7.9

Biologically, this inverse u-shape is due to two kinds of x_3 receptors, one that binds cortisol strongly and saturates at low levels and one that binds x_3 more weakly and saturates at high levels (called the MR and GR receptors). The GR receptor is mainly expressed in the brain in the hippocampus, and in humans also in the prefrontal cortex. As a side remark, note that ultra-low levels of cortisol also cause depression-like symptoms of fatigue and cognitive defects, and can have lethal effects on the heart and other systems (called an Addisonian crisis). The organism seems to strive to keep x_3 at an optimal middle range [see Sapolsky's monumental book 'Behave' that amusingly discusses this knowledge].

Finally, drugs like SSRIs enhance h neurogenesis and functional mass, for example by increasing brain-derived growth factors like BDNF.

If we are talking about Sapolsky's book, it is interesting to note current understanding about the evolutionary advantages of depression. Research in primates and rodents shows that a male defeated by an alpha-male sometimes shows behavioral shut-down similar to depression. It is believed that this strategy helps avoid further damage and may save the organisms life.

We can now write down a full model with the HPA hormones and glands, and h . It turns out that it is enough for our purposes to consider just the adrenal gland A and the hippocampus h as variables that change in the slow timescale.

The equations can be found by averaging over the fast timescales of hours (quasi-steady-state approximation). The adrenal size changes under control of the hormone x_2 , giving our familiar equation from lecture 6 of cell proliferation minus removal:

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

the hippocampus cells originate from stem cells at rate c and are removed at an x_3 -dependent rate. We add here an important detail- the effect of x_3 through the GR receptor is very cooperative (steep). Thus, we can describe the effects of cortisol by a **step function** $\theta(x_3 > T)$. The step function equals zero if x_3 is below threshold T , and one if x_3 exceeds the threshold. This step function make sure cortisol doesn't kill neurons for mild stresses, only big ones. Thus,

$$\frac{dh}{dt} = D + c - (a + b \theta(x_3 > T)) h$$

Note that the production term is c , not c times h , because h cells come from stem cells; h cells don't make new h cells, unlike A cells which divide to make new cells. Since neurogenesis is enhanced by anti-depressant drugs, D , we will represent it by $c + D$.

We still need to write x_2 and x_3 in terms of A and h to have a closed system of equations. We know from lecture 6 Eqs. 1-3, that these hormones can be written as a function of gland sizes (here we use u/h instead of u to represent the effects of h):

$$x_2 = \left(\frac{u}{h}\right)^{1/3} A^{-2/3} P^{1/3}$$

$$x_3 = \left(\frac{u}{h}\right)^{1/3} A^{1/3} P^{1/3}$$

In our case, simulations show that $P(t)$ goes like $A(t)$, so we can plug in $P = A$ and find

$$x_2 \sim \left(\frac{u}{h}\right)^{1/3} A^{-1/3}$$

$$x_3 \sim \left(\frac{u}{h}\right)^{1/3} A^{2/3}$$

Thus,

$$(1) \frac{dA}{dt} = b_A A \left(\left(\frac{u}{hA}\right)^{1/3} - a_A \right)$$

$$(2) \frac{dh}{dt} = c - \left(a + b \theta \left(\left(\frac{u}{h}\right)^{1/3} A^{2/3} > T \right) \right) h$$

This is a circuit in which two organs mutually inhibit each other (Fig 7.10). Such a circuit is called a **toggle switch** in systems medicine. It has two states, in which the two organs have opposite sizes: either large A and small h , or vice-versa. The stress u and drugs D act to flip the switch. The timescale is composed of the turnover time of A , namely about 2 months, and the turnover time of h which includes synaptic-tree changes and slow neurogenesis- we don't know which is more important here. Some changes are reversible and others might be irreversible. So, we might say months or maybe years.

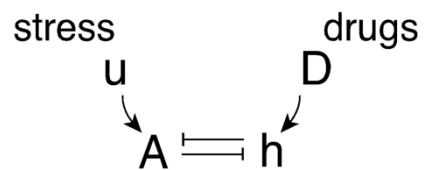


Figure 7.10

Some changes are reversible and others might be irreversible. So, we might say months or maybe years.

The toggle switch can show one or three fixed points, providing bistability

To understand the toggle switch, we can use the method of nullclines that we saw in the lecture on fibrosis. The nullclines are the lines where $dA/dt=0$ and $dh/dt=0$. They are helpful because their crossing points are the **fixed points** where neither h nor A change.

Let's start with the nullcline for $dA/dt = 0$. It is like enforcing a value of h and seeing the resulting steady-state of A . The solution from Eq 1 is $A = 0$. Another solution is found from the term in the parenthesis to zero, namely $(u/hA)^{1/3} = a_A$, giving the following inverse relationship between the organ sizes:

$$h = \frac{a_A^3 u}{A}$$

This is a hyperbola: larger A means smaller h . We can plot the nullcline in the phase plane (Fig 7.11). It divides the plane into a left side where A flows to higher values and a right side where A flows to lower values (arrows in Fig 7.11). This hyperbola shifts up when stress input u increases.

The nullcline for h is a step function that drops from a high value of c/a to a lower value of $c/(a + b)$ (Fig 7.12) at a threshold value of A ,

$$h = \frac{D + c}{a + b \theta(A > A_T)}$$

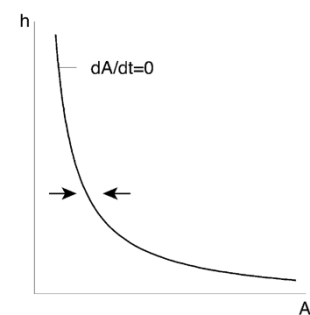


Figure 7.11

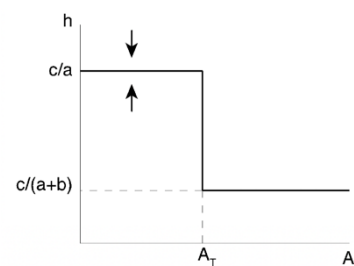


Figure 7.12

The threshold A_T is a function of stress and moves to the left when stress is high¹. Antidepressant drugs D move this nullcline up. The nullcline divides the plane into a lower part where h flows up and an upper part where h flows down, as can be seen by plugging in large and small values of h into Eq 2.

Now we can play with the intersection points of the nullclines. The two nullclines intersect at a single point (Fig 7.13) for certain ranges of the parameters a_A, c, a, b . This situation models people not prone to MDD.

For other parameters, the nullclines intersect at three points (Fig 7.14). There are two stable points with an unstable point in the middle (stability can be seen by understanding the direction of the flow arrows, according to the way the nullclines divide the phase plane). One stable point has large h and small A , which we call the **euthymic state**. The other fixed point has large A and small h - the **depressed state**.

The flow to these fixed points depends on where you start relative to the separatrix (dashed line in Fig 7.14). The separatrix divides the plane into two basins of attraction. Dynamics that start above the separatrix line flow to the euthymic state. Initial conditions below the separatrix flow to the depressed state. The flow takes weeks, according to the timescales of A and h .

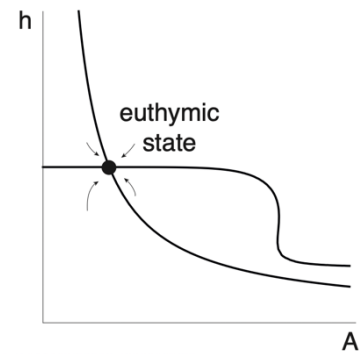


Figure 7.13

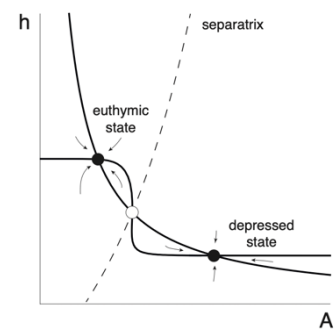


Figure 7.14

Chronic Stress can flip the steady-state into the depressed state

We can use the nullclines to see what the effects of prolonged stress are. Stress input u raises the A nullcline. Note that nullclines change instantaneously- they are simply lines of zero change. The dynamics changes over weeks: a fixed point from the previous nullclines is no longer a fixed point. The system moves away from it to the appropriate fixed point according to the new nullclines.

Enough stress causes the nullcline to move so much that the euthymic fixed point is lost. Now the only fixed point is a depressed state with low h and very high A . If stress input lasts long enough (weeks-months), the size of A grows and eventually crosses the old separatrix (Fig 7.15). The dynamics now flow to the depressed fixed point, denoted as point 2 in Fig 7.16. I say 'the old separatrix' because once the nullclines change, all the arrows change and the separatrix of before vanishes. The separatrix 'reappears' once you return to the old nullclines. Thus, if stress goes away, we return to the

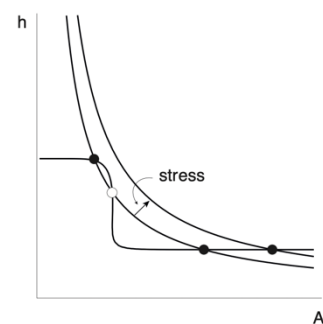


Figure 7.15

¹A step function has a slightly artificial property that the threshold A_T depends on h . Therefore, in the plots, we use a Hill function with Hill coefficient 4, which is approximately the steepness of the Gr receptor dependence on x_3 . Using a pure step function leads to a nullcline shaped like a Z.

original nullclines with their three fixed points. The organ sizes are now below the separatrix and flow to the depressed state (Fig 7.16 point 3). You are stuck in depression.

In this state, one must lower stress to very low levels for the dynamics to return to the euthymic state. This results in a hysteresis phenomenon, as in Figure 7.15. For certain parameters, it may be impossible to exit the depressed state by lowering u because u needs to go to unphysiologically low values.

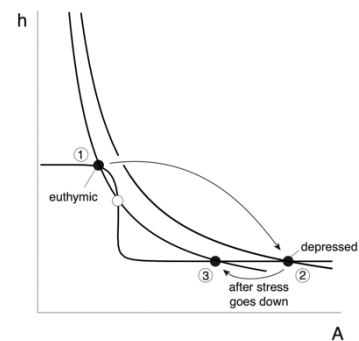


Figure 7.16

If stress is transient, a person starting at the euthymic state 1 will flow away during stress but will not cross the separatrix. The dynamics flow back to 1 after the stress input is reduced. In the case of a single fixed point (person not prone to MDD, Fig 7.13), prolonged stress will result in a flow away from euthymic state, but the dynamics flow back when the prolonged stress is gone, because the nullclines have only a single crossing point at low stress.

Antidepressants can remove the depressed fixed point but only if used for weeks

Let's now analyze the effect of antidepressant drugs D . The drugs move the h nullcline up. If their effect is large enough, this results in a single, non-depressed fixed point with low A and high h (Fig. 7.17). Technically, as D is raised, the depressed and unstable fixed points move closer, collide and annihilate in what is called a saddle-node bifurcation. The dynamics start to flow towards the one remaining fixed point.

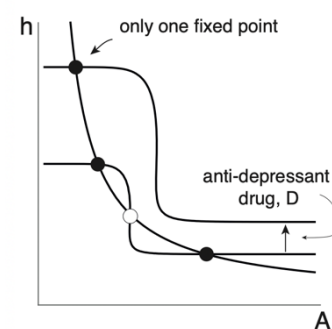


Figure 7.17

If the drug is taken only for a few days, and then stopped, the nullclines return to the three-fixed-point configuration, and the flow is back to the depressed state.

If the drugs are taken for weeks, however, the flow can cross the old separatrix. Then, even if you stop taking the drugs, the flow is towards the euthymic state. There is recovery.

The simulations of a full model with all glands and hormones supports these conclusions (appendix).

The model and inter-personal variability

The model shows bi-stability and transitions between the fixed-point following stress and antidepressants. But these properties depend on parameters. Individual probably differ in the values of their effective parameter values, a_A, a, b and c in Eq 1-2. Different parameter regimes give different behaviors. With some parameters the model has only a single fixed point. Such parameter values suggest that some people are less prone to depression, even in the presence of stressors. In another parameter range, depression can occur after persistent stress input. Antidepressants can have a positive effect if taken for long enough, but depression can relapse after treatment stops. For some parameters, antidepressants don't work at all, or work but need to be taken indefinitely. Such situations unfortunately occur in many patients.

Part of the variation in parameters is due to genetic differences. Genetic variations correlated with MDD are numerous, and each variant has a small effect, as is the case in diseases except rare single-mu.

An interesting fact is that depression is more common in women. This may be due to higher stresses faced by women due to psychosocial and cultural reasons, perhaps resulting in their slightly higher average cortisol (351 nmol/L vs 337 nmol/L) (Fig. 7.18). The model suggests an additional, biological, viewpoint. In many organs including the HPA axis glands and h, there are more cell proliferation events in women than in men due to regulation during the menstrual cycle.

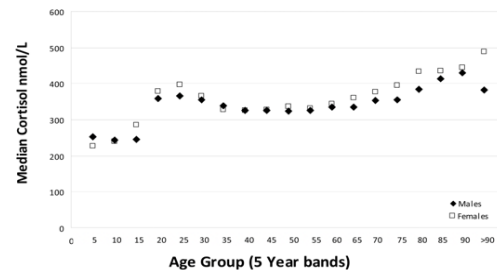


Figure 7.18

This regulation is thought to allow allostasis- an adaptation of organ size and activity to meet different needs in the reproductive cycle. This effect can mean a difference in proliferation-related parameters such as c and a_A . A similar effect can explain why women have more autoimmune diseases of the types studied in lecture 3: higher proliferation in the endocrine glands means more mutations, and thus greater need for immune surveillance ASHM (which we will discuss in one of the upcoming lectures), and thus more probability of autoimmune disease (AID). Interestingly, this idea predicts that there are also more hypersecreting- mutant expansion-diseases in organs without AID such as the pituitary gland and parathyroid. This prediction is confirmed by the higher female prevalence of these hypersecretion diseases. Here we come into the realm of gender medicine. In the past, many studies were on men and drugs were prescribed as if men and women had the same physiology. In recent decades, research has increasingly focused on sex differences and differential treatment. Let's celebrate gender medicine: this year is 100 years to women's vote (Fig 7.19).



Figure 7.19

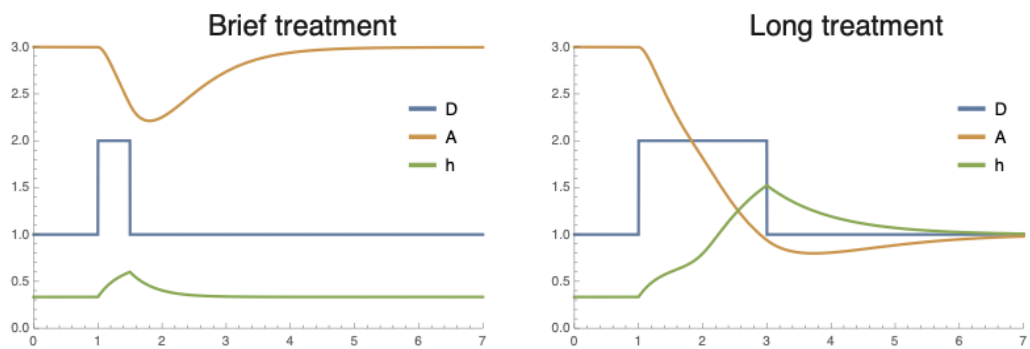
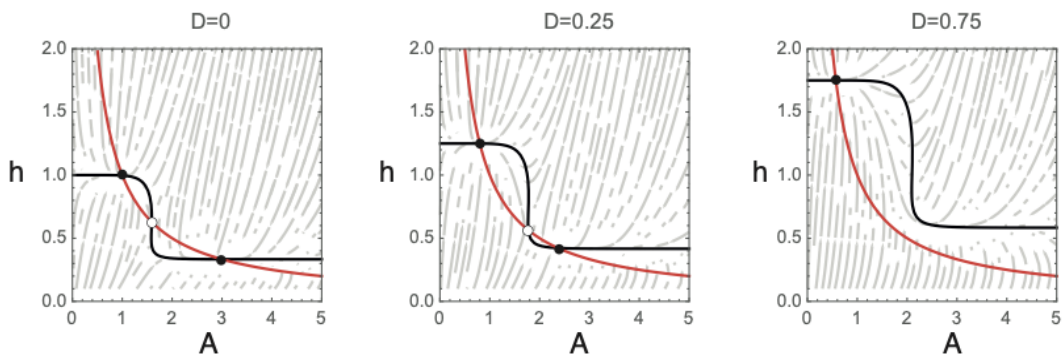
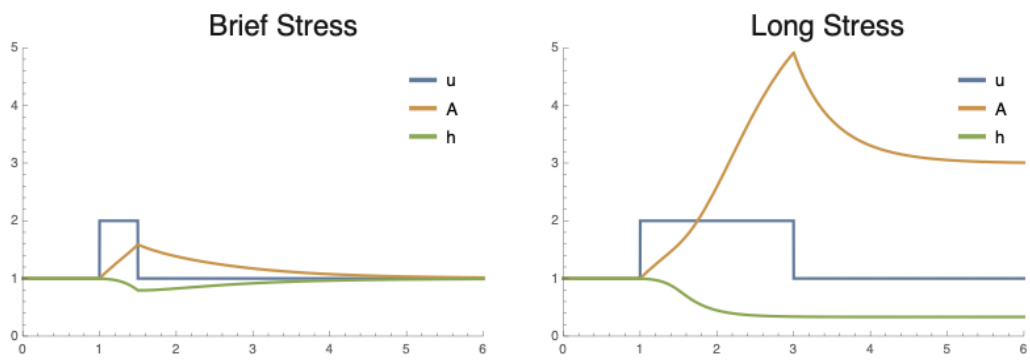
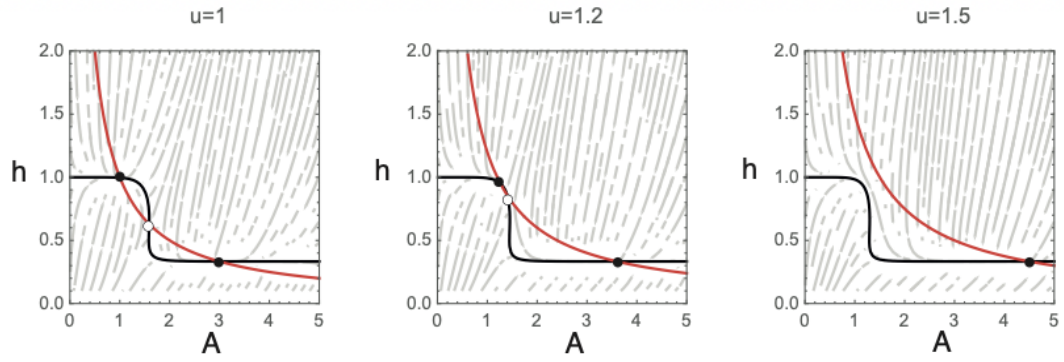
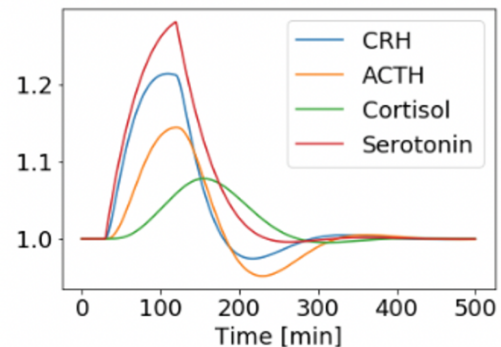


Figure 7.20

Appendix

SSRIs increase HPA activity

Although depression is characterized by higher HPA activity. Paradoxically antidepressants increase HPA activity in the short term [REF]. Our model suggests that this effect is separated from their long-term therapeutic effect. The short-term increase comes from the effect of serotonin on HPA activity and CRH secretion, while the long-term reduction of HPA activity, which we relate to the therapeutic effect of SSRI, comes from the positive effect of serotonin on the hippocampus, which down-regulate HPA activity. Besides the long-term reduction effect seen above, the model predicts a short-term increase of HPA activity following an antidepressant treatment.



Depression as an age-related disease:

With age, neurogenesis rates drop, so c drops. Similarly, a_A rises (this parameter is the ratio of adrenal cell removal and proliferation). Such changes can turn a mon-stable system to a bistable system, because they lower the step-like nullcline and raise the hyperbolic nullcline so that they are more likely to intersect three times. Indeed, cortisol rises on average with age.

Thus depression could be a threshold-crossing phenomenon, with MDD vulnerability arising if proliferation rates drop below a threshold. As we saw in that lecture, senescent cells lower cell proliferation rates. SnC occur also in the brain, primarily in the supporting cells called glia which, in contrast to most neurons, show sizable turnover. Thus, the stochastic process for SnC, together with the threshold crossing feature of depression in this model, can provide an exponentially rising incidence of depression with age, as observed.

References:

Saplosky: Zebras get ulcers

Sapolsky: Behave

Osmosis video: Major depression

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