Systems medicine Lecture notes

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Lecture 5

Addiction

Addiction is a world epidemic

Addiction to substances causes suffering and dysfunction in relationships and work. In addition to ruining a person's enjoyment of life, addiction can end life by overdose. Major addictions include abuse of alcohol, cocaine, nicotine and amphetamines. Addiction to opiates, including heroin and prescription painkillers, has quadrupled in the past 20 years, and opiate overdose is a leading cause of death for teenagers (Fig 5.1). Diseases associated with alcohol (heart disease, liver fibrosis) and smoking (lung diseases, cancer) are major killers of adults. The economic costs of addictions exceed the costs of all diabetes and cancer combined.
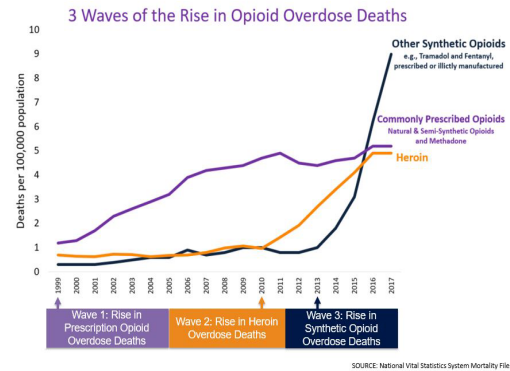

Figure 5.1

I tried to find songs about addiction for this lecture; it was actually hard to find songs *not* about addiction. J.J. Cale (Fig 5.2) wrote

> *"If you want to hang out,*
>
> *you got to take her out, cocaine.*
>
> *If you want to get down,*
>
> *down on the ground, cocaine.*
>
> *She don't lie, she don't lie she don't lie,*
>
> *cocaine."*

By "she don't lie" he might have meant that the addict's world view shrinks to the one truth of obtaining the substance. Things you once enjoyed, like hugs and chocolate, don't bring as much joy anymore.

Figure 5.2

Addiction shows a universal curve

Different addictive substances work in different ways on the brain. Despite these differences, they all share a temporal sequence. In this **universal addiction curve** (Fig 5.3) time is on the x axis and craving is on the y axis. At first there is the **initiation** phase. The substance produces a sense of **euphoria -** an emotional high. This creates **positive reinforcement**, an urge to use the substance again.
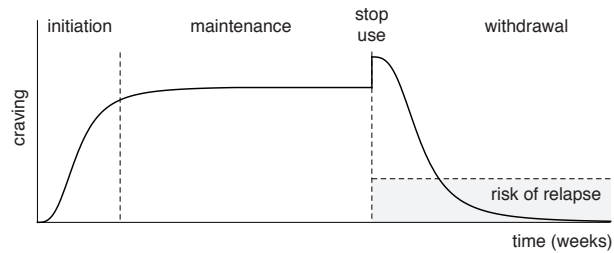

Figure 5.3

The euphoria only lasts a few weeks. Now, to gain the same euphoria one must increase the dose. This is called **tolerance**. Stopping to use the substance causes awful symptoms called **withdrawal** symptoms. These include anxiety, depression, tremors, pain and vomiting. To avoid withdrawal symptoms, one needs to keep taking the substance just to feel normal. This is the **maintenance** phase. Now one is dependent on the substance, fully addicted.

Maintenance is thus reached because of two types of reinforcement: positive reinforcement due to euphoria, in which the person learns to seek the substance, and negative reinforcement due to withdrawal symptoms, in which the person learns to use in order to avoid feeling awful.

The last phase occurs when one stops using, the **withdrawal phase**. In the first few hours and days withdrawal symptoms are very strong. They then reduce in intensity but persist for several weeks. Then there is apparent recovery. The next few months are a sensitive period that has risk of relapse - going back to use. After a year or so the person has adapted and craving is gone. There is a lifelong risk of relapse, however, especially in times of stress or when the people and places from the maintenance period are revisited.

Treatment for withdrawal includes therapy, peer-groups that provide commitment and hold a person accountable, and motivational interviewing which can identify each person's motivations and obstacles for recovery. Medications also help, such as medications that block the opioid receptors.

Thus, rehab centers typically take the person for several weeks to match the timescale of withdrawal - such as the 70 days in the song by Amy Winehouse (Fig. 5.4)

"They tried to make me go to rehab

I said, "no, no, no"

Yes, I've been black

But when I come back, you'll know, know, know

I ain't got the time

And if my daddy thinks I'm fine

He's tried to make me go to rehab

I won't go, go, go

I'd rather be at home with a Ray

I ain't got seventy days"

Figure 5.4

In this lecture we would like to understand the addiction universal curve. What is the origin of the different phases? And where does the timescale of weeks for tolerance and withdrawal come from? This timescale is puzzling because the effects of the substances on neurons, neurotransmitters and receptors are reversed within hours to days after stopping use.

Addictive substances act on reward centers of the brain

The mechanism for each substance is different. They all work on reward centers in the brain. There are two kinds of reward systems and two kinds of pleasure. The first is the anticipation of reward, governed by the dopamine system. The second is the satisfaction of the rewarding behavior or substance, driven by **beta-endorphin**. Beta-endorphins are made after exercise for example, contributing to 'runners high', or during the fight-or-flight response, to act as painkillers and euphoria-generators.

Drugs that work on the anticipation system, like cocaine, give an alert feeling of being in control; those that work on satisfaction like morphine and opiates have a calming, sleepy satisfied effect. They help transiently avoid two kinds of negative emotions: helplessness and despair for cocaine, pain and hunger for heroin.

Let's focus on opiates, the most addictive substances, including heroin and morphine. Opiates bind to opiate receptors on neurons –the receptors that normally bind beta-endorphin -and modulate their function. They inhibit neurons that inhibit other neurons that produce dopamine in reward centers of the brain. This effect leads to euphoria. They also act on neurons in pain centers in the brain and spinal cord - and there, opiates act as **pain killers**.

Beta-endorphin is thus a natural endogenous morphine. External opiates include the addictive substances made by poppy plants, opium and its derivative heroin. In this way, plant mimic the endogenous molecules to manipulate animals. Synthetic opiates are taken as powerful painkillers. They are extremely addictive because the reward centers signal the person to learn to take them.

Other substances also affect neurotransmitters. Cocaine increases the concentration of dopamine and other neurotransmitters in reward centers by a different mechanism from opiates- cocaine inhibits reuptake pumps (like SSRI drugs for depression). Alcohol increases the effect of dopamine and other
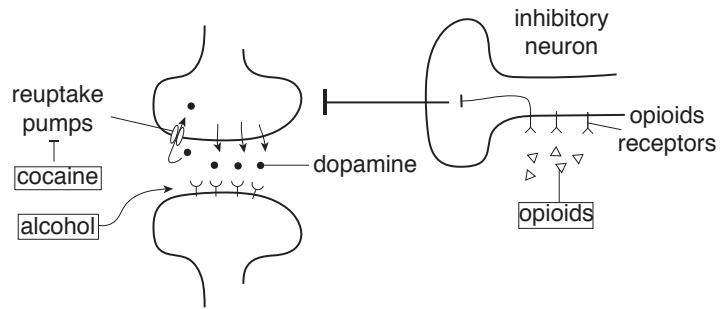

Figure 5.5

neurotransmitters by yet other mechanisms, such as enhancing receptor binding.

Tolerance means that the dose needed for euphoria gradually rises

A universal feature of addiction is **tolerance**, in which the dose needed for the same effect gradually rises after a few weeks. The response to a given increase in dose shows diminishing returns. Going from average use level 1 to 2 and then from 2 to 3 shows smaller and smaller pulses of euphoria (Fig 5.6).
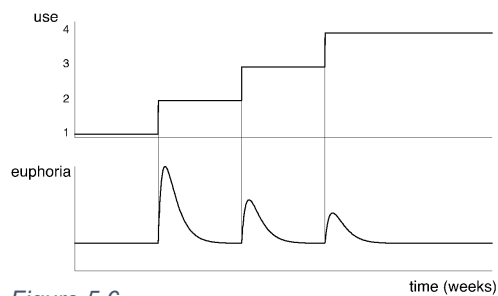

Figure 5.6

That is why drug users increase the dose, until hitting a maximal tolerable level (or money runs out). But constant euphoria is never attainable. As Muddy Waters sings (Fig. 5.7)

> "If the river was whisky, and I was a diving duck,
>
> If the river was whisky, and I was a diving duck,
>
> Id dive right to the bottom, never would I come up."

Figure 5.7

Theories for tolerance focus on receptor downregulation, but this cannot explain the timescale of weeks

The current theory for tolerance is that excess amounts of neurotransmitter X such as dopamine causes the receptors for X to be removed from the cell surface, or chemically modified to bind X more weakly. This is called **receptor downregulation**. Thus, the cells adjust their sensing of X to restore homeostasis of activity levels.

Receptor down-regulation takes hours, and is reversible: once levels of X go down again, receptors return to their normal levels within hours to days.

Such receptor downregulation can explain the early effects of withdrawal: after a long period of use, there remain very few receptors on the neuron surface. Stopping use makes X levels go down to normal. But there are so few receptors that this level of X translates to sub-normal neuronal activity. It takes hours to days for the receptor numbers to adjust and activity to return to normal.

The receptor theory explains the strong symptoms in the first hours and days of withdrawal. But it cannot explain why it takes weeks for tolerance to develop in the initiation phase and why withdrawal symptoms last for weeks. We need a slower physiological process with the timescale of weeks. Our explanation, as in the previous lecture, will focus on the HPA pathway.

All addictive substances activate the HPA pathway

A common feature of all of the addictive substances is that they activate the HPA axis, by making neurons in H secrete the hormone x_1, CRH. This includes nicotine, alcohol, opiates, cocaine, amphetamines and cannabinoids (Fig 5.8). Each substance activates the HPA axis by a different mechanism. The activation is substantial: people with alcohol abuse show about 3 times more average cortisol (averaged over weeks using hair cortisol measurements) than controls.
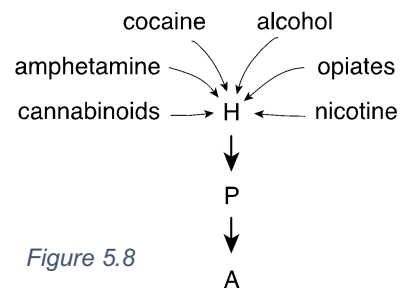
Figure 5.8

The HPA axis plays a key role in addiction because **HPA is a major producer of beta-endorphins.** The hormone x_1 causes the pituitary P to secrete hormone x_2, and at the same time, to secrete beta-endorphin (Fig 5.9). This linkage is because x_2 and beta-endorphins are both made from the same precursor protein called POMC (Fig 5.10). This precursor protein is cleaved by special enzymes in the cell to make x_2 and beta-endorphin. The evolutionary rationale is that responses to events that stimulate HPA activity, such as exercise and fight-or-flight threats, benefit from the pain killing and euphoric effects of beta-endorphins along with the effects of cortisol.
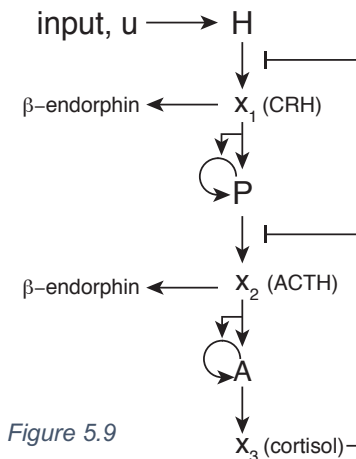
Figure 5.9

The rewarding effects of beta endorphin contribute to positive reinforcement: the person learns to seek the substance during the initiation phase.

From now on, we will use the fact that x_2 and beta endorphins are produced in a 1:1 ratio, and consider the dynamics of beta-endorphins produced by P as equal to that of x_2 in the model. In addition, x_1 (CRH) also induces production of endorphins in the brain, made by POMC neurons (Fig 5.10).
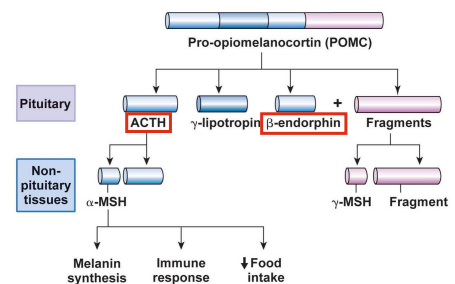
Figure 5.10

HPA is deregulated during addiction, with a blunted x_2 response

During addiction and withdrawal, experiments show that the HPA pathway is deregulated. This is best seen using classic test of the HPA axis, called the **CRH test**. Hormone x_1 (CRH) is injected, and hormones x_2 and x_3 are measured at several time points over the next two hours (Fig 5.11). In control subjects, both x_2 and x_3 rise after the x_1 injection (time of injection is shown by an arrow in Fig 5.11), and then decay after an hour or so. In people in the maintenance phase of addiction, or right after stopping use (acute withdrawal), cortisol x_3 is higher than normal, reflecting the activation of the HPA pathway. In contrast, x_2 responses are lower, a so-called "**blunted response**". This indicates that a given

Figure 5.11

stimulation of the axis provides a lower beta-endorphin reward. This blunted response is the basis for the reduced pleasure from things that used to give joy that is experienced during addiction. This reduction is called **hedonic dysregulation.**
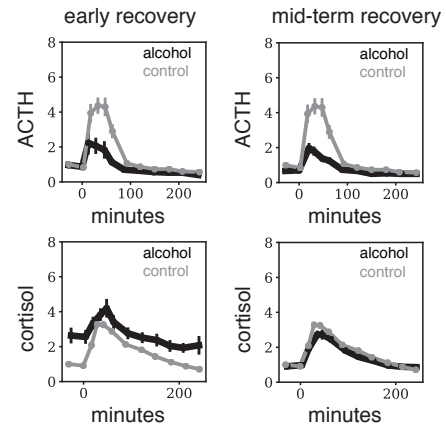
After about a month into withdrawal, the CRH test shows that x_3 returns to normal. Interestingly, x_2 is still blunted (Fig 5.11, right hand panels). This phase is called mid-term abstention. Only after 6-9 months does x_2 response also return to normal, and the axis is no longer dysregulated.

HPA dynamics show long-lasting tolerance with fold-change detection

Addiction can thus be modelled as a chronic increase in the average input to the HPA axis, u. We can think of a long constant input of u averaged over weeks. Solving the model on the slow timescale of weeks shows that the hormones x_1, x_2 and x_3 rise (Fig 5.12). Within weeks, however, x_1 and x_2 both return to baseline despite the increased input u. This feature is called **exact adaptation.**

The important meaning of exact adaptation for addiction is that the euphoria produced by the substance lasts only for a few weeks. Euphoria gradually diminishes and then vanishes because x_1 and x_2 levels adapt, and with them the levels of beta-endorphins, despite the continued presence of stimulus u. This aligns with is the phenomenon of tolerance.

The reason for exact adaptation is the growth of the glands A and P (Fig 5.12), which makes x_3 rise to exactly shut off x_2 back to baseline. The timescale of the glands, on the order of weeks, explains the slow timescale of tolerance.
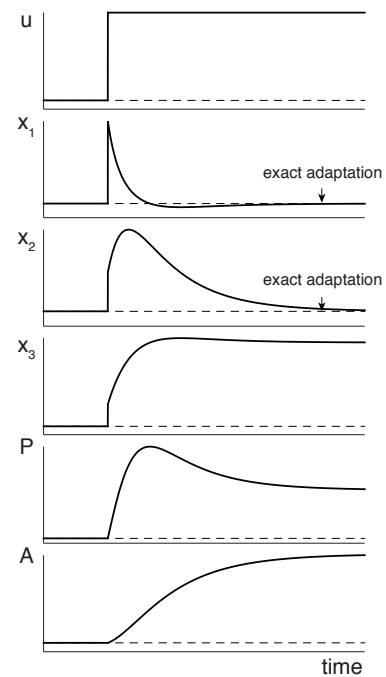

Figure 5.12

Mathematically, exact adaptation of x_2 arises from the equation for the size of A. The cells in A proliferate and are removed, just like the beta cells of lecture 3. Proliferation rate p depends on x2, $p_A = a_A x_2$, and removal rate is constant in this system, $r_A = b_A$. Thus, the change in A total mass is $\frac{dA}{dt} = p_A A - r_A A$, which can be written, by taking A out of the parentheses:

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

The only way to reach steady-state is the term in the parenthesis equals zero. Thus, x_2 returns to its baseline level, $x_2 = b_A/a_A$. When substance is used, x_2 initially rises above baseline making A gland grow (positive dA/dt). The growth of A makes cortisol levels rise, which inhibits x_2 production and makes x_2 return to baseline. A similar equation guides x_1 to adapt back to its baseline, $dP/dt = P(a_p x_1 - r_P)$.

What happens if the substance dose is further increased? Increasing dose leads to a new pulse of x_2, which also eventually adapts. The response to a given increase in dose shows diminishing returns. Going from input level 1 to 2 and then from 2 to 3 shows smaller and smaller pulses of x_2- we saw this graph before when discussing tolerance (Fig 5.6).
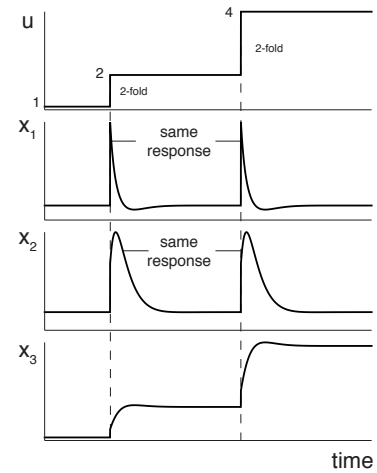
The HPA circuit shows that in order to recover the same euphoria, one needs to increase input u to ever larger doses. In fact, one can show that the HPA circuit shows response to *relative* changes: the x_2 pulse is the same only when the dose is increased by the same factor. To replicate the pulse of x_2 due to a rise of u from 1 to 2, one needs to raise u from 2 to 4 (Fig 5.13). Both steps have a two-fold change. This feature is called **fold-change detection.** Thus, to maintain euphoria requires an exponential increase in dose, from 1 to 2 to 4 to 8 to 16 and so on. Such an exponential increase cannot last long because it eventually hits a ceiling of toxicity.

The origin of fold-change detection in the HPA axis is that the cortisol level is proportional to the steady -state level of input. A new input step needs to overcome the inhibition of the high level of cortisol on x1 and x2 production. Mathematically, the equation for x1 shows that the input u is divided by x3,

$$\frac{dx_1}{dt} = \frac{q_1 u}{x_3} - a_1 x_1$$

Figure 5.13
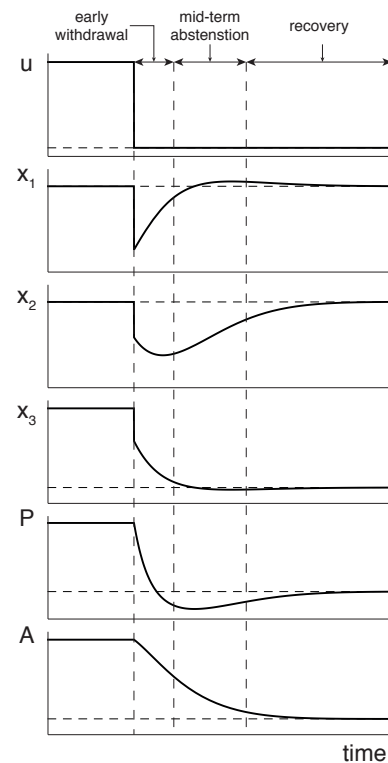

Figure 5.14

And thus the circuit tracks u/x3, and since x3 is proportional to u_{st}, it tracks $u(t)/u_{st}$ and responds to fold-changes in input relative to background input.

Fold change detection (FCD) is an important property fond in biological sensory systems. It is found in senses like vision and hearing, and in the chemical senses of cells. For example, sound is measured in decibels- we respond to relative changes in sound intensity. For a review of FCD in biology see (Adler, 2018). The full mathematical explanation is given in Appendix A.

The HPA model shows withdrawal that takes weeks

To model withdrawal, we set u back to normal levels after a long period of high u. The HPA axis glands now gradually adapt back to normal size over months (Fig 5.14). Interestingly, the P gland adapts faster and reaches its baseline in weeks while A is still large. P then shows an undershoot, creating a period of months where A is normal but P is small. Then P adapts and the HPA axis is fully normal. This is reminiscent of the previous lecture, with the metaphor of pulling the damped spring and letting it go.

This dynamic creates two phases of withdrawal. In the first, early withdrawal, both x_3 and x_2 are dysregulated, with high x_3 and blunted x_2 as found in the CRH test (Fig 5.11 mid panel). In this phase, withdrawal symptoms are most severe. The timescale of weeks arises from the time it takes A to normalize. This corresponds to the 70 days of rehab in the Amy Winehouse song.

A medium-term withdrawal phase has normal cortisol but blunted x_2.

The second withdrawal phase (Fig 5.14) is new and is an unexpected prediction form the model. The second phase begins after A normalizes, and while P is still in undershoot, and can last months. In this phase, x_3 responses are normal, but x_2 (and hence beta endorphin) is blunted. Therefore one expects hedonic dysregulation, where a stimulus u gives less beta endorphins than normal. There is less enjoyment of things that used to give joy.

One may speculate that this midterm withdrawal phase is prone to relapse. Low endorphins may cause anxiety and pain. Since endorphins are low, a person might seek ways to simulate the HPA pathway to recover x_2 levels- namely returning to the habit of use.

The HPA model can thus provide a mechanism for why withdrawal takes many weeks, and point to a new sensitive second withdrawal phase.

Relapse may be triggered by people and places associated with previous substance use

This section is a walk down tangent boulevard. The brain has a clever way to react to habits of substance use. Consider alcohol, which acts to lower heart rate and blood pressure. If a person has a habit of drinking at a given time and place, say 6pm in the living room, the brain learns that pattern. At 6pm in the living room the brain raises heart rate and blood pressure, to counter the expected effect of alcohol, and thus to maintain homeostasis. With cocaine which raises heart rate, the brain instead lowers heart rate at the habitual time and place.

If now a person at 6pm in the living room has no alcohol, the brain still raises heart rate and blood pressure. This feels awful, and creates negative reinforcement to seek alcohol.

Conversely, if alcohol is consumed at an unfamiliar time and place, say at midnight at a party, there is no compensation by the brain. The amount that one usually drinks at 6pm can now cause an overdose.

Finally, if a person has recovered and stops drinking, but returns to an old situation associated with drinking, the brain might again cause the compensation, and the person will feel awful and might be tempted to return to drink. Of course, the psychology of all this is much more complicated than this discussion. Now we return to the main avenue of the lecture.

Addiction is the dark side of a stimulation-taxis function of the HPA axis

In this course we like to think of each pathological condition as a fragility of an essential physiological process. In the case of addiction, this essential process is the ability of the HPA axis to search for beneficial behaviors.

Let's start with the fact that cortisol levels have an optimal middle range, as described by the inverse-U-shaped curve of the previous lecture (Fig 5.15). Low levels of x_3 cause fatigue and depression, mid-levels generate energized and concentrated focus, and very high levels cause depression and anxiety. Thus, organisms seek behavior that leads to stimuli u that keep cortisol at its optimum, namely challenging yet rewarding behavior.
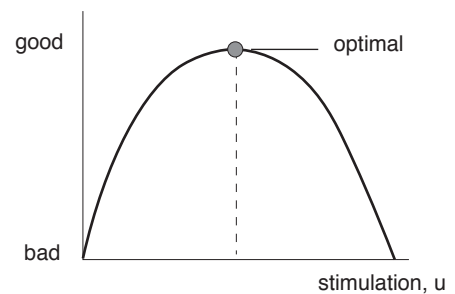

Figure 5.15

What system can guide behavior towards the goal of optimizing u? This search problem can be thought of as a search in a hypothetical **space of behaviors**. One seeks the region of behaviors that provide optimal u. Each behavior in this space brings some averaged stimulation input u, and thus u can be plotted in this space as a kind of topographical map with hills and valleys (Fig 5.16 shows a hill with the optimum at the top). Finding the best behaviors means climbing gradients of u in behavior space.
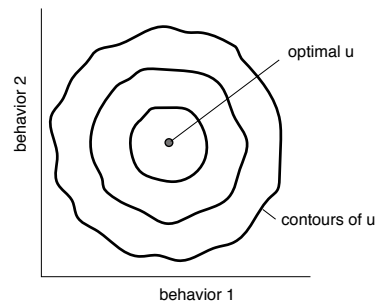

Figure 5.16

An analogous search problem is solved by bacteria. Bacteria are single-celled organisms that can swim in search of food and other attractant chemicals, and swim away from noxious chemicals. Bacteria detect attractants using receptors, and can climb spatial gradients of attractant. For example, if a pipette with attractant such as the amino acid aspartate is placed in a dish of bacteria, they swim and accumulate in the pipette. This process is called **chemotaxis**: you call a taxi and say 'follow that chemical'.
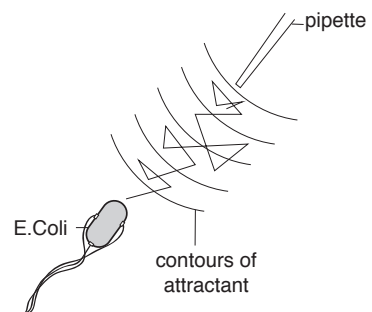
Bacteria achieve this feat despite huge challenges: they are so small that if they try to swim straight for ten seconds, Brownian noise deflects them by 90 degrees on average.

Figure 5.17

They have no notion of where they are. They are too small to sense gradients across their one-micron body. But still they accurately find the pipette across five orders of magnitude of attractant concentrations, climbing tiny gradients as small as one molecule in a thousand difference between their head and tail.

Bacteria perform chemotaxis using a simple algorithm: if things get better, don't change direction. If things get worse, randomly change direction. They can control only the frequency at which their motors make random changes of direction. Thus, bacteria do a random walk, swimming for about a second and then changing directions randomly in what is called a **tumble** (Fig 5.18). They measure the temporal changes in attractant levels. If attractant rises with time, they suppress the tumbling frequency and keep swimming in the same direction. If attractant levels drop with time, they tumble, hoping to return to the right direction.
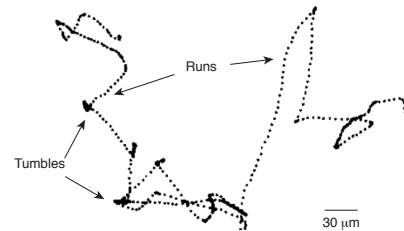

Figure 5.18

Bacteria do chemotaxis using a biochemical circuit inside the cell that analyzes the input from the receptors. The chemotaxis circuit is one of the best understood circuits in biology, and figuring out how it works was one of the pioneering accomplishments of systems biology. Bacteria use separation of timescale, with a slow process that accumulates to provide exact adaptation and fold-change detection of attractant stimuli.

Thus, an experiment that provides a step of attractant makes bacteria stop tumbling no matter what direction they are headed (Fig 5.18). Then after a few minutes, bacteria realize they have been fooled and start tumbling again. They response to a step of input with a pulse of output (tumbling frequency), showing exact adaptation.

In fact, the equations for the biochemical circuit inside the bacteria are *mathematically identical* to equations in the model for the HPA axis. In bacteria, the receptor binding constant K for attractant can be tuned by a slow process of receptor modification called methylation that takes minutes. The equation for K is $dK/dt = K(x - a)$, where x is the tumbling frequency. This provides exact adaptation of x back to a. An analogous slow variable in the HPA axis is the gland size A, governed by the equation $dA/dt = A(a_A x_2 - r_A)$, with a timescale of weeks.
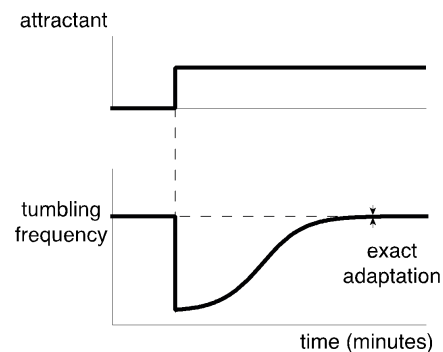

The exact-adaptation feature allows both the HPA axis and bacterial chemotaxis to convert a step change of input u into a pulse (Fig 5.19). This effectively computes a temporal derivative. Thanks to fold-change detection, the temporal derivative is actually of $log(u)$, allowing search over a very wide dynamic range.

Figure 5.19

The endorphins secreted by the HPA axis make sure that a person learns rewarding behaviors. This learning over weeks guides behavior up the increasing arm of the inverse-U shaped curve to optimal stimulus levels. This search process may be called **sitmulotaxis**. This may be a case of

convergent evolution- very different systems converge on a similar mathematical solution to a shared problem. If you want to know more about bacterial chemotaxis, check out lecture notes 6 and 7 from my course Systems Biology.

What about too high levels of stimulation? If behaviors reach too high stimulation, such as unrewarding dangerous behaviors, other processes kick in, described in the previous lecture, including anxiety and depression. These processes are guided by the GR receptor that detects very high levels of cortisol. Depression and anxiety tend to shut down the exploration of potentially dangerous behaviors such as attacking the alpha male baboon.

Thus, the HPA axis provides a navigation system in behavior space. This navigation system can be hijacked by substances which provide pleasure and induce endorphins by activating the HPA axis over a timescale of weeks. The person learns to increasingly seek substance use, with the dire consequences of addiction.

Appendix: Fold change detection in the HPA axis

Fold change detection (FCD) of a variable y(t) in a system with input u(t) means that starting from steady-state, the dynamic response of y(t) to a given input u(t) is exactly the same as the response to the same input multiplied by a constant, λ u(t), with $\lambda > 0$. Thus, a step from input 1 to 2 gives exactly the same y(t) as a step from input 2 to 4, because the second step is twice the first ($\lambda = 2$). A step from 1 to 3 will give a different response, which is the same as the response to a step from 3 to 9 (here $\lambda = 3$).

All systems with FCD show exact adaptation of y(t) (but the reverse is not true, for example linear integral feedback has exact adaptation but not FCD).

In this appendix we will show that the HPA model has FCD for the variables x_1 and x_2. Our strategy will be to use **scaled variables** to arrive at equations that do not depend directly on input u(t), but rather on its **fold-change** relative to steady state, $F(t) = u(t)/u_{st}$. The initial conditions and the equations will depend only on fold change in input, F, and thus the entire dynamics will depend only on fold change.

The HPA model equations from Lecture 4 (notes) are:

$$\frac{dx_1}{dt} = q_1 \frac{u}{x_3} - a_1 x_1$$

$$\frac{dx_2}{dt} = q_2 \frac{P x_1}{x_3} - a_2 x_2 \ ,$$

$$\frac{dx_3}{dt} = q_3 A x_2 - a_3 x_3$$

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

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

The steady-state solution for a constant input u_{st}, as in the previous lecture, show that x$_{1,st}$ and x$_{2,st}$ do not depend on u_{st} whereas x$_{3,st}$, P_{st} and A_{st} are linear in u_{st}. For example, in the dA/dt equation, $x2 = a_A/b_A$, which is independent on u_{st}.

We next construct new equations by changing the variables. Let's assume the system is at steady state for an input u_{st}. Our goal is to get rid of all traces of u from the equations. Since steady-state

P,A and x3 rise linearly with u_{st} , we normalize them by u_{st}, and thus define $\hat{x}_1 = x_1$, $\hat{x}_2 = x_2$, $\hat{x}_3 = x_3/u_{st}$, $\hat{A} = A/u_{st}$, $\hat{P} = P/u_{st}$. We can plug in the new variables to the HPA model equations, to obtain scaled equations. These scaled equations are identical to the original equations, except that instead of input u, they contain the fold-change, $F = u/u_0$.

$$\frac{d\hat{x}_1}{dt} = q_1 \frac{F}{\hat{x}_3} - a_1 \hat{x}_1$$

$$\frac{d\hat{x}_2}{dt} = q_2 \frac{\hat{P}x_1}{\hat{x}_3} - a_2 \hat{x}_2 \;,$$

$$\frac{d\hat{x}_3}{dt} = q_3 \hat{A}\hat{x}_2 - a_3 \hat{x}_3$$

$$\frac{d\hat{P}}{dt} = \hat{P}(b_P \hat{x}_1 - a_P)$$

$$\frac{d\hat{A}}{dt} = \hat{A}(b_A \hat{x}_2 - a_A)$$

The initial conditions (steady-state conditions) for the scaled equations do not depend on absolute input level u_{st}. This is because, as mentioned above, x_1 and x_2 do not depend on u_{st} whereas x_3, P and A are linear in u_{st}. We conclude that since both the equations and the initial conditions depend only on F, so does the entire dynamics. Going back to the original variable, we see that $x_1(t)$ and $x_2(t)$ depend only on fold-change in input, whereas $x_3(t)$, A(t) and P(t) depend on the absolute input level.

To explain intuitively how FCD works in this model, we note that A, P and x_3 act as buffers that can normalize out the input absolute level. The size of A grows proportionally to the mean steady state input. As a result so does cortisol x3. Since cortisol divides out x1 production term $dx1/dt = q1\,u/x3$, it normalizes out the input u(t) by the background input. Mathematically, FCD occurs because of the special shape of the equations. For example, because all cells come from cells the equations for A and P have A and P are outside the parentheses.

Exercises:

5.1 **Initiation after withdrawal**: Discuss the duration of the initiation phase if relapse occurs during acute withdrawal (a few days after withdrawal) versus after total recovery.

5.2 **Dual addiction**: suppose that two substances activate the HPA pathway. The doses taken are D_1 and D_2. The effect on the HPA axis is $u = (1 + D_1)(1 + D_2)$, where $u = 1$ is the baseline input before addiction.

(a) Discuss how the two substances affect each other's tolerance and withdrawal.

(b) What is the effect of stopping one substance while still using the other?

5.3 **Placenta**: During pregnancy, the placenta secretes x_1 (CRH) in an exponentially increasing concentration with time. What is the effect on x_2 and x_3? Is there exact adaptation? What is the evolutionary advantage of this exponential rise in terms of providing the mother and infant with increased cortisol and beta endorphins? What do you expect happens after birth when the placenta exits the body? Read about cortisol binding globulin (CBG) and pregnancy. How could this affect the answer?