THE STRANGE CASE OF COCAINE, BACTERIA AND DIABETES

Can you imagine a possible connection between drug addiction, population growth and type 2 diabetes? Even though it may seem difficult to unveil, the solution is a renewed mathematical equation, which we will discover later on, after having introduced and explained some key features of the three mentioned phenomena, in order to have a better catch on the fundamental rule that regulates their functioning.

Let's take a closer look, first of all, to what happens to the brain of a drug user and why is it possible for a drug to cause such strong and addictive effects on it. When a chemical substance enters the organism, it can access the blood flow and be carried by it: in general, the molecule reaches the central nervous system rapidly and, if it is sufficiently small or has high affinity for some carriers in the blood-brain barrier, it can get to neurons and interact with them. Actually, only a few chemicals are able to access directly the soma (or principal body) of a nerve cell: it is more common that the particle reaches and binds to the receptors that the cell exhibits. Interacting with them, the agent is able to trigger a neural response, which consists in the release of neurotransmitters and in the transmission of an action potential, a sort of electrical discharge that activates a brain pathway. When a drug (for simplicity, we will consider cocaine) gets inside the organism, the cascade of cerebral events that are started generally involves a massive emission of dopamine: in the case of cocaine, the *dopamine rush* is almost immediate, and the person, along with a sense of almightiness and overexcitement, feels an irresistible pleasure, which is several times higher than the one that can be experienced with everyday activities. This mechanism is actually the one causing addiction: the cocaine user seeks for the same sensation perceived the first time, and this leads the person to new encounters with the drug. Nevertheless, after a certain time of substance abuse, the cocaine addict starts to suffer from a sort of dissatisfaction with the activity, and this fact brings him/her/them to a continuous state of need and a constant increase in the dose of drug which is able to fulfil this necessity. This is due to the fact that, having cocaine reached a certain threshold of receptor occupation, the cell starts to sense that there is something unusual and physiologically unbalancing going on in its environment: that's why it reduces the number of binding sites for cocaine and dopamine. In this sense, in order to force the interaction between the substance and the neuron, or between this last one and dopamine, the user needs to take more and more of the drug: after a certain time, the person will experience incredibly high circulating levels of both dopamine and cocaine, but very few competent cells that exhibit the receptors to respond to them.

This reduction in receptors is comparable with the population levelling that occurs after a certain time of exponential growth, in every experiment carried on this phenomenon. In this sense, it's useful to refer to the following simulation obtained with a simple Python code: you start with a population of two bacteria, of a random type (A or B). The only difference between the two is that they reproduce at a different rate: type A passes on two copies of itself to the next generation, whereas B is able to generate only a self-duplicate. It follows that, if we have a A and a B in the first round, in the second one we will have a population made up by: [A, A, B]. Let's also assume that there is a 1:1 correspondence between a bacterium and the bits of resources it needs to survive its whole life: these resources double with each generation passing, so that their increase ultimately won't keep up with the accretion of the population: when the number of individuals outgrows the availability of supplies, the ones in excess are doomed to death. As you can see in fig. 1, starting with 1.000.000 resource units and a population of two bacteria, randomly assigned A or B, if you let the simulation run for 50 generation you get a population levelling at a certain point: bacteria then stay constant at the number reached, because they entered a phase of dynamic equilibrium with the available resources. This fact, obviously, hides a terrible truth: all the individuals that come from the reproduction of the previous generation and that make the population exceed the number of supplies are bound to a destine of death. This is not the sole consequence: as you can imagine, being type A individuals able to

reproduce more and to pass on more of their progeny, they will ultimately outcompete the type B component. This translates, in real-word biology terms, in what is known as genetic drift, a menacing and dangerous loss of genetic variability in a population, due to fitness issues.

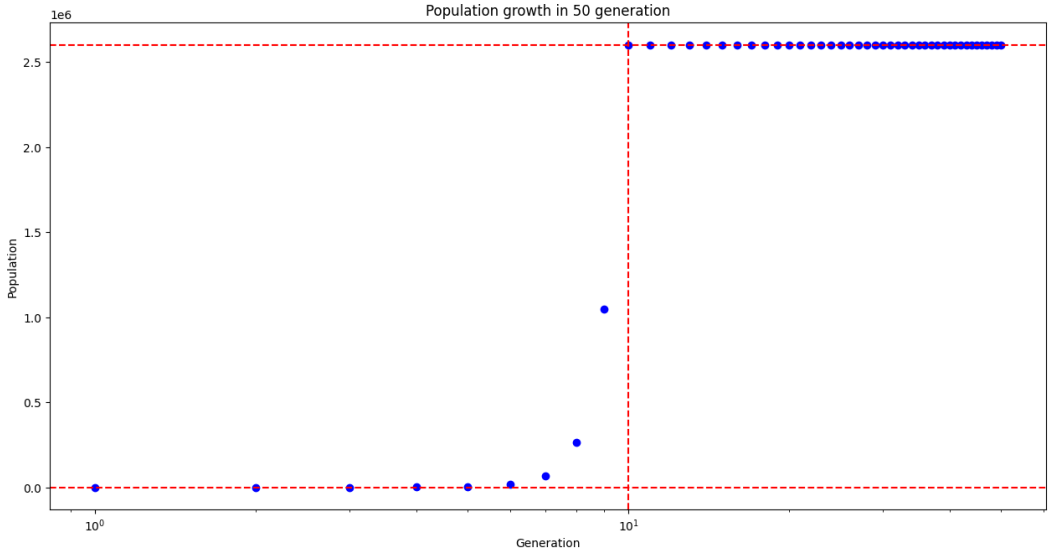

***Fig. 1**: Number of individuals tends to level with time passing. In this 50 generations simulation, we can see it peaks and settles at the tenth round, remaining stable from then on.*

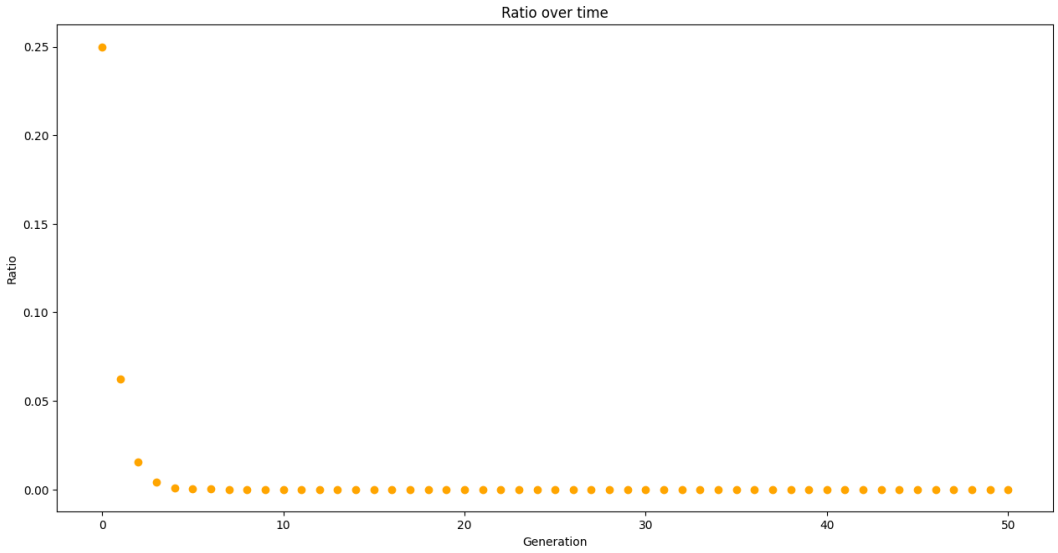

***Fig. 2**: As you can see, the ratio of type B to type A individuals falls to zero over time, following an exponential decrease. This is a symptom of genetic drift*

The same behavior shown by population number in the second case can be found when diving deep into the molecular and cytological causes that determine the onset of type 2 diabetes. This kind of metabolic disease, unlike type 1 diabetes, is not due to an autoimmune or genetic disorder that brings to the degradation of pancreatic B cells, the ones producing insulin: it comes almost exclusively from an excessive and unregulated diet, based on lipids (fats) and complex carbohydrates (such as starch), with little mobility and low levels of physical exercise. How is it possible? It all starts with digestion: our body, after a meal, breaks down the nutrients that were in our food and distributes them

throughout the organism. Insulin is responsible for the absorption and storage of glucose in cells, in the form of glycogen, and the uptake of fats by adipocytes, small cellular units that reside in the adipose tissue, mainly evident on abdomen and hips. On the other hand, glucagon is responsible for the mobilization of these nutrients, in order to give the body the energy it needs to face a dangerous situation or to resist starving. When our nutrition relies heavily on fats and complex carbohydrates and we conduct a quite sedentary life, insulin has generally high circulating levels in the blood, because it is set to catch the extra lipids and sugars that are there and import them into its target cells. The interaction between this small peptide hormone and the cytoplasm is mediated by a receptor, which allows the insulin-dependent enzymatic cascade to start. When cells are exposed to more insulin than usual, they react by upregulating their receptor expression: in this way, they will respond better to the hormonal stimulus. On the other hand, if the insulin excess becomes chronic, cells start to decrease their own receptors, in order to avoid overstuffing. This is especially true with adipocytes, because they tend to grow not in number (hyperplasia) but in dimension (hypertrophic accretion). Obviously, they are not free to expand indefinitely: they are restrained by fasciculi of reticular fibers (made up by collagen), and, when they reach the maximum stretch, they stop responding to insulin trying to import other lipids, as if they were a fully booked hotel that has to say "no" to other incoming tourists. In this sense, they have a more extreme reaction than neurons: they become totally insulin-insensitive. This brings the organism to a positive feedback loop: the more insulin is rejected, the more sugars and fats dwell the blood, the more pancreas is stimulated to produce insulin. This phenomenon leads other cells, that initially were insulin-competent, to develop the same resistance we can now find in adipocytes, and the body in its wholeness stops responding to the hormone. This can cause deposition of lipids in the arteries (arteriosclerosis), renal stress (sugar which is not stocked within cells must be eliminated with urine), but also a constant sense of hunger (overstretched adipocytes tend to go crazy, sending to the brain the hormonal messengers that stimulate appetite, such as ghrelin). If not cured with an appropriate diet and the necessary insulin regulation, type 2 diabetes can be lethal over the long period.

As you may have already reckoned from the presentation of the three phenomena we are looking to, the equation that links them all is the logistic one. In the most general terms, it looks like this:

$$(I) \qquad f(x) = y_0 + \frac{y_{range}}{1 + 10^{(x_{half} - x)(S)}}$$

Where y_0 is the starting value of the function, y_{range} is the difference between the initial and the final outputs of *f(x)*, x_{half} is the abscissa of the inflection point and S is the steepness of the function itself. If you implement this equation on Geogebra, on Python (fig. 3) or on Desmos, you will see a nice S-shaped curve (known also as sigmoid), similar, but more elegant than the one we got as a result of the simulation of the population number. We can then play with the terms involved in it, seeing how the graph will change in response. Doing this on Geogebra, we will see that:

- y_0 is the “floor” of your graph: variating this parameter is like heightening or lowering the basement of a house.
- y_{range} influences the “ceiling” value of the curve: modifying it means that, remaining in the field of the house metaphor, we are levelling the height of our roof
- x_{half} is the input value at which the function reaches the center between y_{min} and $y_{min}+y_{range}$: in this sense, on Geogebra, you will see that a modification will result into a change in the inflection point (which occurs exactly at $x = x_{half}$).
- S quantifies how much your curve is steep: in terms of a population growth model, it tells how fast the number of individuals tends to increase, peak and settle around the y_0+y_{range} value.

Following this track, we notice that the behavior of the logistic function is very simple, yet intriguing. As x approaches $-\infty$, the curve tends to y_0^+ and that’s because the denominator of the fraction goes

to infinity and nullifies the second term of the sum. On the other side of the horizontal axis, with x tending to $+\infty$, the limit of the function is $(y_0+y_{range})^-$, because the exponent of 10 at the denominator goes to negative infinity, and, as a result, the power outputs 0, which translates into the whole bottom portion of the fraction tending to 1. The most interesting part comes when we take into account the middle portion of the function, meaning the values at which it starts to rocket from the floor to the ceiling. As x becomes less and less negative, the denominator detaches from large values and tends to ones comparable with the size of x_{half}, y_0 and y_{range}. In this interval, the power of 10 at the denominator gets substantially bigger than 1, and so the equation can be rewritten as follows:

$$(II) \quad f(x) = y_0 + \frac{y_{range}}{10^{Sx_{half}} \cdot 10^{-Sx}} = y_0 + \frac{y_{range} \cdot 10^{Sx}}{10^{Sx_{half}}}$$

Which ultimately is an exponential function (and if you plot it with Python, as in fig. 4, you can see that it pretty much superimposes with the logistic curve). The interval in which the sky-rocket growth occurs can be approximated with $\left(x_{half} - \frac{x_{half}}{2} ; x_{half} + \frac{x_{half}}{2}\right)$, whereas equation (I) and (II) are comparable in a little shorter range of values, which goes from $x_{half} - \frac{x_{half}}{2}$ to x_{half}, (mean Δy between (II) and (I) computed with Python is 1.01).

To sum things up, we can say that, whether you have to predict the development of drug addiction, the growth of a population or the progression of type 2 diabetes (as well as many other things we haven't dealt with in this paper), you can use the logistic equation: it's a pretty powerful model, isn't it?

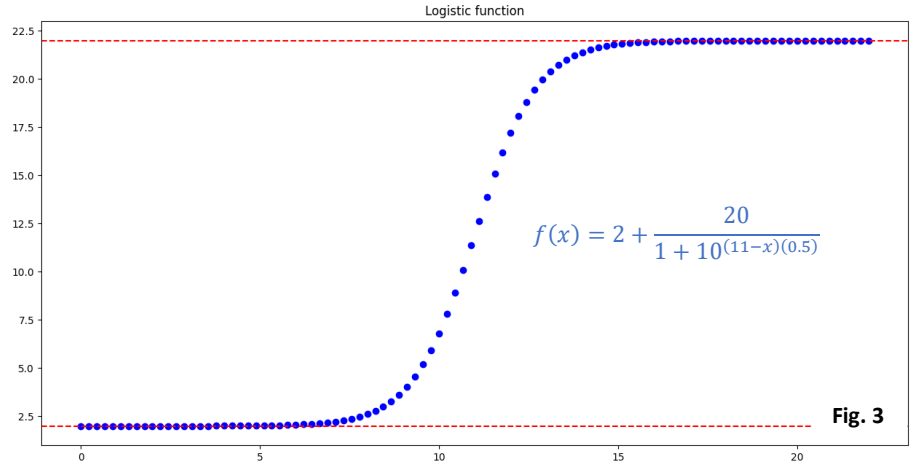

Fig. 3

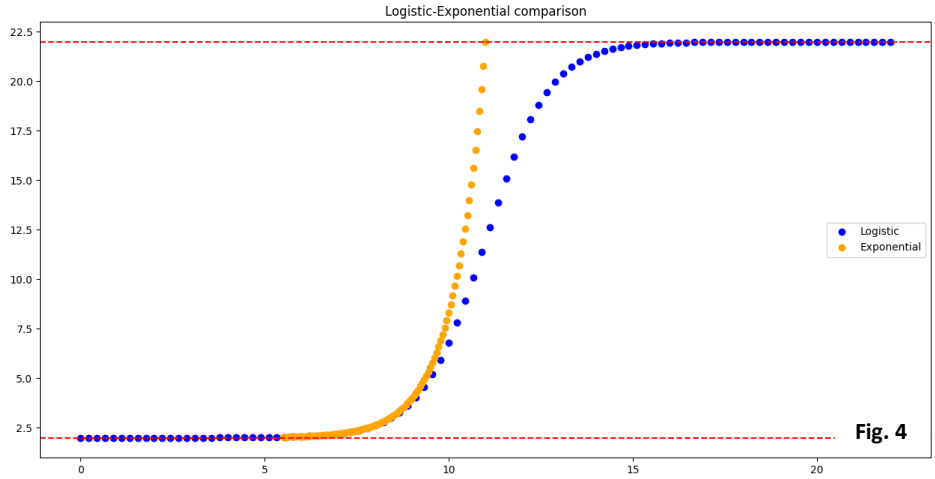

Fig. 4