Using the butterfly effect to predict heart disease: an interview with Dr George and Dr Parthimos, Cardiff University

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What is the butterfly effect? Please can you give some examples of systems that exhibit it?

Let's start with a formal definition:

> The butterfly effect is a phenomenon associated with chaos theory in which a small change in the initial state of a deterministic, nonlinear system can result in large differences in a later state.

It's a beautiful statement about what the butterfly effect is and if we actually break it down to its component parts, I can begin building a visual picture of what it is.

The term "butterfly effect" is attributed to a famous mathematician (Edward Lorenz) working on chaos theory who likened it to the mechanism by which a butterfly flapping its wings in the Amazon may produce a hurricane in Texas. The term, therefore, means that a tiny perturbation in a system is enough to greatly skew, bias, or change the determined events.

The emergence of the butterfly effect in many physical events reveals two fundamental laws that underpin all nonlinear systems. The first principle is known as determinism, which means that the evolution of an event can be followed accurately in the future, as long as we know its precise starting point and the rules of how a situation can change with time.

Life itself, to a certain extent, is an example of a deterministic process, because from the moment you are born, you follow the laws of growing and ageing in a largely determined trajectory.

The second fundamental law that underpins the butterfly effect is the fact that a large number of behaviours coexist within a nonlinear system and are available to be chosen quickly and with a minimal effort in order to adapt to a specific condition or requirement.

A good example is our own ability to respond to minute stimuli, such as a perceived threat, either by calmly reviewing the risk or by promptly recruiting our whole body defensively through a cascade of processes.

This is the case in the "fight or flight" response, when a small sound can raise our heart beat, dilate our pupils, suppress our digestive system and induce a succession of associated changes that prepare us to defend ourselves against a potential danger.

Interestingly, once this chain reaction is initiated, the steps are clearly deterministic and stepping back from this heightened state of alert will require the process to follow its due course. It is evident that the principles embedded in the butterfly effect are so fundamental that they have been employed through evolution as our body's first line of defensive responses.

Another classic example of sensitivity to initial conditions, determinism and coexistence of all possible outcomes within a system is the evolution of the weather.

In a weather forecast, all of the meteorological information is used to define a basal state. So, at a particular time, the air pressure, the wind speeds, surface temperatures, cloud formation can all be measured and integrated to generate a mathematical picture of the weather system in the world.

Now, if you understand enough about those conditions, you can forecast what that weather is going to do, according to the principle of determinism embedded in chaos theory.

What, the butterfly effect refers to is the potential of the weather system to develop into all sorts of diverse atmospheric phenomena under tiny, seemingly inconsequential, disruption of the initial picture, with huge ramifications for global weather.

I don't think the perturbation could be as little as a butterfly flapping its wings, but it could be something like a particularly hot small patch of land in the United States, which causes the air passing over it to rise to an unusual altitude and that event changes the dynamics of the whole system.

Could you please outline how and why healthy hearts are dependent on the synchronization of huge networks of cells?

At the moment, your heart is probably beating at 60-70 beats a minute, but it is beating as a completely organized unit.

Your heart is made up of billions of cells, all of which behave as one organ and if you think back to the chaos theory we just talked through, a disruption in any one of those cells has the potential to ruin the entire synchronization of the heart muscle.

The normal heartbeat depends on cells knowing what their neighbours are doing. What happens in the heart both in disease states and in aging, is that out of those billions of cells, maybe one or two or hundreds or thousands of them might go wrong and because they're coupled to each other, the disruption could spread into those cells that were previously unaffected. The net effect is that relatively large sections of your heart tissue might then stop working normally.

In a heart attack, a huge number of cells die within a very short space of time and the normal cell-to-cell communication across the affected region of heart muscle is abolished. This sets up a number of problems predominantly related to having a chunk of tissue functionally isolated from the rest of the heart. This leads to abnormal rhythm (arrhythmias) and poor muscle contraction.

How many cells need to go wrong for such an effect to occur?

We do not know how many cells need to go wrong, which is why we've turned to computer simulations to help us look at some of these issues relating to what are the critical points that turns a normal (healthy) system into an abnormal (diseased) one.

In the body, important 'gatekeeper' mechanisms normally exist to prevent neighbouring cells from picking up on abnormal signals coming from any cells going wrong; the abnormal cell can be silenced (by being killed) or ignored (by cutting off communication).

However, if you have an ongoing problem or if there is some way in which an abnormal signal is allowed to persist, then it can become a problem and, like in the butterfly effect, a small disruption can be amplified hugely to become a serious issue. How does this message radiate out to communicating parts of the heart?

It is very unlikely that just one cell going wrong will pose an immediate problem in a heart made up of billions of cells. But going back to the butterfly effect, it is absolutely possible in principle that if a really tiny number of cells go wrong, in the wrong place at the wrong time such that it disturbs the basal state of heart cell organization then it can progress become a significant issue.

We believe that part of the reason that tiny events do become amplified to cause disease is the inability of those gatekeeping mechanisms to silence or ignore the abnormal cells.

How did you use the butterfly effect and computer models to better understand what happens in heart disease?

If you followed the arguments that we've made so far about what the butterfly effect is, the crucial point to get across is that the trajectory of a series of events that conforms to these principles is predictable if you understand enough about the initial situation.

We've spent many years investigating cell populations and looking at how each cell communicates with its neighbours and influences its local environment under normal and 'disease-like' conditions.

We therefore have a very good experimental insight into what would happen if, for example, 5% of your cells behaved abnormally from the rest; what would happen if you stopped the cells from communicating in the way that they usually do, what would happen if you physically separated some of the cells from each other or you used chemicals to alter the way in which cells encode information.

We've carried out a huge number of 'flavours' of these types of experiments over a number of years and like to think that we now understand one of the determinants of these initial conditions in great detail, namely how a cell handles a crucial signal- calcium.

The main limitations of 'living cell' experiments though is that if you keep pushing cells to perform beyond their normal range of physiological processes, it usually triggers a terminal gatekeeping mechanism and as a result they will die.

So, we have a limited threshold of cellular tolerance, experimentally, of what we can do before all the cells die - but a computer simulation doesn't. These simulations, provided they are set up to appropriately mimic the initial conditions of a cell network, can explore the what-ifs, the whys and the consequences of moving into the next phase of cell behaviour in a way that is not possible in the laboratory.

What we've done is to feed our experimental data into a computer model that is set up to look at pre-ordained, deterministic paths based on a set number of initial conditions which we have defined.

For example, if you consider a scheme made up of four processes (A, B, C and D), the computer simulations allow us to look at what happens in a 'cause-or-consequence' fashion to B if you change A, what the implications for C or D will be as a result and how the overall interaction between A, B, C and D may change. These simulations allow us to play with the butterfly effect in scenarios that are not possible to perform in living cells.

Does this mean you can begin to understand heart disease more quickly?

The ability to change a range of conditions does allow us to do things at a rate that is not possible experimentally. It's a way of predicting, *in silico*, what the cells will do in response to a certain treatment or exposure to certain stimuli.

The huge advantage of computer simulations is that we precisely (mathematically) define the initial conditions based on our vast archive of experimental findings.

What are 'crisis points' and why are they important?

Every system that you see around you such as traffic flow on the motorways, an aeroplane flying through the air, a butterfly flapping its wings, the way you walk or laugh, are all part of an orchestrated series of events. If we looked back at your life the first twenty years of your life, for example, it would follow a certain trajectory in that you were born, you went through childhood and school and university… there is a path there.

However, at certain points in your life, there will have been phases that have determined how you've made the next decision. Say, for example, you fail all of your A levels and you can't go to the university you want to go to. You've then got to go somewhere else and the path that your life would have taken is fundamentally reshaped.

Biologically, cellular decision-making happens in a similar way. In a cell, information flows via signals produced by biochemical interactions and protein-protein networks. Along these paths are points at which the signal could take multiple options. The number of possible options gives cells their plasticity of function.

As an example, we can liken these points to the use of a keyboard by a touch typist. They write professionally for a

living and have an enormous number of words to choose from to communicate their message. But the entire richness of the language available to them is made up of just 26 characters. They can write anything they want but it is dependent on their ability to control how they use those 26 letters of the alphabet.

Now, let's imagine that somebody comes into the office one morning and says "I'm taking Q off your keyboard." That would mean the typist could no longer write the words "quick "or "quiet" for example. However, they could come up with other ways of writing what they meant. It would be an absolute nuisance, but they could adapt to it.

The crisis point in this instance would be having Q taken off the keyboard because whatever the typist was able to do beforehand is now much more restricted, although they could still communicate reasonably easily.

However, if the decision was then made to remove W, A, and S from the keyboard, the typist would be much more constrained as to what they could write. As a result of this the richness and nuance of their communications would be substantially reduced. The message would have to be simplified to use fewer words.

Each one of those letters coming off the keyboard represents a certain crisis point, where you have a decision to make regarding how to proceed, and the removal of each letter represents successively constrained conditions of the system

To extend the analogy to breaking point, if E, I, O and U were then removed, then the typist would have to admit defeat because they would no longer be able to communicate.

There are certain critical parameters, which in this case would be letters on a keyboard, where out of the 26 letters, there would be a substantial loss of function if only five were lost. It doesn't need all 26 to go, it just depends on what is taken, when and how and what you're left with.

How can the outcome of cell behaviour in response to a 'crisis point' be predicted?

If we I took the letter Q off the keyboard, we could predict that the typist would have to write the word "quick" in a different way; they'd maybe use "rapid," "expedited" or something even more convoluted, because they couldn't write "quick". So, we could predict what they would have to do because we would know what had been done.

In terms of biology, if certain proteins or certain electrically-excitable cells are taken out of the mix, we would be able to predict how that system would adapt because it now can't do certain things. In some instances however, the system may be able to do some things differently that it has never done before and therefore re-learn what to do.

Does that mean you are observing systems doing things that have never been recorded before?

Absolutely. There's an interesting branch of science that deals with the properties of "emergent networks," which investigates how the behaviour of an organized series of components emerges from having been put together in a certain way.

The best way to describe it is as a kind of revelatory appearance of properties that were not a feature of the individual components. That really is fascinating.

Do you think this research will lead to new ways to delay the onset of heart disease and potentially even reverse the process?

Yes, but one of the things that we're very aware of is that the media attention that our work has received has been down our efforts to visualize incredibly complicated phenomena. What we don't want to do is give people the impression that this is going to lead to a new way of treating heart disease in the next two years, for example. It isn't going to do that.

What it is going to do is to get people thinking about the disease process occurring via stages and crisis points and how, if these conform to chaos theory, then it can be predicted if enough is known about the basal state of the system.

What we are ultimately aiming for is the detection of abnormalities at the earliest possible stages of the disease process. People may be some way off developing the symptoms of heart disease at this point.

Since our work shows that the organization of heart cell networks conform to chaos theory, it means that, in

principle at least, it is possible to predict the transition from 'normal' to 'disease' in these networks and eventually, in the heart. We believe that if we understand enough about the normal-to-disease change in the system, we will be able to predict when decisions will be needed and what the consequences of those decisions would be.

It's useful to think of this using another real-life example. Say you're driving across to Wales and you know that in 70 miles time you're going to cross the Severn Bridge, but you know that the bridge is closed due to high winds.

One way you could delay getting to that eventuality and hopefully finding that the bridge would have been re-opened, would be to slow down. A small change to the accelerator pedal would have that effect.

The other way you could avoid the problem of the bridge being closed would be to use your sat-nav and via small turns of the steering wheel select another route that may bypass the bridge by tens of miles, but actually would take less time to complete than if you had to slow down. Each of these choices is a case of the butterfly effect, but the ability of the driver to choose between the two is due to the coexistence of these states within the same system.

In this sense, a diseased system adopts new suboptimal states until it runs out of choices.

Are all systems in the body deterministic? Could we potentially predict diseases in other organs?

We've only looked at heart cells at this point in time, but there's a huge amount of evidence that all body organs work because of synchronization.

For example, your brain's speech centre controls speech production, which relies on the very precise organisation of nerve signals to muscles in your tongue, jaw, neck, which causes your mouth to move, which enables you to speak. Everything is synchronized.

So, this is part of the hypothesis that we're developing, which is that other diseases of a progressive nature involve the sequential unraveling of organ systems according to this predetermined pattern.

Do you think the butterfly effect and computer simulation could help to shed light on cancer?

We don't specifically study mechanisms of cancer cell growth but it is true to say that organ systems in the body depend on synchronization of cells in the same was as the heart does.

So, if you view cancer in a very simple way - as a bunch of cells losing their ability to stop growing when they should, or those cells that start growing when they shouldn't – then the things that we've discussed above are relevant.

It's likely that the problem begins with a very tiny effect, in that the communication between one cell and another breaks down and is not corrected and this then spreads to its neighbours, which then takes other neighbours down etc. etc.. So yes, we would speculate that perhaps the origins of cancer and other diseases (e.g. neurodegeneration) are due to desynchronization, that may be true.

What are your future research plans?

We essentially want to make this larger scale. Everything that we've published and the reason you're now talking to us is because we've looked at an experimental system of two-dimensional heart cell networks. Of course though, our heart does not exist as a simple 2D cell network and our bodies function as a combination of organized, integrated, three-dimensional tissues, organs, and physiology.

Our future research plans are to use this as a framework to go up in scale through the higher orders of three-dimensional tissues, whole organ physiology and the body.

Where can readers find more information?

More information can be found on Chris' webpage: http://medicine.cf.ac.uk/person/dr-christopher-george/research/

About Dr Chris George and Dr Dimitris Parthimos

Chris graduated in Biochemistry in Cardiff in 1995 and followed this with PhD investigating the role of cellular micro-environments in dictating cell-to-cell communication. During this time, he became interested the patterning of cellular Ca^{2+} signals and he subsequently moved his work into the cardiac sphere to explore the link between abnormal Ca^{2+} patterns and genetic arrhythmias.

His group is now investigating broader questions relating to cardiac (dys)function from the perspectives of cellular noise and signalling–network architecture. He has a keen interest in systems-level thinking of 'cause-and-effect'-type scenarios.

Dimitris was born and educated in Greece, where he obtained a degree in Mechanical Engineering from the National Technical University of Athens.

He studied for a PhD in robotics at Northwestern University in Chicago, and subsequently moved to Cardiff University where he has been investigating the fundamental biochemical processes that determine cardiac and vascular disease at the cellular level.

His work combines experimental evidence with mathematical modelling and computer simulations.