Chaos, mitochondria and type 2 diabetes; does type 2 diabetes arise from a metabolic dysrhythmia?

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A B S T R A C T

The increasing incidence of type 2 diabetes transcends all cultures, largely due to populations transitioning from traditional diets and manual occupations, to sedentary, calorific lifestyles. Excess calorie intake leads to intramuscular fat accumulation and insulin resistance. Physical inactivity causes underutilization of mitochondria causing dysfunction and inflammation. Both insulin resistance and mitochondrial dysfunction mechanisms are known to be closely related and to antagonise one another, although the precise nature of the relationship has eluded characterization. It is poorly understood why this mutual dysfunction progresses on to clinical diabetes in only some patients, why progression is often stepwise and why diabetes control only weakly predicts future cardiovascular disease in individuals. Clinical prediction in patients is therefore currently unsatisfactory and current linear assumptions require challenging.

Cells contain networks of oscillating ionic fluxes. Cellular activity is characterised by complex patterns of fluctuation with sudden transitions between patterns. The non-linear nature of these oscillations is well characterised in neuronal activity, cardiac impulses and more recently mitochondria, but not previously in relation to diabetes. Cells under metabolic stress demonstrate complex fluctuations of mitochondrial distribution, coupling strength and synchronisation resulting in periodic or chaotic oscillations of function, causing accumulation of intracellular fat and excess reactive oxygen species (ROS), which exacerbates insulin resistance. Glucose, insulin and HbA1c in patients are also known to oscillate in complex patterns but the mechanisms and significance are largely unknown.

Drawing on existing evidence and models from other diseases, a nonlinear, dynamical hypothesis of diabetes onset and progression is proposed. Insulin receptor pathways and mitochondria are treated as two populations of coupled, phase oscillators. Health or disease states depend on system stability or instability and reflect the balance of substrate supply and energy demand. The implication of this novel mechanism is that diabetes and the complications are not the consequence of a distinct pathological agent or pathway, but more an evolving dysrhythmia of normal cellular energetics systems, resulting from accumulated adverse lifestyle conditions. This hypothesis is proposed with the intention of stimulating research into non-linear dynamical constructs as an alternative to current linear models, to improve risk prediction and trajectory analysis in type 2 diabetes.

Introduction

The disease states of obesity, pre-diabetes, diabetes and diabetic complications are currently managed on an underlying assumption of linear, inevitable progression, fuelled by low grade inflammation and starting from obesity, despite evidence that progression is unpredictable and non-linear [1–3]. This model therefore poorly individualizes risk, affects healthcare by delivering a "one size fits all" approach and is unable to account for some cases where diabetic complications are seen before the onset of diabetes [4,5].

The defining dysfunction in type 2 diabetes is insulin resistance (IR) or reduced glucose uptake of cells relative to stimulation by insulin. But low-grade IR is often found in the normal population and is not in itself sufficient to precipitate the clinical syndrome of diabetes, suggesting other factors are required [6,7]. Indeed IR has been suggested as an inherent cellular protective mechanism preventing excess intracellular glucose [8]. If this is the case then the opposing mechanisms of insulin sensitivity and resistance can be considered to be a dynamic system of glucose regulation, whereby diabetes represents loss of control. However, testing this is challenging if using static observational and phenomenological models to link individual variables with underlying diabetes progression and complications. Use of large-scale longitudinal data can elicit numerous risk factors but still cannot individualize risk or explain temporal patterns of disease progression. The answer may lie in exploring glucose's role as a fuel substrate and the underlying, often non-intuitive, behaviour of non-linear cellular energetics and ATP production.

Main text

Energy availability, via ATP production, underpins all cellular metabolism and function and is itself dictated by the laws of thermodynamics. Cells derive energy by employing chemical systems held far from equilibrium, using the quantum properties of the mitochondrial

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electron transport chain (ETC) and harnessing the resulting proton-motive force to drive ATPase and produce ATP [9,10]. The electrons for the ETC in mitochondria are mostly provided by glucose, which needs to be rapidly available in order to meet sudden and enormous changes in energy demand, particularly in skeletal muscle. Glucose is first converted via pyruvate into acetyl CoA by glycolysis in the cytoplasm, which then enters the mitochondrion. The tricarboxylic acid (TCA) cycle then transfers the electrons from acetyl CoA onto the electron carriers NADH and FADH2, for transport to the ETC [11]. These processes are substrate-driven not rate-limited, such that the higher the rate of fuel supply, the higher the reaction rates. Therefore for living cells to maintain stable states of high thermodynamic potential (or low entropy states) requires constantly balancing the rate of substrate supply with the rate of energy demand, to avoid either cell collapse, from ATP depletion, or the cytotoxic effects of substrate overload. As a result, substrate supply and ATP production necessarily oscillate, slightly out of phase with each other, due to the lag-time of feedback mechanisms and the underlying enzymatic reactions being oscillatory.

Oscillatory behaviour is ubiquitous in cellular processes and elsewhere [12]. As cells contain many thousands of oscillating reactions the net behavior can be complex. Unlike simple periodic motion, a key feature of multiple adjacent oscillators is coupling, whereby individual motion becomes modified by the oscillations of neighbours. With sufficient coupling, oscillators fall into phase, or synchrony. Synchrony is found in many physical and biological systems and is even less characterized than multiple oscillator systems. Christian Huygens in 1665 first demonstrated how two pendulum clocks, separated on a wooden beam, would eventually start to tick together, even returning to synchrony if they were perturbed [13].

Well known examples of coupled oscillations are; synchronized firefly displays, audiences clapping, cardiac cells and circadian rhythms [14–16]. The phenomenon of coupling in oscillator systems was modeled by Kuramoto with a set of low dimensional, coupled differential equations and has been widely applied across biological and physics contexts and been generalized for oscillator clusters, phase resetting and heterogeneous frequencies [17]. Coupled oscillator network models require oscillators to operate independently but be coupled physically or chemically. It is precisely the unstable oscillatory properties of coupled individuals that enables synchrony and global stability of the network. Conversely perturbation to the whole system or reduced coupling by spatial separation can lead to instability.

Within human physiology, oscillatory behaviour is found at cell, tissue and organism levels [18,19]. This probably arises as many underlying molecular processes are inherently oscillatory (Calcium channels, membrane potentials) which leads to oscillatory, non-linear behaviour of more complex enzymic systems (glycolysis, TCA cycle, free-radical production). Glycolysis activity for example is pulsatile over a 15 s cycle [20]. Mitochondria, which host oxidative phosphorylation and electron transfer processes, communicate with the cytosol, where glycolysis occurs, by calcium and ROS with complex waveforms, with 1–2 min periodicity [21]. In a recent key publication Kembro et al demonstrated complex oscillatory, non-linear dynamics in the antioxidant enzyme superoxide dismutase (SOD) in mitochondria, with experimental perturbation triggering chaotic dynamics and featuring sensitivity to initial conditions, positive Lyapunov exponents, and strange attractors which defines chaotic behaviour [22].

To maintain dynamic energetics balance, an efficient metabolism requires the ability to switch rapidly between oxygen dependant oxidative phosphorylation (ox phos) and anaerobic glycolysis when oxygen supply fails to meet demand or in glucose excess. Type 2 diabetes displays both impaired rates of fatty acid oxidation (ox phos) in fasting states and the inability to switch rapidly to glycolysis in the post-prandial state. This phenomenon is known as metabolic inflexibility [23]. It is interesting to speculate in skeletal muscle, as a principal consumer of energy substrate, whether muscle mitochondrial function is likely to have a prominent role in whole body energetic

balance and therefore diabetes pathogenesis. However the precise relationship between metabolic flexibility, insulin resistance and mitochondrial dysfunction is unclear as they are mutually interdependent [24]. This is further confounded by raised plasma fatty acids and intramyocellular lipid accumulation which can be causes or consequences of each process.

As cellular metabolism has evolved over millions of years within dynamic oscillatory environments, it is likely that metabolic oscillatory are more than merely features but have some biological significance. Oscillatory enzyme cascades show greater energy transfer efficiency than steady state processes [25] and oscillatory networks enable rapid local control and global stability, through spontaneous self-organisation, without the need of an external controller. The change in oscillation frequency of gonadotrophin hormones in females, to trigger monthly ovulation, was one of the first recognised examples of control through phase encoding and demonstrates the emerging field of chronobiology [26]. It is now accepted that 10–30% of the genome is under the control of circadian molecular clocks [27] emphasizing the importance of researching not just the nature of pathways, or treatments, but also temporal behaviours.

Coupled oscillatory systems show non-linear dynamic properties. Non-linear means that parameters interact to become more than the sum of the individuals. Dynamic systems change according to their previous state.

Non-linear dynamical networks seem to be a phenomenological fit for modeling mitochondrial oscillations, which have been observed to transition from asynchrony to synchrony under external stress [28]. The degree of coupling depends on neighbour proximity and overall network shape. By altering intracellular microtubule structure and hence network shape, synchrony is modulated, affecting stability, net mitochondrial activity and overall cell energetics [29]. Microscopy studies of mitochondria demonstrate pattern changes within minutes of external stresses. The significance of this is unknown, but may represent an example of local self-regulation controlling overall energetics function, when there are up to 10,000 mitochondria per cell.

Oscillatory networks provide an ideal mechanism for cellular energetics self-control within tight physiological parameters, evolved over millennia. However, with complex dynamics, behaviour becomes less intuitive, when there is loss of stability, in the face of more unnatural conditions. For example, prolonged calorific diets or physical inactivity, impose perturbations on the system that risk sudden deviations of oscillations into either new phase orbits or chaotic states. This leads to activation of insulin resistance pathways to prevent excess intracellular glucose, but if prolonged progresses to type 2 diabetes.

Non-linear dynamical systems can be modelled with sets of often simple differential equations. However when the products are continuously fed back into the equation set, very complex and divergent behaviours can result. Within physiological parameters, the motion plotted in time can vary from simple oscillations to non-linear oscillations (Fig. 1). Plotted in phase space, motion orbits in a limit cycle around a simple attractor. Physiological perturbations from external influences, such as energy demand, can drive divergence of orbits, the shapes of which depend on the initial values and boundaries reached until the edge of system stability is reached and values reach criticality. In this transition zone, further perturbation provokes bifurcation of activity into oscillating in two steady states, called bistable or period 2 behaviour. This becomes more visible on a logistic map where parameter net stability is plotted against system growth (Fig. 2). A logistic bifurcation map shows that when the growth rate of the overall system, r, increases, the activity level of the system oscillates between 2 then 4 then 8 steady states. Known as period doubling this process increases until chaos is reached. Chaotic behaviour appears random but is deterministic and arises under certain conditions in non-linear dynamical systems [22].

Unlike periodic oscillations having simple attractors, a chaotic system oscillates around astrange attractor, never retracing itself or
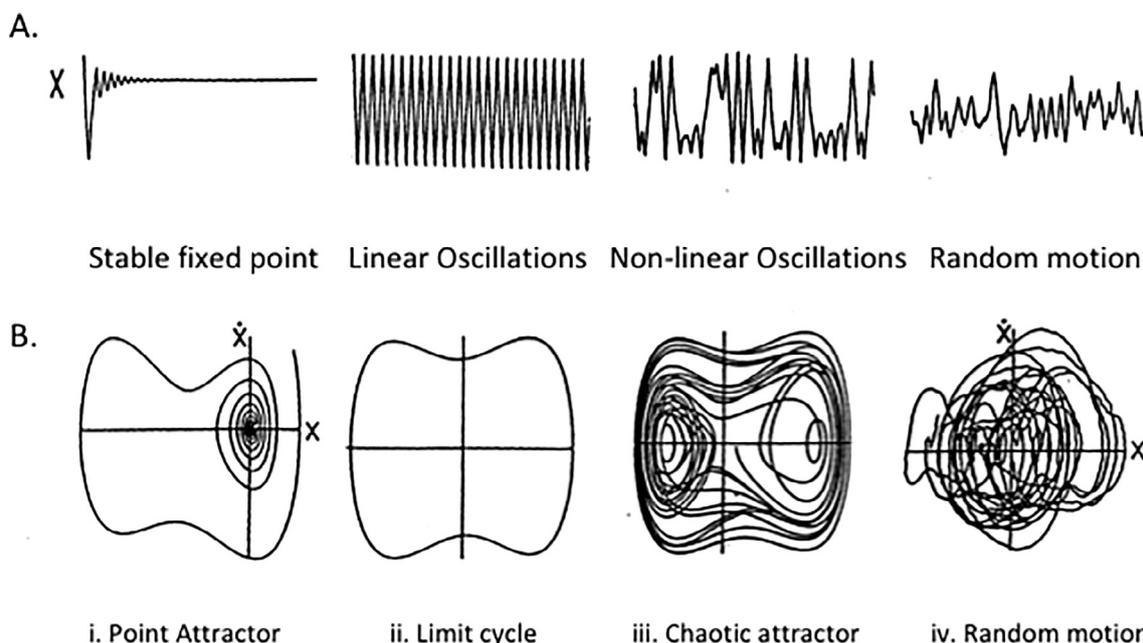
Fig. 1. A. Time series of a damped forced oscillator system in four modes of motion. B. Plots of different modes in phase space where parameters are plotted according to the change in relation to their previous state, showing movement independent of line.
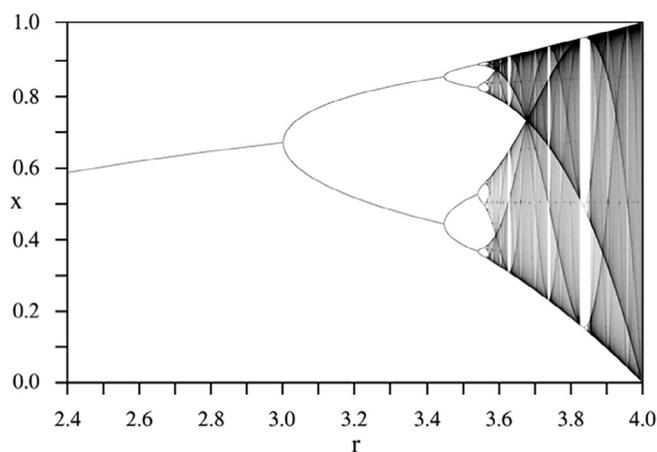

Fig. 2. Bifurcation diagram of the level of the parameter **x** against **r**, the growth rate of the system. At r = 2.6. The input and output of the system balance and a single steady state exists about a single point attractor (x = 0.61). If the parameter is increased, r increases and at 3.0 system stability bifurcates into two steady states known as period doubling. At r = 3.5 x oscillates between 4 frequencies in a limit cycle corresponding to ii in Fig. 1. At r = 3.5–4 the system enters chaos or non-periodic oscillations in never-repeating patterns, known as a stranger attractor and having properties.

settling into a steady state. The attractor has fractal form in that the patterns within it are repeated at all scales to infinity. In phase plots of chaotic systems, adjacent orbits diverge exponentially making long-term prediction impossible due to small differences in initial conditions of the system. Notwithstanding this, much information about current system stability can be measured by mapping the divergence of consecutive orbits. Further features of chaos such as fractal dimensions and entropy also provide insights into the nature of a metabolic system [30].

There is still debate as to the significance of chaos in biology and whether this represents loss of control and a disease process or whether it confers robustness to a network, allowing adaptability [22]. In clinical medicine chaos has been best characterised and associated with arrhythmias in cardiac disease [31]. There is much less research in the application of chaos theory to metabolic systems and disease and less still in diabetes. Experimental study of glycolysis in yeast cells shows chaos can be induced and controlled by changes in glucose substrate rate and timing not dissimilar to the conditions cells experience in dietary excess [32]. In patients the dynamics of some postprandial blood glucose profiles can be described by a continuous data-driven nonlinear stochastic model capable of differentiating diabetic and non-diabetic profiles [33]. Therefore, while struggling to provide future predictive value per se, chaos models may have use in differentiating patients into higher and lower risk of future complications, using the temporal information from tests already in clinical use.

Complex coupling effects within cells between networks of insulin receptors and mitochondria, potentially enables a chaos model to account for variations and timing of diabetes disease outcomes, according to which network predominates. For example, loss of stability of mitochondrial function leads to excess ROS which can produce cardiovascular disease independently of insulin resistance [34]. As type 2 diabetes is defined clinically by an internationally set level of glycated haemoglobin (HbA1c) and does not include mitochondrial criteria, this may partially account for why "good" diabetes control correlates only weakly with diabetic cardiovascular disease, or how diabetic complications are sometimes seen in pre-diabetes [35,5].

Although the oscillation frequencies and configuration, or topology, of combined insulin resistance and mitochondrial networks is more complex than simple models, coupling still occurs. Numerous studies describe complex heterogenous communities of phase oscillators within networks which are still reducible to simple sets of coupled, low dimensional equations and behave according to models [36]. According to these models both local and global coupling have an effect on synchronous behaviour. The importance of this is that cells are able to maintain energetics stability and respond rapidly to stresses from local and global sources through coupling, without the need of complicated, external control mechanisms. However a condition of dynamical systems, is a reliance on regular physiological perturbations to maintain quasi-stability such as dietary intake and regular exercise.

In the face of abnormal demand, or even underdemand, these systems are more vulnerable to instability and chaos and therefore the design represents what Chandra terms "a trade-off between efficiency and robustness" [37]. This is in contrast to the concept of stationary

stability in homeostasis. Homeostasis, being non-dynamic, would not account for example, for sedentariness inflicting such adverse effects on glucose control.

The communities of oscillators involved in cellular energetics include insulin-mediated glucose uptake, glycolysis and mitochondrial TCA and ETC. As the oscillatory systems of insulin sensitivity and mitochondrial function are tightly coupled then dysfunction is mutual and progressive. Insulin resistance reduces PGC1-α production which reduces mitochondrial biogenesis [38]. Mitochondrial dysfunction disturbs SOD balance and increases ROS production, which increases insulin resistance. Elucidating which of the two paths is the most critical step in progressing to diabetes remains undetermined, despite intense research and numerous reviews [39].

Viewed from a chaos paradigm, however, there may be no critical step or pathway at all. Modelling cell function as complex oscillatory dynamics, implies that continued stress from even modest food excess and physical inactivity, risks system jumps into diabetes or complications, with no apparent provocations or triggers or indication on conventional clinical diabetes tests. However given the paucity of understanding of metabolic control in insulin resistance it is important to resist ascribing specific nonlinear features to phenomena in diabetes.

Clinical applications

In practice system stability is determined by a logistic map of the non-linear difference of the measures of the variable against the number of iterations or orbits. The growth rate, r, determines if the dynamic system will remain stable, decline or expand into chaotic motion over time. The level of stability is calculated by the deviation of successive orbits in phase space: the Largest Lyapunov Exponent (λ), or stability index [40]. This and other techniques are increasingly used in complexity science and recently health trajectory analysis, to dictate when to intervene to alter, or phase reset, a system's trajectory onto a more desirable clinical path. Theoretically, applying a chaos oscillatory network approach to modelling diabetic and mitochondrial variables could predict when a patient is verging on converting from a pre-diabetic state into diabetes, or at a later stage, the imminent onset of complications. However similar to weather prediction the deterministic instability of complex dynamical systems prevents accurate prediction of exact system status.

By measuring the stability of phase patterns in people with pre-diabetes or diabetes, oscillatory phase modelling offers the potential of predicting imminent criticality ie sudden disease progression, in individual patients and the optimal points in phase space to intervene with phase-resetting techniques. A feature therefore of treating disease in non-linear biological systems, which reflects underlying chronobiology, is the importance of the "when" of treatment as much as the "what" [26]. Low calorie diets in diabetes are an area of current interest [41]. The dramatic effect on lowering HbA1c is hard to explain by conventional understanding but would be accounted for by phase resetting. Phase resetting may also be occurring in pre-diabetes, where weight loss is known to prevent nearly half of cases progressing to diabetes [42]. Improving the accuracy of these non-linear dynamical models for clinical use in predicting loss of stability and the risk of disease and therefore timings of treatment, will require high sampling rates and large datasets of variables in individuals. The advent of wearable technology promises to realise this possibility.

Summary

Significant proportions of patients, within the categories of obesity, prediabetes and diabetes will not progress to the next category and progressions, if they occur, are often unpredictable and sudden. This is not explained by current clinical measures of diabetes and assumptions of linearity.

The novel concept is proposed of considering type 2 diabetes

pathogenesis in terms of a dynamic oscillatory process of cellular energetics control involving the balance of energy substrate supply and energy expenditure. Insulin sensitivity and mitochondrial ATP production therefore fall on opposing sides of this balance. This concept therefore places mitochondrial function on an equal par with insulin resistance in the development of diabetes. Oscillatory networks in biology are advantageous, as they are spontaneously self-organizing and rapidly responsive to local needs without requiring central control. However, under extreme stresses, dynamic stability is lost and responses can become chaotic and disproportionate. It is hypothesised that long term excessive diet or physical inactivity, perturb the oscillatory network in such a way as to precipitate sudden phase-space bifurcations. This triggers cellular events such as insulin resistance or mitochondrial dysfunction and eventual involvement of both processes.

From this perspective, there is no distinct pathological pathway or agent required to trigger obesity-related type 2 diabetes. The condition is more a chaos response of physiological cytosolic and mitochondrial coupled oscillatory networks to lifestyle conditions beyond their stability threshold. Further research in the exact nature of the biochemical oscillators far from steady state equilibrium should provide better understanding of the constraints of nonlinear dynamics in these systems and the control needed to achieve controlled state, particularly when arguing that stressors could lead to loss of control resulting in disease.

There are four features of this chaos-driven hypothesis. Firstly, that type 2 diabetes can appear to arise spontaneously after prolonged periods of unchanged clinical diabetes measures. Secondly, with the non-scalability of chaos-based models, the response to long term sedentariness and excessive diet, may be fractal; ie will be similar at cellular, organ, person and even societal levels. Thirdly, the complications associated with either insulin resistance (microvasculopathy) or mitochondrial dysfunction (cardiovascular disease) can predominate in any one individual, depending on local conditions and timing. Equally, the effectiveness of treatments will also be condition and time dependant. Fourthly, chaos-based models are exquisitely sensitive to small differences in initial conditions. As a result, small incremental lifestyle choices in early life can impact significantly on health trajectories decades later.

This observational evidence-driven hypothesis is proposed with the intention of stimulating experimental research into mitochondrial insulin resistance interactions, to enable future mathematical modelling to improve risk prediction and trajectory analysis in people with type 2 diabetes.

Declaration of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.03.032.

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