



An intelligent systems explanation of type 2 diabetes and a narrative to promote lifestyle change

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Academic Editor: Marcela Brissova, Vanderbilt University Medical Center, USA

Received: July 3, 2026 **Accepted:** September 15, 2026 **Published:** October 10, 2026

Cite this article: Hyland ME. An intelligent systems explanation of type 2 diabetes and a narrative to promote lifestyle change. *Explor Endocr Metab Dis.* 2026;3:101483. <https://doi.org/10.37349/eemd.2026.101483>

Abstract

Type 2 diabetes is an error in the glycemic control system caused by insulin resistance. Self-organizing control systems use artificial intelligence to monitor and correct how they function and are used in modern applications of robotics. The development of type 2 diabetes is gradual and reversible through lifestyle changes, and this is consistent with insulin resistance being formed through a self-organizing or intelligent control system rather than the traditional control system on which current biomedical control systems are modelled. Lifestyles that induce high levels of glycemic variation would, in an intelligent control system, be detected as excessive oscillation, and an intelligent system can reduce oscillation by reducing the amplification. Insulin resistance represents low amplification in the glycemic control system. Intelligent control system functioning requires a network architecture, so if the glycemic control system is self-organizing, then it should be part of a network system that provides intelligent functioning for other control systems, and error in the glycemic control system would contribute to errors in other control systems and to a state of general network dysregulation. Intelligent systems theory explains how the comorbidities of type 2 diabetes and obesity would form through the dysregulation of a network of metabolic, immune, endocrine, and neurological pathways. The theory predicts that medical and lifestyle interventions for type 2 diabetes could improve comorbidities, but that comorbidities would reduce the effectiveness of those interventions. Studies are proposed to test this new theory that provides a non-blaming narrative for patients and could form a prequel to patient education.

Keywords

homeostatic dysregulation, artificial intelligence, networks, lifestyle, comorbidity, adherence

Introduction

Type 2 diabetes is a disease whose pathophysiology is well understood, and risk factors are known. This paper describes an intelligent systems explanation for these risk factors, why they cause type 2 diabetes in



some people and not others, and why type 2 diabetes and obesity are comorbid with other diseases. Suggestions are made for theory testing and how the theory can form a non-blaming narrative for patients.

Theoretical foundations: the intelligent body

Two types of control systems are used in technology: traditional and self-organizing. Traditional control systems have been known for more than four centuries. James Watt patented a control system in 1788 using a rotating fly ball that ensured that steam engines ran at a constant speed. The same principle of feedback control is used in biology and medicine, though the components differ. A self-organizing control system is a recent development made possible through the application of artificial intelligence (AI). A self-organizing control system combines the functionality of the traditional control system with the machine learning of AI. Machine learning is a technique that enables a machine to learn how to solve problems through a process of feedback. A self-organizing control system is one that learns to function correctly from repeated feedback as to whether the control system is functioning correctly according to some predefined criterion or pattern of functioning. If the control system fails to function according to the criterion, then the parameters of the control system are changed so that the control system functions correctly. The self-organizing control system can be envisaged as a traditional control system whose parameters are altered and controlled by AI. Self-organizing control systems are used in modern robotics [1].

Diagrammatic representation of biological control systems can give the impression that the control system always functions effectively. However, control systems function effectively only if the system variables (properties of the system as a whole) are correct. The amplification factor is a system variable that represents the strength of causal connections around the components of the control loop. The amplification factor determines the level of response to a given level of disturbance, where higher amplification creates a greater response. Combined with lag (the time taken for the causal steps between the components to complete one loop), the amplification factor determines how the control system functions. If the amplification is too low in relation to lag, then the system will fail to control the controlled variable or does so too slowly. If the amplification is too high in relation to lag, then the system oscillates. The values of amplification and lag need to be precise, and in 1868 James Maxwell [2] published a mathematical treatise describing the calculations needed to achieve effective functioning of the steam engine control system originally developed by James Watt.

The amplification and lag of mechanical control systems are calculated by a control engineer using maths. In a self-organizing control system, such as that used in robotics, the maths is made correct through feedback as to whether it is functioning correctly. The system 'learns' to get its parameters correct using known principles of AI.

The amplification factor in biological control systems is represented by the causal strength between ligands and receptors of the components of the control loop. Insulin resistance means that insulin has a reduced effect on cells of the body, and therefore insulin resistance represents a lowered and therefore suboptimal causal strength in the control system. Insulin resistance creates a glycemic control system when the amplification factor is too low.

Both traditional and self-organising control loops can suffer damage and therefore malfunction. Insulin resistance could be caused in two ways: by some kind of damage to the production of insulin or insulin receptors, or by a process of self-organisation that has led to the amplification becoming too low. There are two reasons for concluding that the error of insulin resistance is more likely to be a self-organizational fault rather than caused by some form of damage. First, type 2 diabetes develops gradually and is related to lifestyle. Damage tends to be more abrupt and have a specific cause in time, whereas self-organization change is a gradual process of learning. Second, and more importantly, type 2 diabetes is reversible with a low-calorie diet [3]. Type 2 diabetes can be cured by a diet that is the opposite of the diet that acts as a cause. Damaged parts of machines do not self-repair. By contrast, self-organization is a reversible process that can be achieved by reversing the conditions that cause the system to self-organize in the first place. A reasonable conclusion is that the biological error of type 2 diabetes is more similar to the control system error in an intelligent robot rather than the control system error of a steam engine.

Although type 2 diabetes could be similar to a fault that could develop in an intelligent robot, there is a difference. The robot is not alive. Robots and humans differ in the way they are organized. The robot is entirely modular. There are different parts or modules of the robot that are connected, each part having a separate function. Modularity is also a feature of the living body, and this is reflected in medical practice. There are different disease specialties, each dealing with errors in different parts or modules of the body. However, the body is only partly modular. It is also partly a connectionist or network system. The body's biological network has been described by Ivanov [4] as the body's physiome.

A network consists of multiple nodes with simultaneous causal connections between the nodes. This network architecture forms the basis of AI. A self-organizing control system is an intelligent control system. The intelligence of a modern robot is provided by a computer that, like all machines, is modular. However, because modern computers can perform more than a billion calculations per second, this allows the robot's computer to simulate the network structure of the brain. If the glycemic control system is a self-organizing control system, then, because it is also an intelligent control system, it must exploit the body's network architecture in some way. The self-organizing control system should be the consequence of a whole-body network of metabolic, immune, endocrine and neurological pathways that enables the body to function in part as an intelligent system [5, 6]. Intelligent systems theory is predicated on the assumption that intelligent functioning is not limited to the brain.

If the glycemic control system were part of a wider intelligent system, then insulin resistance would cause two kinds of error in the way the body functions. First, there is the specific dysregulation of the glycemic control system. Second, there is the general dysregulation caused by the effect of the specific dysregulation on the rest of the network. These two types of dysregulation, specific and general, will be considered separately.

Theory development: the specific dysregulation of the glycemic control system

If type 2 diabetes is caused by a self-organizing glycemic control system, then the control system must be responding to biological information. Information relevant to the level of amplification will take three forms: that the amplification is correct, that it is too high, and that it is too low. Glycemic levels that are constantly too high will indicate that the amplification is too low whereas glycemic levels that are constantly too low would indicate that the amplification is too high. In addition, a control system oscillates if the amplification is too great in relation to the lag, so an oscillating glycemic control system indicates that the amplification needs to be reduced. These three types of information could all have an impact on the amplification factor, but how they do this depends on the genetic programming of the body, because the functioning of the glycemic control system must be genetically specified. Genes can vary, so it is plausible that the relative contribution of these three types of information to the level of amplification varies, and for some people the impact of glycemic oscillation plays a comparatively greater role than increased glycemic levels, thereby making type 2 diabetes more likely when exposed to diets that cause oscillation. This hypothesised mechanism would explain the genetic predisposition to develop type 2 diabetes as an epigenetic effect where there is an interaction between genes that are sensitive to glycemic oscillation and lifestyles that vary in the level of glycemic oscillation.

The body could detect glycemic oscillation in several ways from a changing pattern of glycemic levels, and the theory cannot predict what form of glycemic variation this might be. The available data indicate only that the general concept of glycemic variability is an important factor. Meals with fast absorption characteristics create greater extremes between hyperglycemia and hypoglycemia and increase the risk of type 2 diabetes [7]. Hyperglycemic spikes followed by postprandial hypoglycemia are associated with risk for type 2 diabetes [8, 9]. The risk of diabetes can be reduced by activities that reduce glycemic variability such as slow eating rate and high eating frequency [10], exercise [11, 12], and stress reduction [13, 14]. Remission of type 2 diabetes can be achieved by a very low-calorie diet that produces little glycemic variability [3, 15]. Metabolic disturbance is a shared risk factor for type 2 diabetes and cardiovascular

disease [16], and evidence that variation in HBA1C levels, rather than mean levels alone, is a risk factor for cardiovascular disease [17] suggests that glycemic variation over longer time periods plays a role in the development of pathology.

The hypothesis that glycemic oscillation causes insulin resistance cannot predict how oscillation is detected from glycemic variability. There are several ways that the body could detect oscillation from glycemic variation. These include (a) the standard deviation of glycemic excursions, (b) the coefficient of variation, (c) the mean amplitude of glycemic excursions, (d) the average rate of change of glycemic excursions, and other possible statistical parameters that involve longer time periods. These alternatives cannot be established without empirical studies.

The theory predicts that glycemic variation is detected in some way as excessive oscillation, and the consequence is a gradual increase in insulin resistance over a period of time. This is a difficult hypothesis to test because glycemic levels and insulin resistance vary over the day, but long-term longitudinal data are needed for testing a theory of gradual change. The research question is: What statistical pattern of glycemic variation produces long-term change in insulin resistance? A possible design would be a week of continuous glucose monitoring with repeated measurement of insulin resistance, with the same assessments repeated at least one year later. The analysis would need to determine what statistical patterns of glycemic variation observed at the two time points (assuming they are the same) map onto changes in the average insulin resistance between the two time points. The population should include some people who are at risk of type 2 diabetes to allow comparison between people with different clinical profiles, and a comparison of glycemic variation at the two time points would indicate to what extent behavior has been constant between the two time periods; both are needed to help interpret the data. This study could establish a causal relationship between glycemic variation and change in insulin resistance, but other shorter studies can also be useful. The relationship between glycemic variation and variation in insulin resistance over a week could, using a mixed population, provide information about how a complex system varies in the short term, and such variation could be indicative of long-term change.

Theory development: general dysregulation of the network and comorbidities

The hypothesis that the body acts as a network system of interconnected causal pathways is supported by evidence [4, 18], and if the body functions as a network, then the network structure has the capacity to produce intelligent functioning. Poor functioning of this network would produce a state of dysregulation of the network as a whole [5, 6, 19] that should produce correlations between biomarkers indicative of different pathologies. These correlations would reflect variation in the level of general dysregulation within a population, and because general dysregulation contributes to the specific dysregulation of diseases, intelligent systems theory predicts that diseases will tend to be comorbid and that comorbidity reflects the degree of disturbance to the network as a whole. Network structures differ between people even with similar pathology [20], so the pattern of comorbidity should differ and create individual differences in the way comorbidities influence each other.

In a longitudinal study of healthy children, principal component analysis was applied to biomarkers that included insulin resistance, triglycerides, C-reactive protein, cholesterol, systolic and diastolic blood pressure, and body mass index [21]. Analysis revealed a strong first factor on which all biomarkers loaded, consistent with a biological state of general health where metabolic health plays a major role. Data were collected at two-year intervals from the age of five until 18, and factor loadings (as represented by the percentage variance explained) increased from age five onwards, with the greatest increase between ages five and seven. These results are consistent with the hypothesis that general dysregulation differs between people as early as seven years of age. A measure of mood was collected at age 18 years, and poor mood was associated with poor metabolic health independently of adiposity, showing that poor mental states are related to disturbance across multiple biomarkers [22].

A network system of interconnected control systems should create comorbidity, so type 2 diabetes should be associated with other diseases through metabolic, immune, endocrine, neurological, and other causal pathways. Type 2 diabetes and obesity are comorbid with life-threatening illnesses, such as heart diseases [16] and cancer [23], with mental illness such as depression and anxiety [24], and with chronic inflammatory diseases such as rheumatoid arthritis, ulcerative colitis [25], and asthma [26, 27]. In a network system, there will be bidirectional effects between comorbidities, so if type 2 diabetes is a specific type of network error, then type 2 diabetes will contribute to and be increased by other comorbidities. The theory also predicts that the comorbidities of type 2 diabetes will vary between patients because the causal strength of nodes of the network can vary between patients [20].

If the body functions as a network, then a state of high general network dysregulation should make changes to individual control systems more difficult. Obesity and other comorbidities reduce the effectiveness of biologic treatment in severe asthma [28], a finding that has been explained by general dysregulation counteracting the effect of treatments for specific dysregulation by anchoring the system in its pathological state [29].

The intelligent systems theory predicts that medical and lifestyle interventions targeting one disease could also improve outcomes of comorbid diseases as well as improving mood. However, if a medical intervention that improves the functioning of a specific control system has an adverse effect on the wider network, then comorbidities may not be reduced. Corticosteroids reduce the inflammation of inflammatory disease but, because of their effects on multiple systems, could harm general regulation, thereby explaining oral corticosteroid side effects. Monoclonal antibodies have a more targeted effect on inflammatory pathways, are therefore less likely to adversely affect the network and more likely to achieve benefit on comorbidities. Lifestyle improvements, by contrast, are unlikely to have adverse effects and should cause a wide range of benefits across the whole of the network both in terms of biomarkers and symptoms. Studies that confirm these predictions would support the theory being proposed.

If the body acts as an intelligent network system, then treatment for type 2 diabetes could alter the connections across the network and alter network parameters such as connectivity and fragmentation. A possible study would be to measure biomarkers in obese people and assess network connectivity and fragmentation between the biomarkers before and after a treatment, such as glucagon-like peptide-1 (GLP1). Changes in network connectivity provide information about how a system operates as a whole [30].

Clinical implications: lifestyle and patient narrative

The intelligent systems theory predicts that the effectiveness of lifestyle interventions for type 2 diabetes should vary for three reasons. First, patients who have multiple comorbidities should have high levels of general dysregulation and should exhibit weaker and slower responses to lifestyle changes than those with few or no comorbidities. The reason is that general dysregulation should anchor the system in a pathological state [29]. Lifestyle modifications that are multimodal, as those suggested by the American College of Lifestyle Medicine [14], are more likely to be helpful than those that involve only one form of lifestyle change, as multimodal improvements would be expected to have a wider impact on the body. Second, patients who are genetically sensitive to glycemic variation should, according to the theory, require a stricter dietary regimen to effect change compared to those who are less genetically sensitive. A third reason is that lifestyle change is not easy. Motivated behavior is achieved through behavioral control systems [31], and eating is a motivated behavior. The behavioral control systems that determine food preference evolved before or during the Paleolithic periods (before 12,000 to 10,000 years ago) when diet consisted of large quantities of varied vegetable matter, and fish and meat [32], a diet known to have health-promoting properties in modern humans [33]. Preference for sweet foods evolved to promote consumption of the preagricultural vegetables and fruit that contained only small amounts of sugar. Sugar preference is genetically programmed into the body. The modern environment makes healthy lifestyle choices difficult because the body and mind are adapted to the diet and exercise of a hunter-gatherer lifestyle, not the modern environment of sweet foods and screens. The modern environment is the consequence of cultural rather than biological evolution [34], and type 2 diabetes is the consequence of a conflict between culture and biology.

According to the intelligent system explanation of type 2 diabetes, type 2 diabetes results from a conflict between two control systems, behavioral and glycemic. The control systems worked effectively in the environment in which they evolved but can cause type 2 diabetes in the modern environment. Although further evidence is needed to test the theory, the theory can form a narrative for patients as a prequel to education and advice about coping strategies.

A computer analogy has been used as a way of drawing on existing patient knowledge to help patients understand fibromyalgia [35]. The computer analogy provides patients with an external rather than internal attribution of blame [36] and thereby avoids negative self-attributions and self-blame that can be inferred from lifestyle advice. Although the analogy is limited because computers are not alive, the narrative can be supplemented by information about how the body works as a whole system. A possible script that can be included at the start of patient education [37, 38] is shown below.

A script explaining the intelligent systems theory of type 2 diabetes for patients:

“In some ways, the body is like a clever computer whose programs evolved hundreds of thousands of years ago. One of those programs encourages you to eat sweet foods, because ancient vegetables and fruit contained small amounts of sugar. Another program causes type 2 diabetes when modern sweet foods and unrefined carbohydrates are eaten. This happens because large variation of sugar in the blood is detected by the body as an error, and the body corrects this supposed error by changing its programs to make type 2 diabetes. Unfortunately, some people’s computer programs detect this error more readily, making type 2 diabetes more likely. Getting healthy again means reprogramming your body with diet and exercise more like that of our ancient ancestors. This takes time and can be difficult because your body is also programmed to eat food when it sees it, so you may need to trick your body into doing what you want it to do.”

Abbreviations

AI: artificial intelligence

GLP1: glucagon-like peptide-1

Declarations

Author contributions

MEH: Writing—original draft, Writing—review & editing, Conceptualization. The author read and approved the submitted version.

Conflicts of interest

The author declares that he has no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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