Information-feed pathways in biological systems as evidence for occurrence of non-natural stimulus-functional response pairing

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This paper explores a possible underlying tenet of classical information-feed pathways (feedback and feedforward) as seen in metabolism and signaling in biological systems. We intend to determine whether information-feed pathways derive from spatial and temporal overlap of event occurrences involving connection points of the information-feed loop. We shall revisit three known and established biological phenomena involving information-feed, in an attempt to deduce the principles governing such phenomena. We propose that such principles involve anticipatory associations.

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Introduction

We aim to realize the presence of (if any) anticipatory associations in well-studied and established biological phenomena. Of utmost interest, are those biological phenomena involving information feedforward and feedback. These phenomena have been previously shown to be the means of control and regulation of metabolic processes such as seen in transcriptional networks[1, 2, 3]; in addition to signal mediation as with autocrine-, paracrine-, and hormonal-based signaling regimes. For this work, we shall attempt to demonstrate a possible underlying tenet: that such forms of communication stem from existing anticipatory associations between involved points.

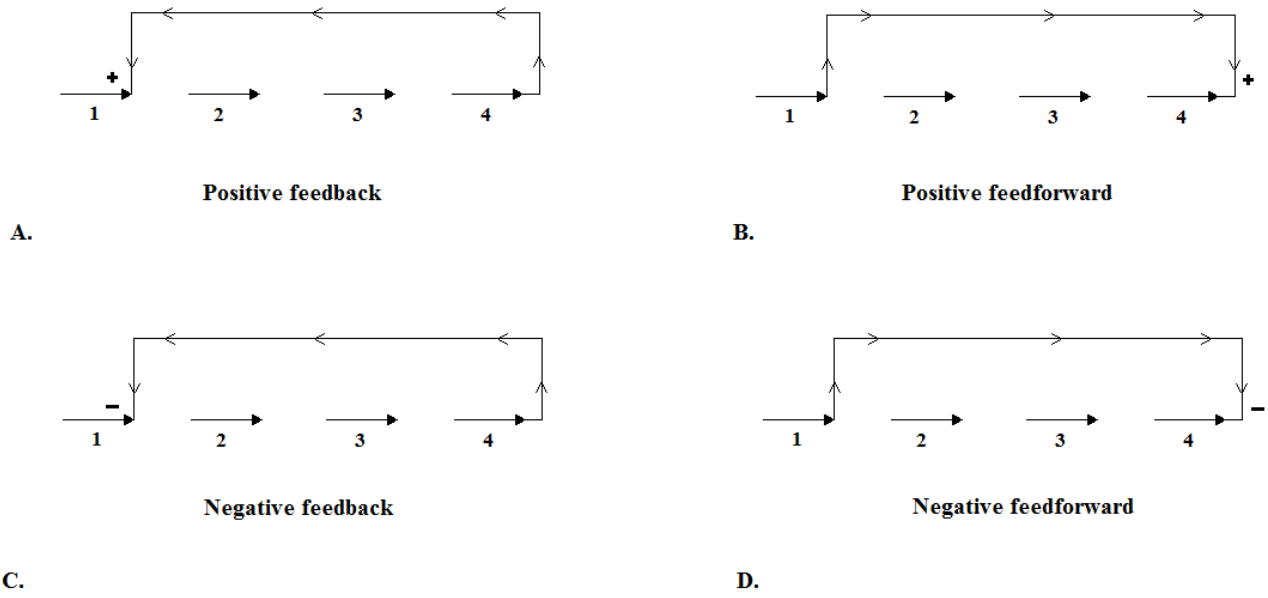

Figure 1.0 Illustrates information-feed pathways (stick arrows) for both feedback and feedforward paths. Note that both direction of information-feed can give rise to either positive or negative controls.

For the previous work, Jeff-eke, 2015c, we stated that for a **preceding event** (**PE**) to affect a natural functional response for an **anticipated stimulus event** (**ASE**), it [PE] must be able to affect a property of the system (manifested as a change in state of the affected property from a zero point- to an arbitrary state), and therefore a functional response and yield must follow such that the yield attempts correction of the s-value of the property affected. Thus, the PE is a natural stimulus for such a functional response of the system. We concluded that a PE can be both a **natural stimulus** and a **non-natural stimulus** (a mediator of natural functional response processes for ASEs).

Also, an event that is considered an ASE under one analysis, can be considered a PE under a different analysis; as long as it meets the set of criteria for such considerations. Thus, an ASE can both be a natural and a non-natural stimuli. In essence, a PE may be considered an ASE, and an ASE may be considered a PE, depending on whether it is associated with occurrences of past and future events. In addition, both these events can be natural and non-natural stimuli.

We can also infer from the requirements for formation of anticipatory associations[4], that it is feasible for PEs to be consequential effects of either deviation- or functional response processes, and as such can be either concrete, well-defined entities, such as a defined signaling molecule; or intangible, but physical

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phenomena such as thermal fluctuations. Thus, such consequential effects may be considered non-natural stimuli if they share anticipatory associations with natural stimulus-functional response pairs.

The significance of occurring phenomena to the system

As stated in the opening of Jeff-Eke, 2015a; the use of the term "intention" in descriptions of biological phenomena is an inappropriate position. Instead, we repeatedly applied the term *significance* when describing such phenomena. To illustrate this point, consider the question: *What is the intention of pancreatic islet cells in their secretion of insulin?* As opposed to the form: *What is the significance of the phenomenon defined as insulin secretion to the system wherein such secretion occurs*. Whereas the former denotes a sense of purpose-driven secretion of insulin for which islets are "aware"; the latter does not evoke such a drive. Instead, the latter question evokes a sense of implication of insulin secretion (by islets cells) for the system. Thus, we approach the following discussion from this position.

We suppose that occurrence of phenomena such as that of a natural stimulus, and its ability to affect its natural functional response pair is of ***principal significance*** to the system. Thus, occurrence of phenomena such as PEs with an ability to affect natural functional responses of ASEs are not of principal significance to the system. Instead these non-natural stimuli merely originate from chance spatio-temporal overlapping of occurrences of both non-natural stimuli and natural stimulus-functional response pairs[4]. We describe occurrence of such phenomena as being of ***adaptive significance*** *to the system*. However, when considering the given PE as a stimulus for its [PE] natural functional response pair-part[4], we conclude that it is of principal significance to the system.

Occurrence of phenomena that involve the intrinsic nature of comprising entities are said to be of ***inherent significance*** to the system. In other words, we suppose that these phenomena derive from the chemical and physical characteristics of involved entities. All other phenomena that do not fall into any of the above classifications are considered to be of an undefined significance to the system and as such their occurrences are said to be of ***unspecified significance*** or merely of significance to the system.

If occurrence of a phenomenon is seemingly of multiple significance to the system, one of these must take precedence over other(s). We suppose that inherent significance takes precedence over principal significance, and principal significance takes precedence over adaptive significance. The rationale is that if we are to observe the earliest occurrence of phenomena in the evolutionary lineage of organismal systems, it is more-likely that these occurrences involve the nature of involved entities rather than the ability of these entities to auto-correct state values of properties –as with a natural stimulus-functional response pair. In terms of precedence between principal and adaptive significance, we already stated that an adaptive significance of an occurrence of a phenomenon stems from anticipatory association between the occurring phenomena and the natural stimulus-functional response pair. Thus, occurrence of a phenomenon of adaptive significance depends on the presence of an occurrence of principal significance. Hence, the precedence of principal over adaptive significance.

Our aim is to determine whether or not such adaptive significance can be found in biological systems, and to accomplish this feat, we shall discuss three known processes in multicellular organisms (mainly humans). In order to pinpoint processes for which occurrence of a given phenomenon may be of an adaptive significance, we can either compare the involvement or activities of the phenomenon in two or more given processes, or activities of two or more known phenomena in the process for which we have

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the greatest index of suspicion is of adaptive significance to the system. For cases involving phenomena with few known processes for which they are involved, we may instead apply one of the above comparisons. We now attempt identification of adaptive significance.

Case in point 1: Possible adaptive significance for activities of adenosine monophosphate (AMP) and insulin in Glut IV recruitment

Under physiological conditions, pancreatic release of insulin follows after glucose enters islet cells. Following glucose entry, ATP levels within these cells has been shown to increase as a result of increased glucose catabolism. The increased ATP concentration increases the probability that ATP molecules bind to so-called "constitutively open" ATP-gated K^+ channels, with concomitant closure and decreased efflux of K^+ ions from islet cells. The resultant effect is depolarization of these cells with fusion of insulin-laden vesicles and eventual release of insulin into blood; by way of the rich capillary system in close proximity to these [islet] cells [5, 6].

It is known that glucose uptake by skeletal muscle cells is enhanced by islet cell-derived insulin molecules. Thus, uptake of glucose by skeletal myocytes can be said to depend on occurrence of the above sequence of events involving pancreatic islets. The mechanism by which insulin affects skeletal muscle cell uptake involves recruitment of an isoform of the predominant and most studied glucose channels, Glut IV; from cytosolic vesicular membranes to the sarcolemma [7]. At the sarcolemma, it is believed that Glut IV in addition to other isoforms (Glut 1, 5, 12) function as routes for glucose entry into myocytes, thereby increasing glucose influx. Thus, recruitment of Glut IV to the plasma membrane increases the rate of glucose influx into myocytes, as opposed to a case where such recruitment is impeded [7].

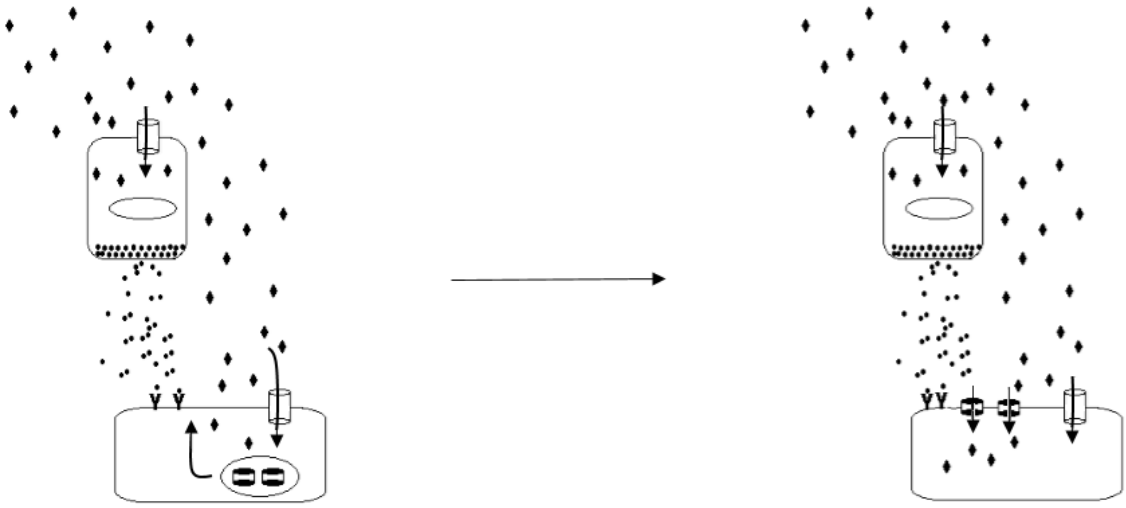

Figure 1.1. An illustration of the effects of insulin (dots) on muscle cells (lower cell) in the presence of glucose molecules (diamond shape). The increase in glucose levels affect an increase in secretion of insulin by pancreatic cell(s) (upper cell) which in turn binds to insulin receptors on myocytes with resultant increase in recruitment of glut IV transporters to the sarcolemma. The increase in glut IV content of the sarcolemma increases the permeability of myocytes to extracellular glucose.

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In addition to enhancing skeletal myocyte uptake of glucose, insulin has been shown to increase myocyte synthesis of hexokinase and glycogen synthase [8], ***thereby decreasing the intracellular glucose concentration in the absence of glucose sources***. Of the numerous effects of insulin on skeletal muscle cells, we focus on the arm of insulin effect on decreasing intracellular glucose concentration that mainly occurs by catabolic consumption of glucose.

In synergy with the effects of insulin, both exercise and increased AMP-kinase activity have also been shown to affect an increase in Glut IV recruitment [9, 10]. AMP-kinase activity has been shown to be elevated with an increase in AMP to ATP concentration ratio. Such increments can occur in a setting of increasing ATP and ADP hydrolysis and phosphorylation events. The drop in ATP levels and/or an attempt to restore ATP levels result in an increase in glucose flux through catabolic pathways, thereby increasing the rate of glucose consumption. ***Thus, a decrease in intracellular glucose concentration should follow marked ATP consumption.*** This would be more so in a setting of diminished glycogen content and/or low extracellular glucose concentration. Under such conditions, there would be a decline in the rates of intracellular glucose replenishment.

We therefore surmise that all three effectors (insulin, exercise, and AMP) can, in principle, affect an increase in catabolic consumption of the intracellular pool of *free* glucose molecules; and by such means, can potentially affect reduction of intracellular glucose concentration. As stated previously, one mechanism for glucose replenishment following such reductions is characterized by glucose influx from the extracellular space. Thus, increments in Glut IV recruitment can be considered a processing step for this influx mechanism. Refer to Jeff-Eke, 2015b for a more detailed explanation of processing steps, processes and mechanisms.

We formally define the significance of an occurrence of G*lut IV recruitment in the presence of other isoforms of glucose channels as: an attempt* ***to increase glucose influx in the setting of low intracellular glucose concentration.*** *Thus, Glut IV recruitment and activity is an essential component of a functional response mechanism. In keeping with the concept of natural stimulus-functional response pairing, it should follow that the* natural stimulus for Glut IV recruitment is *a decrease in intracellular free glucose concentration from a baseline value*. Using terminology from gauge analysis, this would translate to: a shift in s-value of the primary property (intracellular glucose concentration) such that either or both a direct and/or indirect effect (as a result of delta drift) of low intracellular glucose affects an increase in recruitment of Glut IV (functional response); which in turn increases glucose influx into affected cells, and by so doing increase the intracellular glucose concentration. Thus the increase in intracellular glucose concentration is the **yield of functional response** (**YFR**). We now attempt to determine the significance of intracellular AMP and insulin to the process involving Glut IV recruitment.

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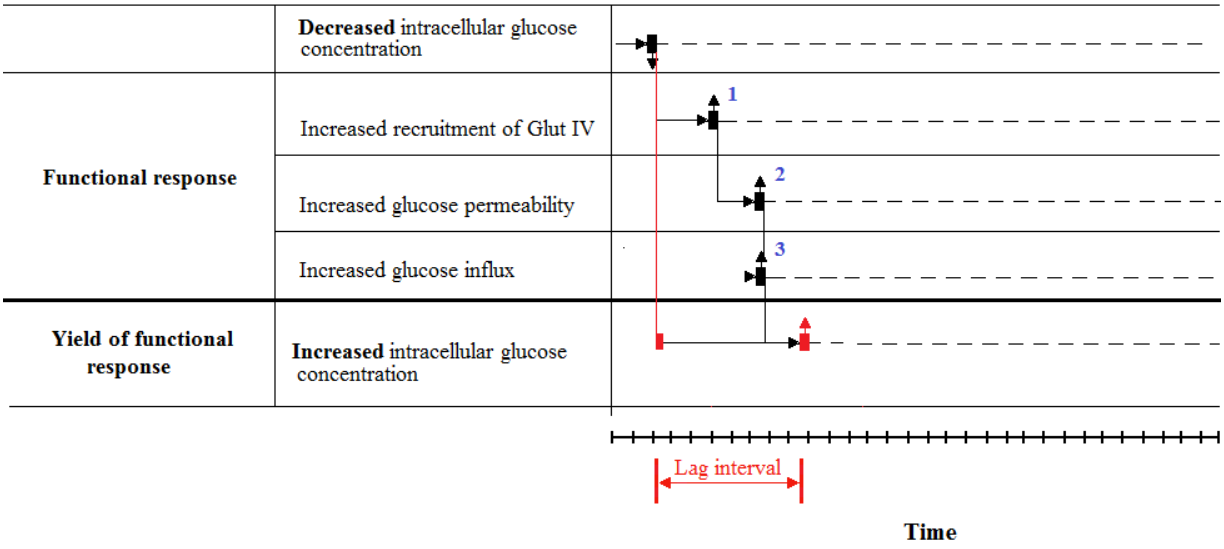

Figure 1.2. A gauge-based representation of natural functional response processes of a decreased intracellular glucose concentration of a myocyte. The YFR is an increase in the intracellular glucose concentration. Note that the lag interval is the time interval from the moment of decrease in intracellular glucose concentration by a given quantity (as depicted by downward facing arrow and height of arrow bar), to the point of availability of appropriate YFR (as depicted by the upward facing arrow and height of arrow bar; all in red). Note time axis not drawn to scale, but merely reflects the sequence of events.

We can define the change in intracellular AMP concentration as a change from the zero-point state of the property defined as AMP concentration. Also, since this is a property of the system, it should follow that there exist a challenge stimulus and functional response that results in the stated changes and correction of such changes (return to zero point state), respectively. We can consider the challenge stimulus and/or the change in intracellular AMP levels to be a natural stimulus for the functional response that corrects such change.

Since an increase in Glut IV recruitment has no immediate corrective effect on the property defined as intracellular AMP concentration, it should follow that neither the challenge stimulus that incites change in intracellular AMP concentration nor the actual change in intracellular AMP concentration is a natural stimulus for the functional response defined as Glut IV recruitment. Instead, changes to intracellular AMP concentrations may be preceding- or overlapping events to/with the natural stimulus for Glut IV recruitment –that is, a decrease in intracellular glucose concentration. Changes to AMP concentration can therefore be considered a non-natural stimulus in this regard. Thus, an anticipatory association may exist –by way of spatio-temporal overlap between these events. That is, spatio-temporal overlap between an increasing intracellular AMP concentration and an increasing Glut IV recruitment. If the above claim holds true, then formation of anticipatory association between these events must have occurred in a setting of spatial and temporal overlap of occurrences of:

i. An increasing intracellular AMP concentration (due to consumption of ATP and/or ADP in hydrolysis and phosphorylation processes);
ii. A decreased and/or decreasing intracellular glucose concentration, and
iii. An increasing recruitment of Glut IV channels that typically follows reductions in intracellular glucose concentration.

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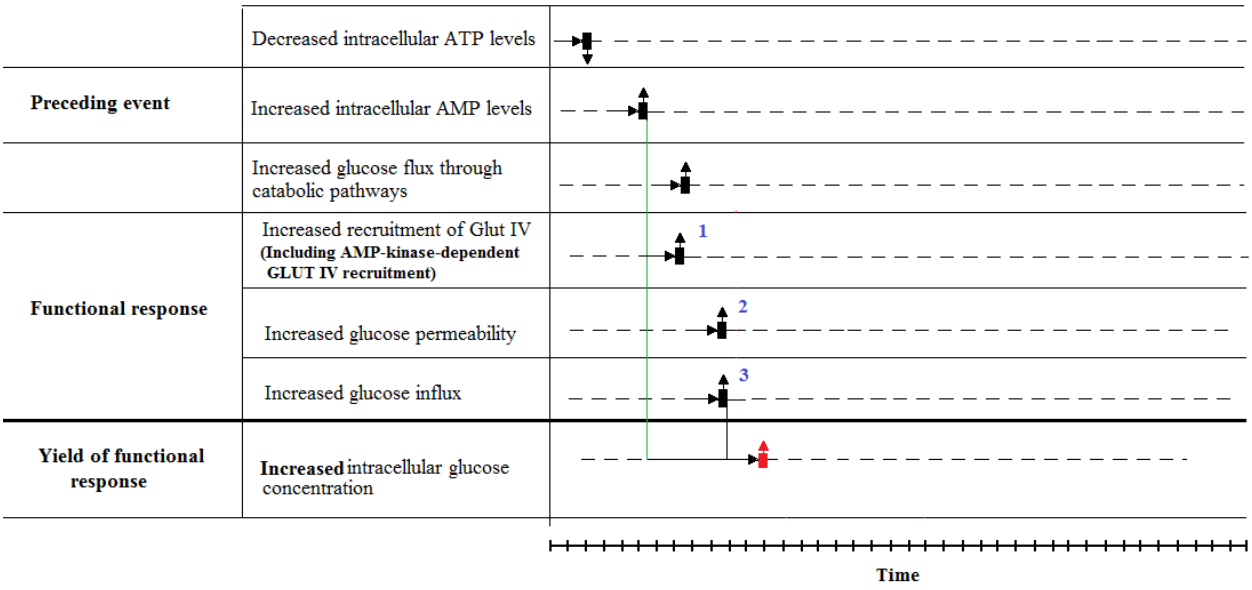

Figure 1.3. A gauge-based representation of a series of preceding events to a natural functional response process for a decreased intracellular glucose concentration (anticipated stimulus event) of a myocyte. We exclude the anticipated stimulus event to highlight the concept: that preceding events (increased intracellular AMP) can result in the same functional response process and yield as the anticipated stimulus event. Compare and contrast with figure 1.4.

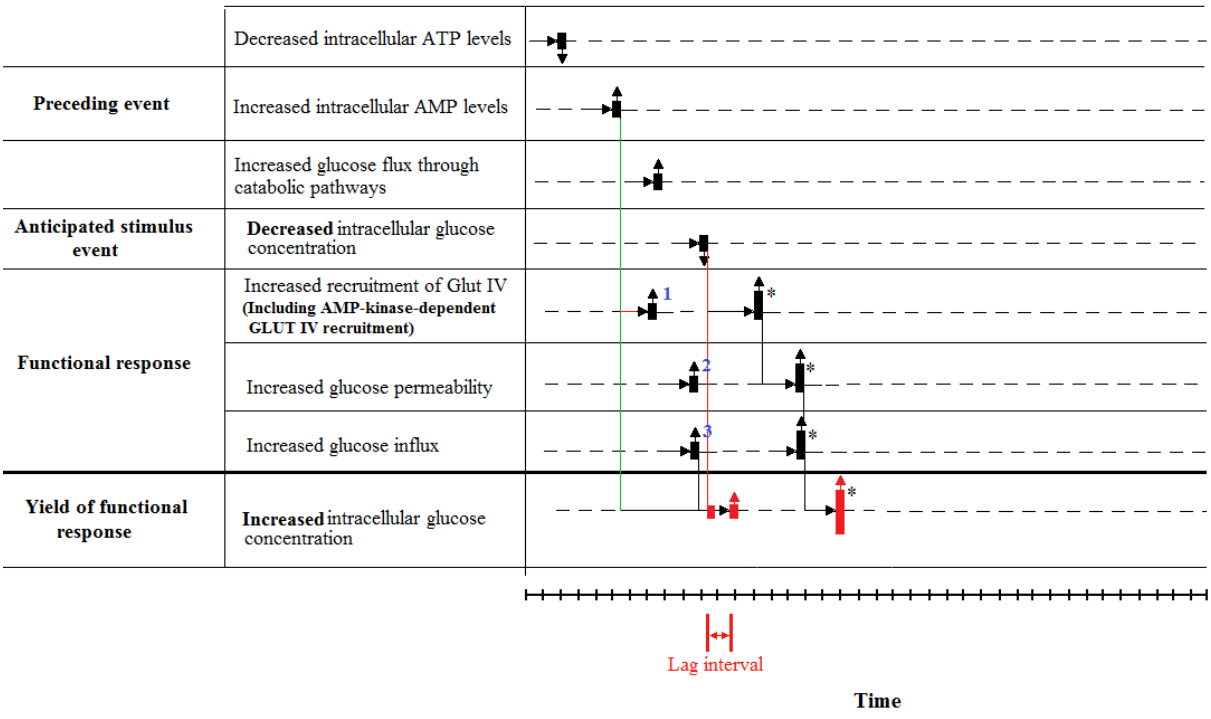

Figure 1.4. A gauge representation of a series of preceding events to a natural functional response process for a decreased intracellular glucose concentration of a myocyte. Here we show both preceding and anticipated events. Note that for rows with double arrows, the preceding arrow for each event arises due to anticipatory association between an increase in intracellular AMP levels and increased recruitment of Glut IV via AMP-kinase-dependent pathways (indicated by green vertical line). On the other hand, the second, longer arrows for each row (asterisk) indicates the cumulative effects of preceding and anticipated [stimulus] events on the functional response process and YFR.

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We can also apply the same logic to the significance of insulin molecules in glucose uptake. Since an increase in Glut IV recruitment has no immediate corrective effect on the property defined as ambient insulin concentration, it should follow that neither the stimulus that incites change in ambient insulin concentration nor the actual change in ambient insulin concentration are natural stimuli for the functional response defined as Glut IV recruitment. Thus, similar to increasing intracellular AMP concentration, the effect of an increasing ambient insulin concentration may be preceding- and/or overlapping events to the natural stimulus for Glut IV recruitment. Thus, an anticipatory association may exist between an increasing ambient insulin concentration and an increasing Glut IV recruitment. If the above claim holds true, then formation of anticipatory association between these events must have occurred in a setting of spatial and temporal overlap of occurrences of:

i. An increase/increasing ambient insulin concentration that follows increased/increasing blood glucose levels;
ii. A decreased and/or decreasing intracellular glucose concentration (resulting from increase in glycolytic enzyme content and activity); and
iii. An increase in recruitment of Glut IV channels that typically follows reductions in intracellular glucose concentration.

This is especially so, considering that insulin increases glycolytic enzymes which, as stated previously, allow for increased glucose catabolism, thereby increasing the potentiality for reduction of intracellular glucose concentration.

Thus, in principle, we can uncouple pancreatic insulin secretion from myocyte recruitment of Glut IV channels, and if other positive effectors of myocyte glucose uptake (exercise, ATP) are present, then it should follow that Glut IV recruitment still occur. That is, with glucose infusion into blood, insulin secretion and Glut IV recruitment still occur, albeit independently. Thus insulin is not a necessity but is instead a sufficient requirement for Glut IV recruitment.

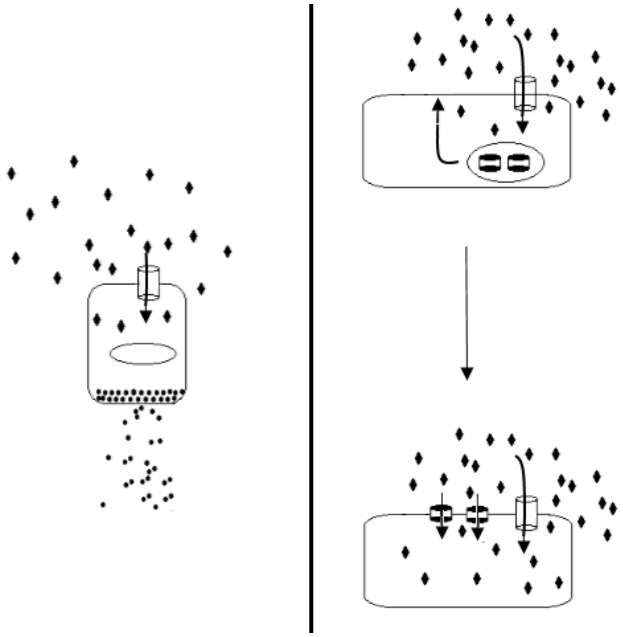

Figure 1.5. An illustration of both insulin secretion by pancreatic cell(s) (left image) and increased recruitment of Glut IV to sarcolemma with resultant increase in glucose influx (right image). Both images are shown separately to indicate that these events may have been naturally

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independent of one another, but came to be coupled following anticipatory associations resulting from spatio-temporal overlap of their occurrences.

Case in point 2: Possible adaptive significance for the activity of interferons in cellular responses to the presence of viruses

It is known that some mammalian cell types release certain mediators when their cytosolic contents are invaded by full-fledged viruses, or their [viral] constituent parts [11]. Of interest to us here is a special type of mediator termed interferons. Two examples of mediators of interferon production are: double stranded RNA and viral proteins [12, 13]. One of many important activities of secreted interferons is related to the effect they have on cells devoid of viral agents, hence have not yet been infected by viruses [11]. This effect is an increase in vigilance of [uninfected] cells toward pending viral infections, and such vigilance derives from an increase in expression of antiviral machineries. It is by way of these machineries that these cells produce their antiviral effects: prevention of both the virus' nucleotide replication and packaging of its parts. Interestingly, both these components of viruses and interferons have been shown to affect an increase in expression of similar genes [12]. Thus, similar to IFN molecules, we can consider these viral constituents inciting stimuli for cellular antiviral response.

The question that arises then is: *Of these two mediators and their respective activities, which is of principal significance to these cellular systems?* To answer this we compare the natural stimulus and functional response pairing relationship. We define the functional response(s) of cells to either of these mediators as an increase in the expression of peptides and proteins involved in prevention of viral replication. The yield of functional response in turn is the actual hindrance of viral replication. We thus can conclude from knowledge of the functional response process and YFR that its natural stimulus is related to the presence of viruses or viral elements about intracellular spaces. Based on analysis of both mediators posited, viruses and their parts are more likely the natural stimulus than are the secreted interferons. Thus, it should follow then that the involvement of viruses and their parts in the viral response process are of principal significance to cellular systems.

Thus we conclude that, unlike viruses and their parts, activities of interferon molecules are of adaptive significance to cellular systems. The resultant association thus would derive from spatio-temporal overlaps between:

i. Occurrence of an increase in interferon levels about the vicinity of affected cells; as a result of induction by viral infection at cells completely infected;
ii. Presence of (free) viral component parts and/or initiation of viral infection at cells incompletely or not infected;
iii. Increase in gene expression and activity of the antiviral machinery that naturally follows from the presence of viruses and their component parts at incompletely or not infected;.

Viral infection or presence of its component parts in and about cells can stimulate an increase in synthesis and secretion of interferon molecules [11, 12, 13], thus allowing for the possibility of overlap between these mediators [viruses, viral parts, and interferon molecules] in space (at the cell) and time.

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Case in point 3a: Possible adaptive significance for the activity of nitric oxide in vasodilatory function: Comparison between microbial and vasodilatory activities of nitric oxide

Here we consider the significance of occurrence of nitric oxide (NO) activity in biological systems. To determine such significance, we compare the activities of NO in two known processes.

NO production involves oxidation of L-arginine by NO synthase, which occurs in three isoforms. The reaction products are NO and citrulline [14]. In addition, there are two major utilization paths for NO: a microbicidal path (involving endothelial /macrophage/ neutrophil-derived immune response processes) and vasodilatory path. The microbicidal path involves utilization of NO in formation of highly reactive intermediates, the so-called reactive nitrogen species. NO reacts with oxygen free radicals (a reaction also involving consumption of NADPH), with production of peroxynitrite, a highly reactive agent. In turn, peroxynitrite reacts with microbial membrane components, rendering them damaged. Thus, affecting microbial cell death [15, 16].

On the other hand, NO activity in vasodilatory response process which may be elicited in response both to inflammation and to an increase in shear stress (from a baseline level) on vascular endothelial cells. The former is related to inflammatory reactions which could occur in response to cell/tissue death, the presence of either foreign bodies or microbial agents[15]. Thus, in terms of an inflammatory origin, its vasodilatory and microbicidal activities are related. The vasodilatory activity of NO involves inhibition of smooth muscle contraction. Hence it favors an increased extent of vasodilation of vessel walls, and by so doing, decreases shear stress on involved vessel segments[14].

Considering that NO involvement in inflammatory response processes can be ascribed to (at least) two paths, we can conclude that it [NO] plays a multi-dimensional activity in inflammation. However, if we consider these activities in detail, we can conceive that they are quite different. To identify the significance of the occurrence of NO in each of these paths, we compare activities of NO in the aforementioned processes.

As stated in the opening, occurrence of phenomena that involve the chemical and physical characteristics of involved entities are said to be of inherent significance to the system.

The free radical chemical nature of NO is exploited in damaging microbial cell structures. A process for which NO is involved via a single step reaction in formation of the highly unstable peroxynitrite. Although, for the case of vasodilatory activity, the chemical nature of NO also allows for its initial interaction and binding to its receptor on smooth muscle cells (SMCs), [however] it is not the chemical or physical nature of NO that directly affects the consequential vasodilatory effects. Instead, NO can only affect vasodilation by its ability to initiate a cascade of downstream events that, compared to its microbicidal function, are far removed from the response yield. To validate this point, let us consider the sequence of events that are required for NO-induced vasodilatory response:

1. NO initially binds to a G-protein-coupled receptor on vascular smooth muscle cells (SMCs) [14].
2. Binding of NO to this receptor results in activation of receptor-G protein complex, with conversion of GTP to cyclic GMP (cGMP) [14].
3. Increments in cGMP levels increases the probability that cGMP molecules bind to and activate protein kinase G (PKG) molecules[14]. Thus, at a critical concentration of cGMP, PKG activity can be appreciated: with PKG activity involving phosphorylation of myosin molecule[14].

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4. At a critical level of myosin phosphorylation, the contraction cycle (involving repeated myosin-actin adherence and subsequent separation with shortening and unshortening of vascular lumen radius, respectively) is hindered. Thus, leaving these SMCs in a relaxed state.

Thus we conclude that occurrence of NO activity is of inherent significance to the system, and that such significance can be appreciated as a manifestation of the microbicidal activity. To explain why we ruled out a principal significance from the get go, consider the absence of a change in NO concentrations (or pressures) as natural stimulus for the change in NO that is observed to occur for both microbicidal and vasodilatory paths. Since the vasodilatory activity of NO is neither of principal nor inherent significance, it should follow that it is of adaptive significance to the system.

Case in point 3b: Possible adaptive significance for the activity of nitric oxide in vasodilatory function: On formation of anticipatory associations between occurrences of: shear stress, natural stimulus for vasodilation response, and nitric oxide synthesis.

Let us suppose we restrict the vasodilatory response that would normally follow from increasing shear stress. In other words, the involved vessel lumen is maintained at a fixed radius. If we now suppose an increase in shear stress (by way of increasing blood flow through the vessel segment), it should follow [eventually] that a critical shear stress level would be attained, such that endothelial cell injury and death occur. In turn, the inflammatory response should ensue, so as to initiate the clearing and replacement process that is required to maintain continuous and viable endothelial cell presence about the involved vascular segment. Thus, by way of inducing injury and cell death, shear stress on endothelial cells can incite an inflammatory response. As stated previously, the inflammatory response involves an increase in production of NO both by endothelial cells and by the phagocytic system of cells (macrophage and neutrophils). Based on this sequence of events, it follows that shear stress can potentially affect an increase in NO production, thus a drift path which constitutes shear stress (as the affected lower order property) and NO production, can be defined. With persistently elevated levels of shear stress, the two events (increasing shear stress and NO production) may share a close temporal proximity about the vicinity of the involved vascular segment.

If we now suppose that instead of the situation wherein shear stress-induced endothelial injury (that was said to have derived from a blunted vasodilatory response) now derives from shear stress effects in excess of a vasodilatory response. It should follow then that even with an increase in vasodilation (by way of its natural stimulus), shear stress still occurs. In this setting, the increase in shear stress; natural stimulus for vasodilatory response; vasodilatory response; and NO production can occur concurrently thereby satisfying requirements for formation of anticipatory associations between these events. Moreover, the vasodilatory response is derived from SMCs and it must follow that both the natural stimulus and non-natural stimulus (NO) for such response occur at the SMC containing tunica media; further supporting the notion that they satisfy the spatial requirement for anticipatory associations. Thus, NO induced vasodilation of vascular segments may derive from anticipatory association that have resulted from previous spatio-temporal overlap between occurrences of:

i. An increase/increasing shear stress on involved vascular segments;
ii. An increase in the natural stimulus for the vasodilatory response as a result of a shear stress-induced delta drift;
iii. Increase in endothelial cell injury and/or death as a result of increasing shear stress.

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iv. An increase in inflammatory response to endothelial cell injury and/or death that results from shear stress at vicinity of involved segment;
v. An increase in NO production by endothelial cells at vicinity of involved segment as a result of occurrence of its [NO] natural stimulus.

Conclusion:

From cases presented above we can surmise that the respective involvements –of mediators and metabolites– in processes ranging from: signal transduction, flux and metabolite shuttling between metabolic pathways; signaling by autocrine, paracrine, and hormones: may be of anticipatory significance to the system wherein they occur, and therefore derive from anticipatory associations. With the resultant effect being an interlaced and convoluted network of phenomena. We now turn to the question posed in Jeff-Eke, 2015c: That is, whether or not such anticipatory associations can be produced in individual organisms or whether they are relics of a by-gone era, that are merely passed down from parent to offspring. The following discussion focuses on the possibility that such novel associations can occur at the level of the individual. For this last analysis, we turn to a possible role of anticipation in constitutive phenomena, and how this might affect inferences made from observation; if not taking into account.

A possible role for anticipation in origins of some constitutive and autonomous functions.

Most so-called constitutive phenomena are labeled as such due to findings that they do not fall under the general regulations of other known and related phenomena. Thus, this categorization follows as a "fall-out from convention". For some processes, the constitutive designation results from the absence of regulation at steps for which evidence has repeatedly shown to be involved in regulatory function(s). Whereas for others there are no known stimuli for which the functional response follows after. For example, some forms of secretion are said to occur in the absence of an inciting stimulus, which is in contradiction to well established regulatory forms. Thus, these automated forms of secretion are termed constitutive. However, if there exist stimuli for the constitutive phenomena, but with such stimuli being exceptionally different from conventional considerations, then these stimuli will be seemingly ghost-like on observation of the specific event; thereby resulting in an apparently automated phenomena. Consider the following scenario involving observation of an event that is mediated by an unappreciated stimulus.

Observer interpretation of "ghost" stimuli effects on functional responses:

Let us suppose that we can observe an occurrence of a natural stimulus-functional response pair. That is, we can observe an initial occurrence of the stimulus, and the resultant functional response that follows.

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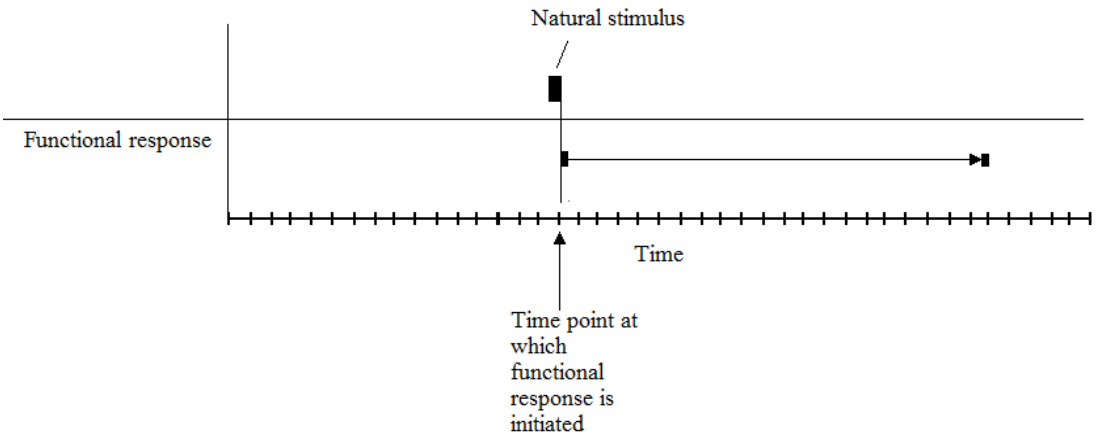

Figure 1.6. Illustration of a natural stimulus-functional response pair. Note initiation of functional response follows occurrence of the natural stimulus. Thus, time point of initiation of functional response is immediately after natural stimulus.

Let us now suppose a novel anticipatory association occurs between a second stimulus (stimulus-2) and the stated pair. With stimulus-2 preceding occurrence of the natural stimulus. Thus, stimulus-2 and the natural stimulus can be considered preceding and anticipated stimulus events, respectively.

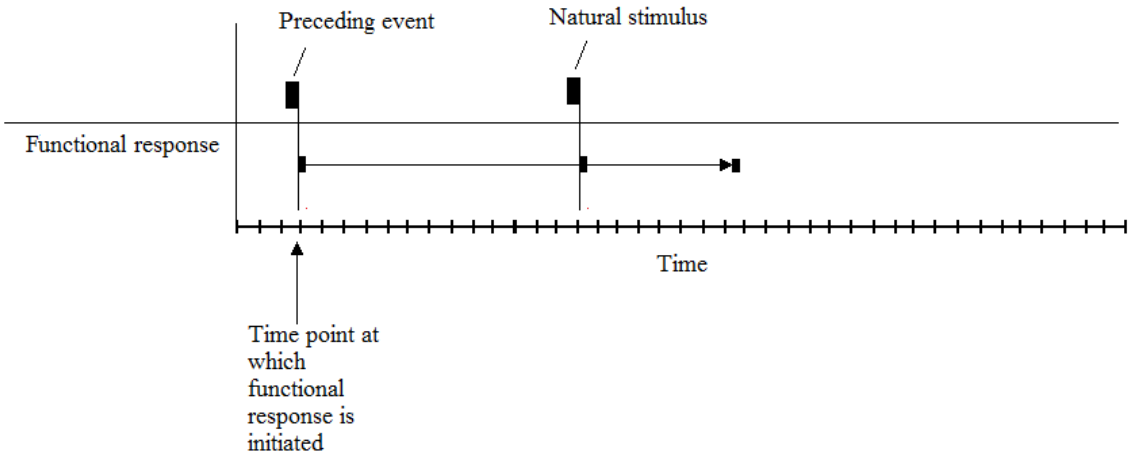

Figure 1.7. Illustration of a preceding event, and anticipated stimulus event (natural stimulus) and functional response that naturally follows anticipated stimulus event. Note that initiation of functional response follows immediately after preceding event, but occurs before anticipated event.

If we suppose that stimulus 2 is either not perceived by the methods and techniques used for observation or not considered an experimental parameter by the observer. In other words, stimulus 2 is a "ghost" on observation. It should follow then that presentation of this stimulus 2 prior to occurrence of anticipated stimulus event can induce initiation of the functional response for the anticipated stimulus event. However, on observation the resulting phenomenon would be seemingly constitutive. That is, a functional response would be initiated prior to occurrence of its natural stimulus. If the observer approaches such a setup with a preconceived dogma of *responses occurring/initiating only after stimuli*, then the observer may not appreciate the natural stimulus in figure 1.8, since it occurs after initiation of functional response.

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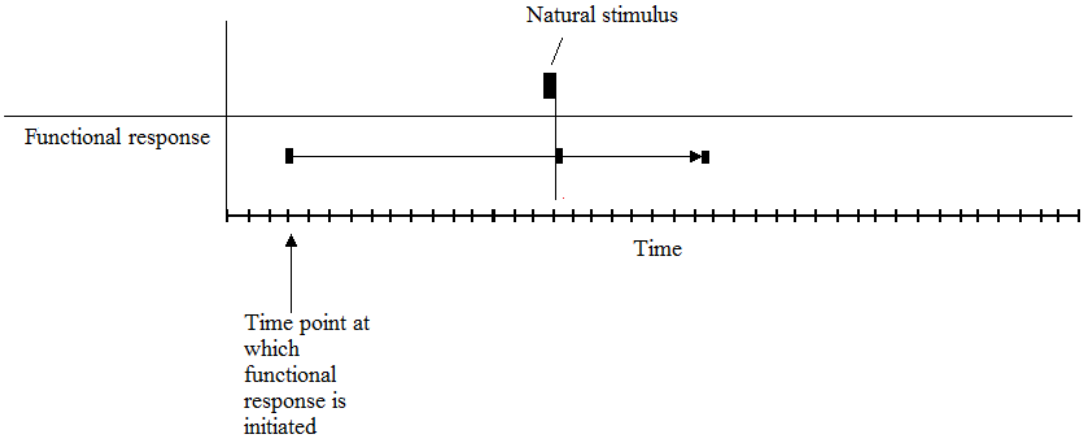

Figure 1.8. Note that this illustration is identical to figure 1.7, the only difference is that it represents the observer's perception of the sequence of events. To the observer, the functional response is initiated prior to the natural stimulus, and does not follow from any preceding event. Thus, from this viewpoint, we can consider the functional response an automated process.

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