A Proposed Solution to the Problem Posed by Reduction(s) in Osmolyte Infusion Interval:

A Theory on the Origins of Non-Natural Stimulus-Functional response pairs in biological systems.

Imadol V. Jeff-Eke*

This work follows as a response to a problem posed in a previous work (Jeff-Eke, 2015b). Here we propose and explore a probable solution to the posed problem of how well a cellular system can tolerate random changes to the frequency of osmolytes infused into an intracellular space of interest. The proposed solution involves the ability of biological systems to anticipate occurrences of imminent challenge stimuli, with such means involving alignment of moments of initiation of the required functional response mechanism(s) to stimuli, in relation to moments of initiation of occurrences of these stimuli. The resultant outcome is reduction of the lag interval for the functional response mechanism. We also present propositions on the means by which these anticipatory relationships may be formed, and some consequences for biological systems. By stating anticipatory roles in biological systems, we are suggesting a possible origin for non-natural stimulus-functional response pairing.

* Contact info: email ivjeffeke@gmail.com
M.D candidate at Morehouse School Of Medicine

Introduction:

In a second work (Jeff-Eke, 2015b), we described a functional response mechanism and process elicited by a unicellular system, following changes in the frequency of free osmolytes infused into an intracellular space of interest. Although not explicitly stated in previous works, the frequency of such infusion events is the multiplicative inverse of the infusion (pulse) interval. That is,

$$Frequency = \frac{1}{(t_{p_f} - t_{p_i})}$$

For the osmolyte infusion event, $\boldsymbol{t_{p_i}}$ refers to the instantaneous moment during which a most preceding pulse (to the most subsequent pulse at t_{p_f}) of osmolytes are introduced into an intracellular space of interest; and $\boldsymbol{t_{p_f}}$ is instantaneous moment during which a most subsequent pulse (to the most preceding pulse at t_{p_i}) of osmolytes are introduced into an intracellular space of interest. For Jeff-Eke, 2015b, we concluded that it would be problematic for an obligate regulator system, if sudden increments in frequency of osmolyte infusion events were to occur; with the total intensity enough to cause failure of the conformer system. In other words, the change is a spontaneous, rapid and extreme reduction in infusion interval. We indicated how such a problem stems from the limited rate at which the system can acquire the required number of channels –and therefore the required functionality– such that it can affect the mandatory reduction in lag interval length. In an absence of such reductions in lag interval length, the delay interval –which decreases with decreasing infusion interval– will be decreased. If the resultant delay interval is less than lag interval, then the resulting impact is an increase in the aggregate measure of systemic failure, and failure ensues. In order to comprehend the terminologies and operations used here, it will be beneficial to the reader to review both introductory papers[1] for a more detailed explanation; most especially the second work (Jeff-Eke, 2015b).

$$(t_{d_f} - t_{d_i}) = \frac{\eta \cdot (\tilde{N} - N)}{k \cdot \left[Y + \left(Y(n-1) \cdot (C_f)\right)\right]}$$

Where,

$$C_f = e^{-\left(\frac{(t_{p_f} - t_{p_i})}{(t_{L_f} - t_{L_i})}\right)}$$

Delay interval = $(t_{d_f} - t_{d_i})$

For this work, we explore a probable solution to the stated problem.

[1] Jeff-Eke IV. (2015a) A Gauge model for analysis of biological systems. *PeerJ PrePrints* 3:e1477 https://dx.doi.org/10.7287/peerj.preprints.1148v3

Jeff-Eke IV. (2015) A Gauge model-based analysis of: Reduction(s) in osmolyte infusion interval and its effects on the aggregate measure of systemic failure for a unicellular system. *PeerJ PrePrints* 3:e1490 https://dx.doi.org/10.7287/peerj.preprints.1163v2

Proposed solution:

Let us suppose that osmolyte infusion occurs via a mechanical infusion device, whose sole function it is to infuse free osmolytes into an intracellular space of interest. For simplicity, we also suppose that the infusion device is the natural means by which osmolyte infusion occurs for the cell of interest. Let us suppose that prior to infusion, the device must be introduced via permeation of the encompassing membrane –from the cell exterior to interior. With the significance of such permeation event being to establish an infusion route. Thus, the membrane must be mechanically disturbed (without loss of membrane integrity) in order to generate a route for infusion. We suppose that prior to mechanical disturbance of membrane, the device must be placed in a media wherein the cell is located. Lastly, we suppose that the media must also be mechanically disturbed in order for device entry. It should follow then that the sequence of events that precede presentation of the challenging stimulus at **C**.**)** (free osmolyte infusion) are: **A**.) mechanical disturbance of media by infusion device and **B**.) mechanical disturbance of cell membrane by infusion device. We suppose that the stated procession of events is in agreement with the means by which the challenge stimulus presents in nature.

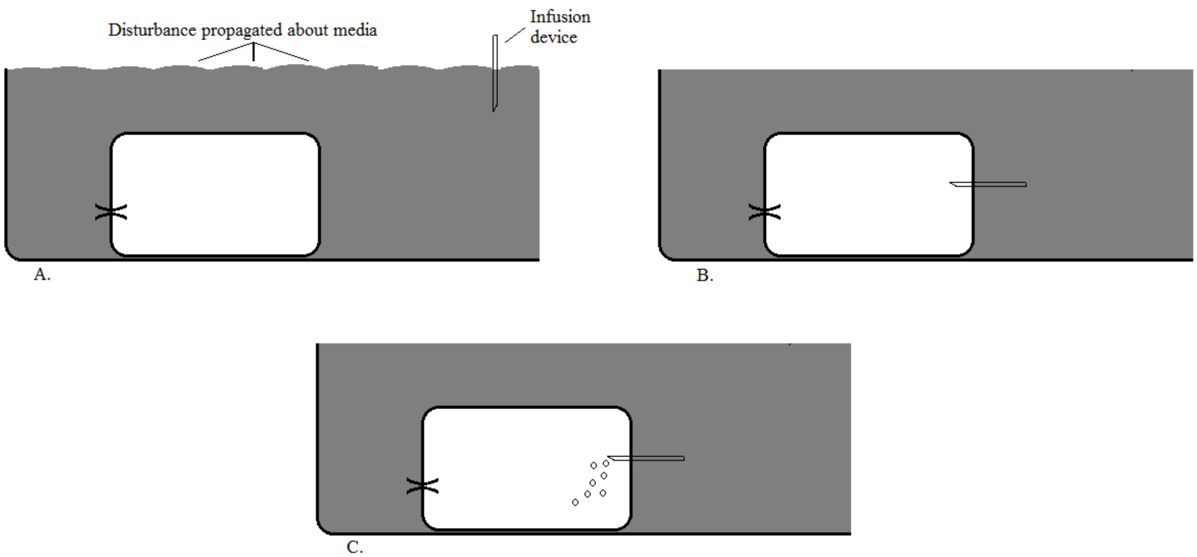


Figure 1.1. Depicts the sequence of events by which osmolyte infusion occurs for a cell. (A)Infusion device is introduced into media, and results in disturbance of media. This in turn is followed eventually by (B) disturbance of cell membrane as the device penetrates the membrane. (C) Free osmolyte infusion is then initiated resulting in increased intracellular osmolarity.

If we now suppose that either one or both of these preceding events (**A** and/or **B**) can directly result in both initiation of functional response mechanism and availability of the appropriate **yield of functional response (YFR) (**osmolyte efflux with resultant decrease in intracellular osmolarity), then it should follow that initiation of osmolyte efflux can precede osmolyte infusion by way of disturbance at either the media, the encompassing membrane, or both. The resultant advantage is that such a means of **anticipation**[2] allows for a shorter lag interval (figure 1.3) than does a

[2] Although the theory on Anticipation must be credited (especially) to the works of Alfred North Whitehead, Nicolas Rashevsky, Robert Rosen, Mihai Nadin, and a list of contributors too numerous to mention. It must also be mentioned that the details of this work precede knowledge of either personhood or works of these authors. Instead, the derivation of the posed problem and deductions of its possible solution are the means by which the idea was derived.

stimulus-only mode of YFR induction (figure 1.2).

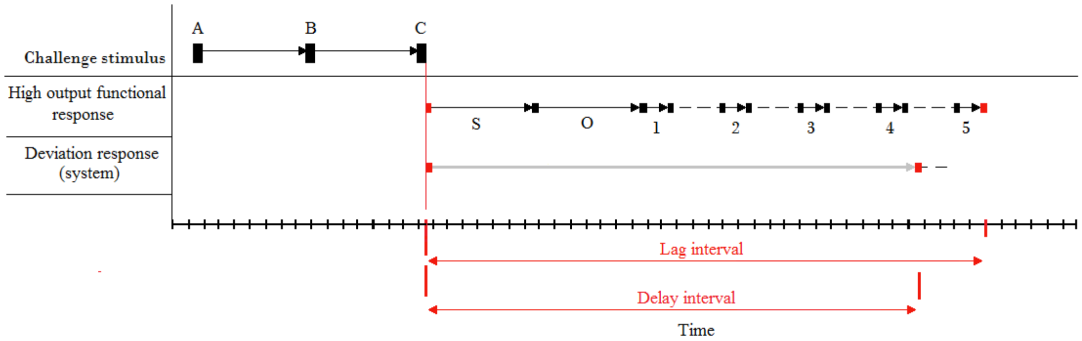


Figure 1.2. Shows events A, B, and C, as they precede initiation of a high output functional response. Note the delay interval is less than the lag interval, indicating the lowest inverse likelihood of systemic failure, and thus the highest possible value for the aggregate measure of systemic failure. The length of the deviation response is equivalent to the delay interval. If delay interval is less than lag interval then the system progresses to failure as a result of the challenge presented at the given moment; if greater than lag interval, then the system is unlikely to reach failure state as a result of the challenge presented at the given moment.

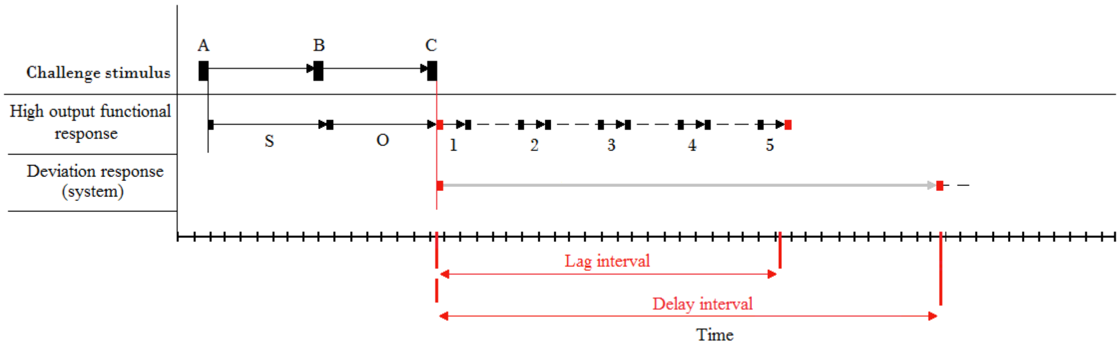


Figure 1.3. Shows events A, B, and C, but with only event A (and not B) affecting initiation of the high output functional response (black vertical line/tail off **A**). Note how the lag interval is less than deviation (delay) interval with neither the rate of processes or delay interval being altered (as compared to figure 1.2). Instead, the lag interval is decreased by alteration of the time point of initiation of functional response, thereby altering the alignment between lag and delay interval.

Since occurrences of **A** and **B** precede occurrence of the anticipated challenge stimulus, we shall call these occurrences **preceding events (PE)**. Since **C** is the anticipated challenge stimulus, we term its occurrence the **anticipated stimulus event (ASE)**. We state that anticipation has occurred when occurrence of one or more PEs (such as **A** and/or **B)** results in initiation of the natural functional response for an ASE (**C),** prior to occurrence of the ASE**.** Natural functional response, as used here is properly defined in the initial work: Jeff-Eke, 2015a. If this occurs, then we state that PEs **A** and/or **B** share anticipatory associations with the ASE**.** Based on this initial analysis, we propose that:

Proposition 1*: In order to prevent failure that may result from spontaneous presentation of a challenge stimulus with an intensity such that it can otherwise lead to failure of a biological system, the system must anticipate the stimulus.*

Proposition 2*: Anticipation of impending stimulus occur by way of association of: the stimulus and its natural functional response with events that precede the stimulus in occurrence.*

On key requirements for anticipatory association of events

1. **The anticipated stimulus event must follow after occurrence of preceding event(s) if anticipatory associations already exist:**
Let us suppose that one of two distinct subsequent events can follow from a single PE: either event C_1 or event D, but never both. It should follow then that if event C_1 follows, then no event D occurs; and if event D follows, then no event C_1 occurs.

Let us suppose that event C_1 is a challenge stimulus that affects a primary property, P_1, of a system, such that a natural functional response process follows deviation of primary property state. In addition, we suppose that a resultant YFR_1 occurs after a lag interval. Hence, occurrence of event C_1 can be said to affect occurrence of an appropriate YFR_1. Let us suppose that the natural functional response for stimulus event C_1 can also follow from occurrence of the stated PE, such that the challenge stimulus is anticipated. It should follow that occurrence of either PE or C_1 is a minimum requirement for initiation of functional response and availability of appropriate YFR_1.

Let us suppose an instance wherein the PE is followed by event D as opposed to C_1. Since a minimum requirement for YFR_1 is occurrence of either PE or C_1, it should follow that, for the instance under consideration, the functional response that follows C_1 is initiated following the PE, even in the absence of C_1. Thus, YFR_1 occurs even if the challenge stimulus event, whose effects it corrects, does not occur. Since availability of YFR_1 occurs for a property still at its zero point state, it should follow that YFR_1 does not affect systemic progression away from failure. Instead, occurrence of YFR_1 negatively impacts the system. To demonstrate the last point, we introduce a second challenge-response relationship independent of the former.

Let us suppose that a second event C_2 is a challenge stimulus that affects a primary property, P_2, of a system, such that a natural functional response process follows deviation to the state of primary property P_2. In addition, we suppose that a resultant YFR_2 occurs after a lag interval. Hence, occurrence of event C_2 can be said to affect occurrence of an appropriate YFR_2. Let us suppose that both events PE and C_2 are concurrent but independent occurrences, with initiation of functional responses with resultant YFR_1 and YFR_2 following after PE and C_2, respectively. In addition, we suppose high output functional responses are required for both events, and therefore a greater-than-normal requirement for resources. It should therefore follow that availability of YFR_1 is limited by availability of YFR_2, and availability of YFR_2 by that of YFR_1. Such limitations would result from competition for a limited availability of resources required for both high output functional responses.

If events C_2 occurs concurrently with PE, and PE is followed by occurrence of event D, (that is, no event C_1 occurs), then occurrence of YFR_1 (but not YFR_2) has no benefit to the system. It should therefore follow that occurrence of YFR_1 is of a greater limitation on the availability of YFR_2, than YFR_2 is on YFR_1. Under such a condition, availability of YFR_1 can increase the aggregate measure of systemic failure as a result of an insufficient YFR_2 (which manifests as an increased lag interval for the functional response that results in YFR_2). Thus, for anticipation to be beneficial to the system, occurrence of the challenging stimulus must always follow after PE.

On the other hand, the challenge does not have to be preceded by the specific PE. This is because occurrence of challenge in absence of specific PE does not affect the system in terms of resources. Hence, we can conclude that: *although occurrence of ASE must always follow occurrence of a specific PE, occurrence of ASE does not necessarily indicate an initial occurrence of a specific PE. The last statement holds if other preceding events are associated with the given ASE.*.

2. **Preceding event(s) as stimuli:**

If a PE can affect an *appropriate YFR* for the given challenge, then it [PE] must be conspicuous to the system and is therefore able to affect a change in s-value of (at least) a given property. From our definitions of a challenge as: a component of the surrounding that can affect any property of the system by way of its effect on the property s-value (Jeff-Eke, 2015a). We conclude that such PE is itself a challenge (challenge-P). Hence, in addition to its effects on YFR, such an event must also affect availability of a given functional response and its resultant yield (**YFR-P**). We consider the PE and functional response that results in YFR-P a natural stimulus-functional response pair. On the other hand, the PE and functional responses that follow the ASE can be considered a **non-natural stimulus-functional response pair.** Since, the challenge must follow after [preceding] event, it should therefore follow that both YFR and YFR-P must follow the PE. Yet again, a conundrum arises on allocation of resources and its effects on the tendency of failure. To resolve the problem, we suppose that neither YFR nor YFR-P are limitations of one another. For this to occur, it must follow that: an excess resource requirement by any one yield is followed by a decreased requirement for the other.

3. **On spatial requirements:**
   For the above example, the mechanical disturbance of either or both the extracellular media and/or the encompassing membrane must affect a property of the system, with a resultant YFR. With regards to mechanical disturbance at the media, an effect on the system would require that the disturbance be propagated from an initial point of disturbance to the spatial location of the system. Hence, a spatial requirement. We can conclude therefore that for a PE to affect the natural functional response and YFR that follows from an ASE; the PE or its effects must also occur at the spatial locality wherein the system occurs. If propagation of disturbance does not occur or does occur, but does not extend to the system, then disturbance of the extracellular media does not affect any property of system. Thus, for such a situation, PE(s) cannot affect the natural functional response for the ASE.

4. **On temporal requirements:**
   Let us suppose that the system can be displaced from the extracellular media with negligible disturbance to the media. If we now suppose that disturbance of the media is initiated and propagated by introduction of infusion device, but in an absence of the system, then it should follow that the propagated disturbance does not affect the system. Similarly, if the system is re-introduced to a region within the media, only after disturbance has propagated through, then the system is not affected by the propagated disturbance. Therefore, in addition to spatial requirement, there is a temporal requirement that the PE or its effects permeate the spatial location of the system at a moment when the system exist at the spatial location.

Proposition on a requisite for formation of anticipatory associations:

We suppose that prior to formation of associations between PE and ASEs, an occurrence of the PE has no bearings on the occurrence of a natural functional response for the ASE. In other words, functional responses only follow their natural stimulus.

We stated previously that a stringent requirement for anticipatory associations is that: occurrence of PE must always be followed by the anticipated event, as this *ensures that* the resulting functional response and yield affect the property in question, and thus *resources invested are not wasted*. Thus, the sequence of occurrences that must follow (in order of initiation) are: *the* PE*; the* ASE*; and the natural functional response and yield for the* ASE.

Although such requirements hold for initiation of occurrences, we do not hold such restrictions on the duration of occurrences. That is, the duration of the PE may extend far beyond the initiation of succeeding events. Thus, a time interval may exist during which these occurrences are concurrent. Let us suppose therefore that this time period of concurrent occurrences does in fact exist. The sequence of occurrences therefore becomes: *initiation of occurrence of* PE*; concurrent occurrences of PE (continuation of initiated occurrence) and ASE; and initiation of natural functional response for ASE, with resultant yield.* In addition, a time interval may exist wherein the stimulus and its natural functional response occur concurrently. As an example, consider the case of osmolyte infusion into the cell.

We stated that for a continuous infusion, efflux must also be of continuous duration, so as to prevent deviation to failure state (Jeff-Eke, 2015b). Since both infusion and efflux events are said to occur continuously it should follow that over their respective durations, a time interval exist during which occurrences of these events overlap. Hence, even with varying initiation times, occurrences of all three mentioned events can, in principle, overlap in time.

We also mentioned a spatial requirement; which holds that the PE must affect the system at its [system] spatial location. Since the ASE is said to affect an s-value of a property of the system, it therefore would follow that in order for this effect to occur, it also affects the system at its spatial location. Lastly, since functional responses derive from the system, it should follow that these functional responses occur at the spatial location of the system. Thus we can surmise that concurrent occurrences of all three events can occur at the spatial location of the system. To further illustrate this spatio-temporal requirement, let us suppose three spatial foci exist with each representing the initiation point of a given event (refer to **figure 1.4).**

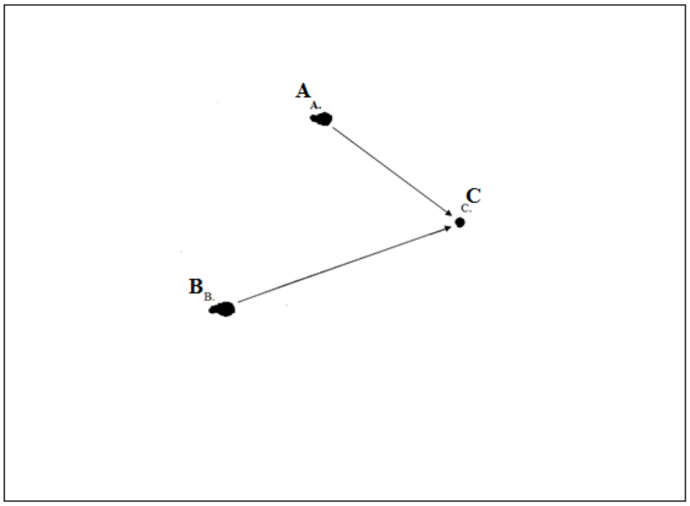
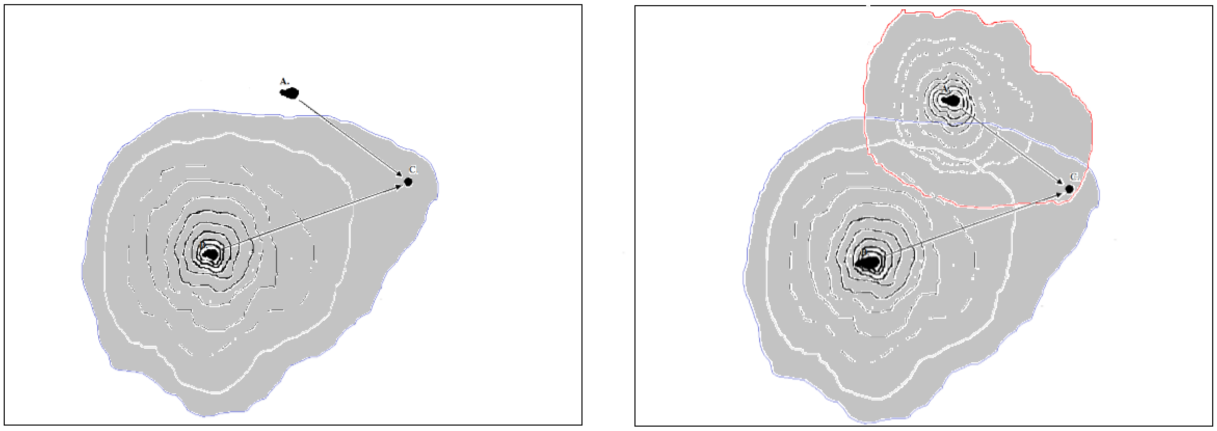


Figure 1.4. Illustrates three spatial foci of events (A, B, C).

Let us suppose that point **A** is the focus of initiation of a stimulus event. **B** is the focus of initiation of a PE to the stimulus; thus initiation of event at **A** follows after initiation of event at **B**. In addition, we suppose that initiation of event at **A** is not affected by event at **B**, and the event at **B** is not affected by the event at **A**. Thus occurrences of both events can be said to be independent of one another. We shall formally make this declaration in a subsequent section but for now we suppose this to be the case.



a. **b.**

Figure 1.5. Shows events initiated and propagated at 2 of 3 foci. (A) Shows event generated at B with no effects on foci A or C. (b) An illustration of events generated at both foci A and B.

We suppose that **C** is the focus of initiation of the natural functional response to the stimulus event at **A**. Thus, initiation of an event at **C** follows initiation of an event at **A,** and initiation of an event at **A** is followed by initiation of event at **C.** From our discussions, it should follow that in order for event at **A** to affect event at **C**, occurrence of event at **A** must propagate to point **C.**

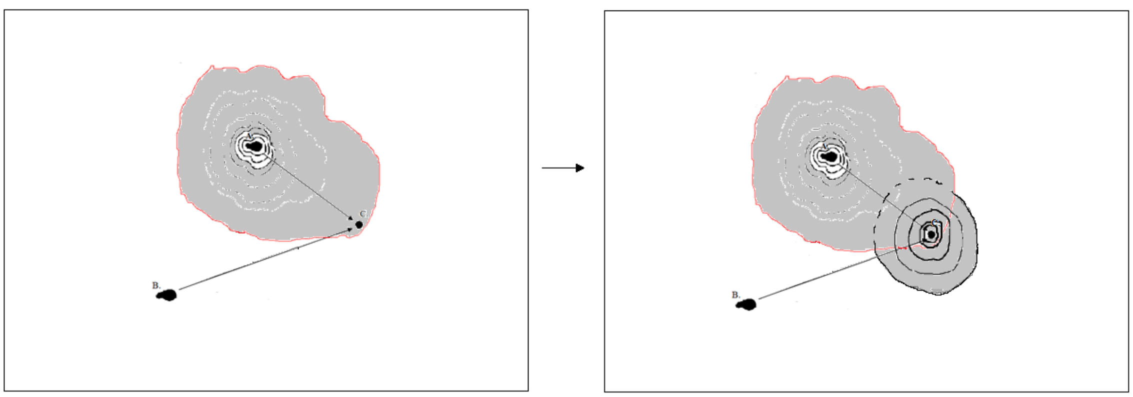


Figure 1.6. An illustration of an event initiated at focus A and propagated through **C**, with a consequential functional response generated at C.

We state that occurrences at **A**, **B** and **C** are spatially and temporally overlapping at point **C**, if:

I. Occurrences of events initiated at **A, B,** and **C** propagate through spatial point **C**.
II. There is a moment during which occurrences at **A** and **B** concurrently propagate through **C,** while event initiated at **C** occurs.

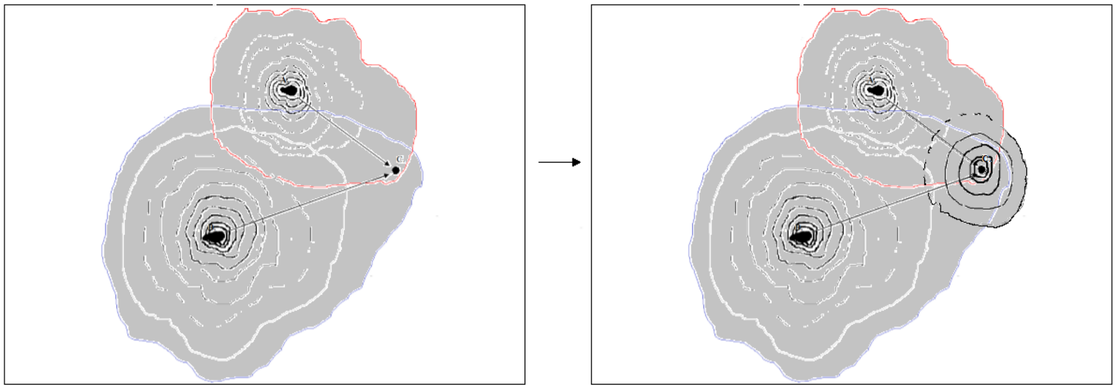


Figure 1.7. An illustration of independent events concurrently occurring at foci A and B, (albeit, different moments of initiation) with propagation through point C, and initiation of event at C as a consequential effect of occurrence and propagation of event A to spatial focus C.

If on the other hand,

I. A moment exist during which occurrences at **A**, **B** and **C** are concurrent, but only occurrence of event initiated at **A** (and not **B**) propagate through spatial point **C**. Then there isn't a moment during which occurrences at **A** and **B** concurrently propagate through **C** and therefore occurrences **A**, **B**, and **C** are not spatially overlapping at **C**.

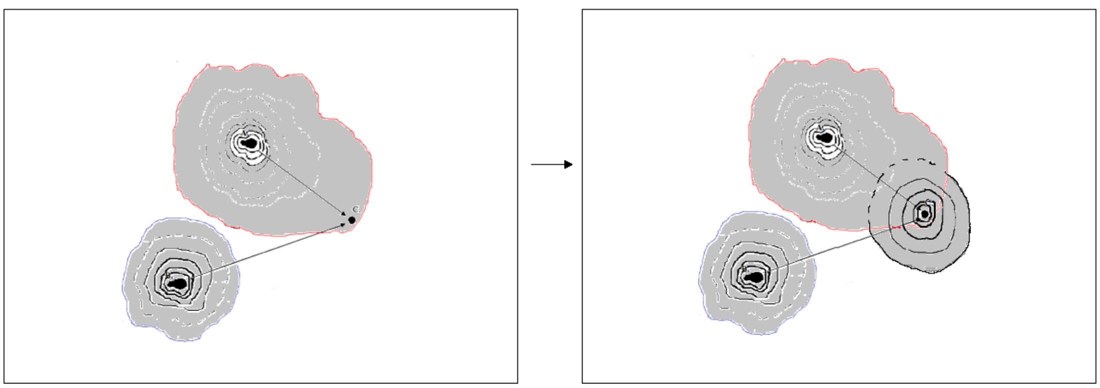


Figure 1.8. An illustration of independent events concurrently occurring at foci A and B, but unlike the situation shown in figure 1.7, event initiated at A but not B propagates through point C. Thus although events from foci A and B are concurrent, they do not overlap in spatial focus of event C.

II. If occurrences of event initiated at **A** and **B** propagate through spatial point **C**, but there isn't a moment during which occurrences at **A** and **B** are concurrent. Then there isn't a moment during which occurrences at **A** and **B** concurrently propagate through **C** and therefore occurrences **A** and **B** are not temporally overlapping at **C**.

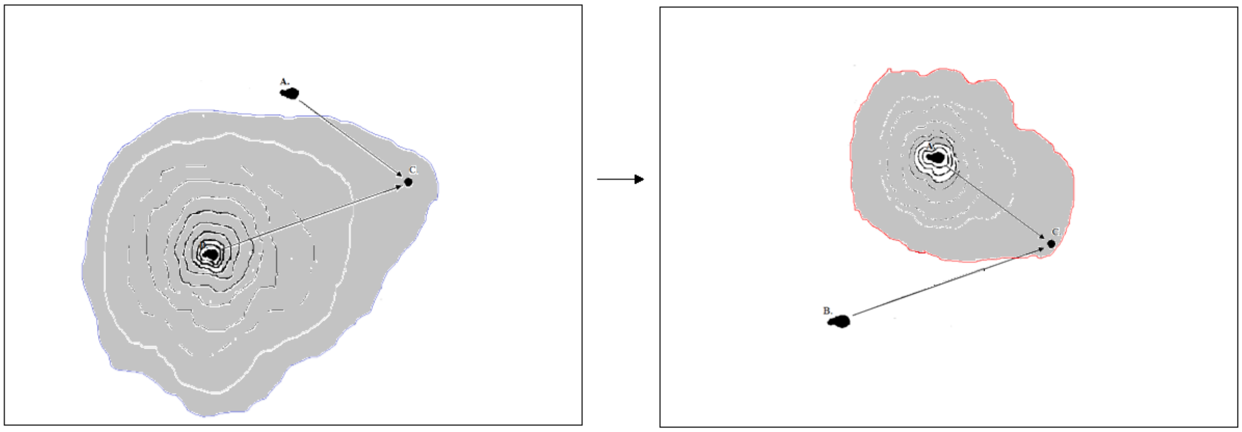


Figure 1.9. An illustration of independent events at A and B, with both occurrences propagating through point C. However, unlike figure 1.8 these events occur at their respective foci at different times, and do not concurrently propagate through C.

In essence, it follows that all three events can overlap both spatially and temporally and we propose that these overlaps are the fundamental requirements for the formation of anticipatory associations. From this analysis, we propose that:

Preposition 3*: Requisites for the formation of anticipatory associations between* PE *and* ASEs *are spatial and temporal overlap of occurrences of: the* PE*, and the natural stimulus-functional response pair for the* ASE.

Consequences of anticipatory association formation by spatio-temporal overlap of events

The relationship between preceding and anticipated stimulus events need not be that of a cause and its effect: We infer from the discussion on spatial and temporal requirements for anticipatory association, that there need not be a cause-effect relationship between PE and ASE. Instead all that is required to anticipate the challenge is that the effect of the PE both precede and overlap that of the ASE and its natural functional response.

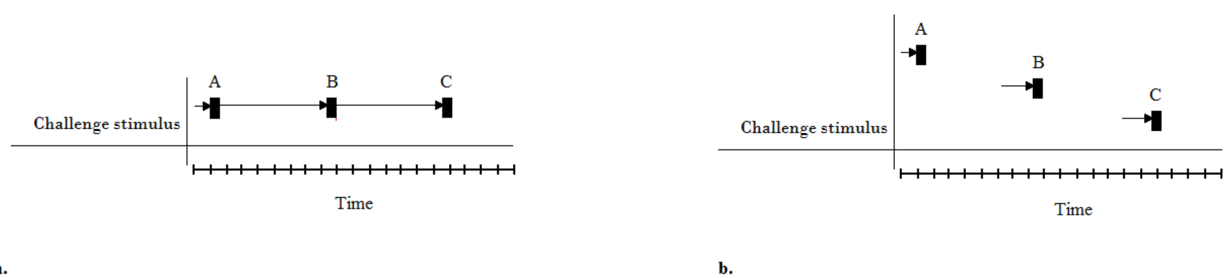


Figure 1.10. Depicts the temporal relationships between a stimulus (C) and events preceding the stimulus (A and B). Note that in both cases A and B precede C, and it does not matter if: **a**) occurrence of A results in B which results in occurrence of C; or **b**) whether A and B are independent occurrences, and only precede C without an influence on its occurrence. The only requirement for anticipatory associations is that A and/or B precede C. Thus we consider both equivalent depictions of the sequence of events that precede an anticipated stimulus event.

To illustrate this, imagine a sequence of two unrelated events. That is, a sequence for which occurrence of one event has no influence on occurrence of the other, and vice versa. Suppose these events are only oriented such that they occur within a close spatial and temporal proximity to one another, with spatial and temporal overlaps between events. Thus, under such settings, requirements are satisfied thereby making anticipatory associations possible. We propose that such spatial and temporal relationships are the frameworks on which evolution of such anticipatory traits occur.

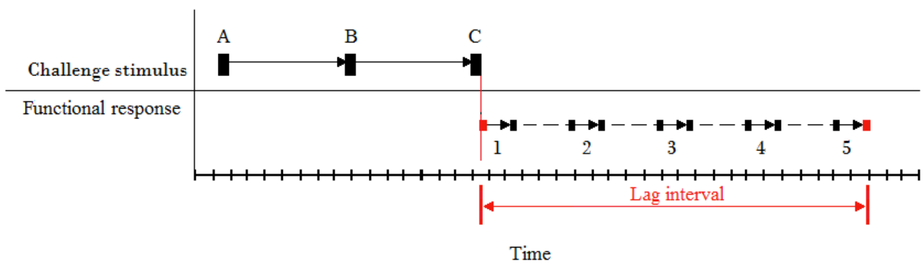
***Proposition 4**: Spatial and temporal overlap of events is a requirement for evolution of anticipatory traits involving such events.*

Points of association along a sequence of events:

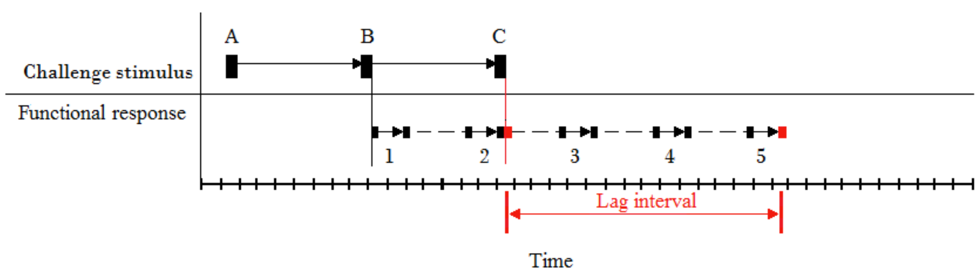
We can conclude from the above points that, in principle, an association can exist between any sequence of events for which individual events are spatially and temporally overlapping. Thus, any one of a number of PEs can potentially affect the natural functional response and yield of an ASE, thereby anticipating occurrence of the ASE.

Points of association along functional response path:

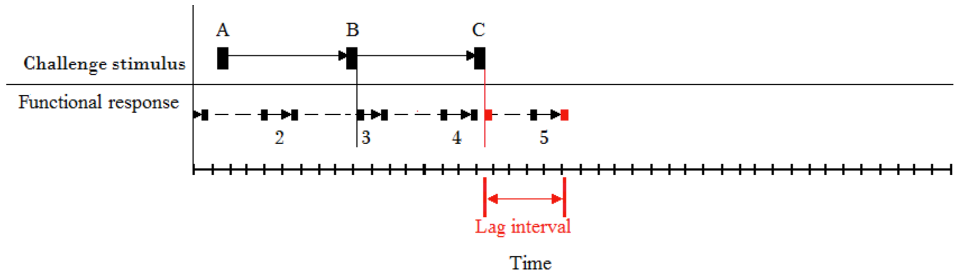
In addition to the possibility of having any one (or all) PEs affect a given functional response and yield, such a possibility also exist of having any one of the steps for a response process affected by a given preceding step. We must reiterate that this is theoretically possible, if and only if, the PEs and functional responses are spatially and temporally overlapping. Refer to **figure 1.11** for an illustration.



a.



b.



c.

Figure 1.11. An illustration showing that a point of association (black vertical line at B) between preceding event, B, and functional response(s) can occur at any step of a functional response process. **(a)** The natural stimulus response in the absence of anticipatory association. **(b)** An anticipatory association occurs between event B and step 1 of the response process. **(c)** An anticipatory association occurs between event B and step 3 of the response process. Also note the lag interval decreases in going from figures **a** to **c**.

On the anticipated event:

So far we have mainly considered a single functional response at the primary property, but there also exist a possibility of functional responses at other properties within a drift path (Jeff-Eke, 2015a). Consider the properties of a drift path involving a change in s-value of a primary property and a resultant change in s-value of a secondary property. We suppose that in order to prevent further deviation of the given secondary property, functional responses follow at this [secondary] property. Refer to **figure 1.12** for an illustration.

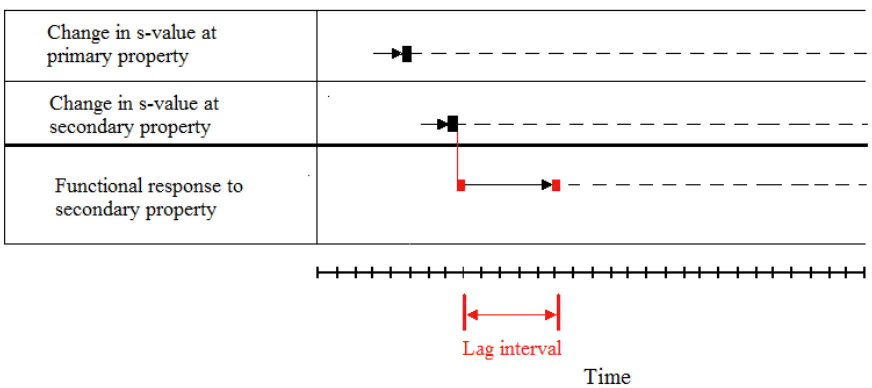


Figure 1.12. An illustration of a functional response resulting from a change in s-value of a secondary property. In addition, the functional response attempts to prevent further deviation of the secondary property.

If there exist a spatial and temporal overlap between changes in s-values of both primary and secondary properties, in addition to the functional response to changes in s-value of the secondary property; then an anticipated change in s-value of secondary property can occur, with induction of functional response to secondary property following after change in s-value of the primary property; even without occurrence of change in secondary property. Thus, both the PEs and ASEs need not involve a challenge (in the sense of surrounding influences on the system), but can also involve properties of the system.

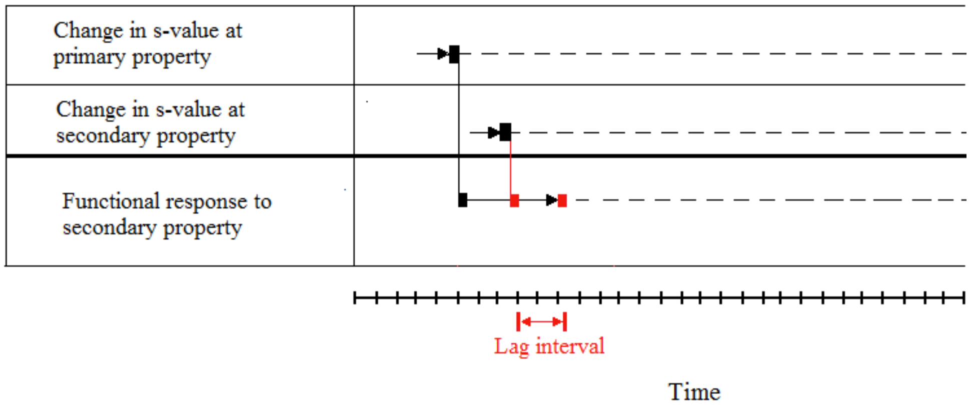


Figure 1.13. An illustration of a functional response to a secondary property resulting from a change in s-value of a primary property.

<u>On possible evolution of anticipatory associations</u>

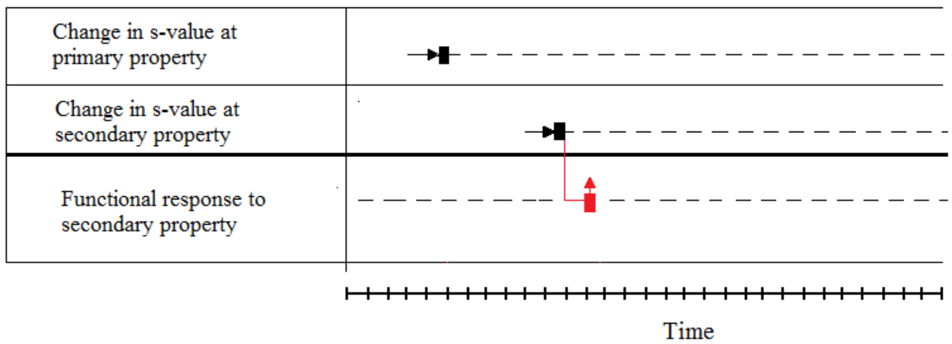
To illustrate how anticipation can be an adaptation, consider a population of biological systems, consisting both of systems capable of stimulus anticipation and those that lack this trait. It should follow that those with the capacity of stimulus anticipation would be less likely, than their counterparts, to undergo systemic failure from spontaneous, rapid, and extreme changes in intensity of inciting stimulus. Hence, based on this notion, we propose that stimulus anticipation is an adaptive trait.

<u>Proposition 5</u>: Anticipation is an adaption, thus allows for an increased fitness for those systems that harbor such a trait.

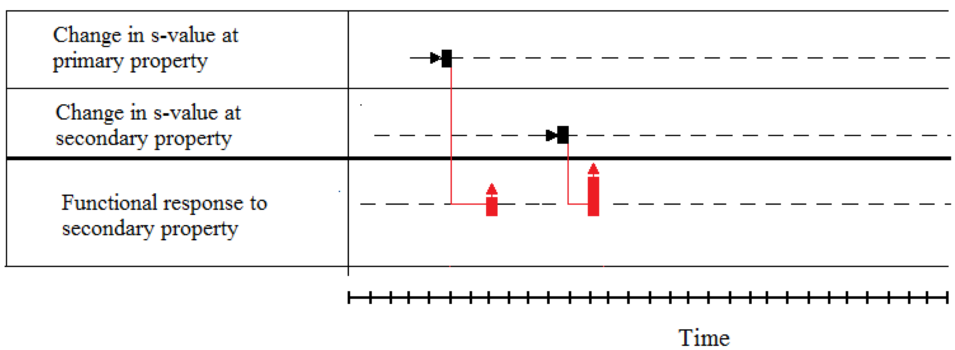
A question that arises is in regards to whether natural selection, by way of chance, would have afforded systems the ability to anticipate some events as opposed to others; or whether organisms have been afforded the ability to form novel and unique anticipatory associations. The former would mean that the assortment of anticipatory associations for a given organism are constant fixtures of the system that have been passed down from parent(s) to offspring(s), thus the organism cannot form novel associations. On the other hand, the latter scenario would mean that such associations are dynamic, with novel associations formed based on certain factors which may include satisfaction of requisite conditions. The presence of novel constitutive functions, most especially in the settings of sporadic adenomas point toward the possibility that such associations are formed at the level of the individual organism. We shall discuss these constitutive functions in the next work. If in fact such novel associations do occur, then the ramifications on the biological sciences will be substantial.

Cumulative effects:

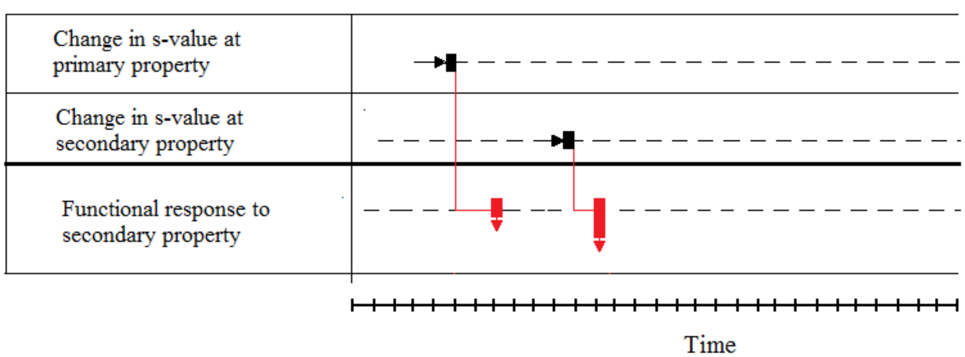
So far we have stated effects of a PE on the natural functional response for a subsequently occurring stimulus as though these events occur in isolation. We briefly discuss the impact of multiple such stimuli on a given functional response yield. Since the natural stimulus event follow after the PE whose effect is anticipatory, it should follow that both events (occurrence of PE and ASE) affect the same functional response and yield. Thus, there is a cumulative effect of both stimuli on the magnitude of yield produced. If both stimuli affect an increase in YFR, then the cumulative effect is a greater increase in YFR than that resulting from any one of these stimuli acting alone. If both stimuli affect a decrease in YFR, then the cumulative effect is a greater reduction in YFR than that resulting from any one of these stimuli acting alone. On the other hand, if each stimulus affect different directions of changes (an increase and decrease in YFR), then the cumulative magnitude of YFR is closer to the value of the stimulus that affects the greater magnitude of change.



A.



B.



C.

Figure 1.14. The arrow shows the direction of change in YFR: upward and downward facing arrows indicates an increase and decrease in YFR, respectively. The magnitude of change in YFR is depicted as the vertical length of each arrow bar (red bars). **A)** Shows the natural stimulus and functional response relationships between a secondary property and one of its functional response. **B)** A preceding event (change in s-value of primary property) also affects an increase in magnitude of the natural functional response to the secondary property, by way of anticipatory association. Note the double arrows for the functional response row. Whereas the shorter arrow bar represents the magnitude of effect of the change in s-value of primary property on the YFR, the longer bar results from cumulative effects of both properties on the YFR.

References:

Jeff-Eke IV. (2015a) A Gauge model for analysis of biological systems. *PeerJ PrePrints* 3:e1477 https://dx.doi.org/10.7287/peerj.preprints.1148v3

Jeff-Eke IV. (2015) A Gauge model-based analysis of: Reduction(s) in osmolyte infusion interval and its effects on the aggregate measure of systemic failure for a unicellular system. *PeerJ PrePrints* 3:e1490 https://dx.doi.org/10.7287/peerj.preprints.1163v2