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

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Abstract

This is a companion to *A Gauge model for analysis of Biological systems*. Here we reconcile the gauge model with a *"real"* system, which in this case is a unicellular system. We address effects of infusion of free osmolytes into an intracellular space of interest, and how changes to the frequency of infusion affects the aggregate measure of systemic failure. We also describe limitations to the functionality of the system that may stem from a limited availability of resources. We end by introducing a theoretical problem related to how well the system can tolerate random and extreme changes to the frequency of osmolytes presented via infusion.

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Introduction:

In a preliminary paper: *A Gauge model for Analysis of Biological Systems*; I introduced a framework for description and analysis of biological systems. For that work, I laid emphasis on the general operations of a hypothetical biological system, without giving much consideration to its specific nature. For the following discourse, we apply the gauge model to a unicellular system. In order to fully be acquainted with the terminologies and processes of the following analysis, it will be beneficial to review the initial work[1]. For the current paper, we attempt to determine how a unicellular biological system responds to changes to the osmolarity of an intracellular space of interest. We begin by restating two assumptions that were made in the previous paper:

1. *The ultimate significance of biological functions is prevention of failure of the system*
2. *Real biological systems attempt the functionality of ideal regulator systems:* where an ideal regulator is a biological system that constantly adopts a zero-point state.

Also note that, for the following discourse, we are supposing that functional responses to challenging stimuli occur such that they are in agreement with these assumptions.

A prototype system: Application of the gauge model to a unicellular system:

For the following discussion, we define a biological system as a unicellular organism. In addition, the single-celled organism can be considered a property of a larger undefined system (point definition), and itself, a set of properties (set definition). We also suppose two separate hypothetical forms of the organism exist, with one being an obligate conformer and the other an obligate regulator.

Let us suppose that the defined system experiences a given challenge for which we define as an increase in the intracellular osmolarity of the cell –by way of infusion of free osmolytes (i.e. osmolyte infusion in absence of fluid/water). It should follow then that the corresponding primary property is the osmolarity of the intracellular space. For the purpose of this discourse, we suppose that all infusion events affect an increase in intracellular osmolarity. We also suppose that prior to infusion, intracellular spaces are isosmotic and isotonic with the surrounding medium. In addition, there is no change to the osmolarity of the surrounding medium during and after infusion events. We can therefore define a drift path that illustrates the order of these properties. Below is an illustration of a *potential delta drift path*. The drift path of interest includes properties defined as: osmolarity, intracellular volume and turgor pressure. In addition, we suppose that each property initially occupies a given zero-point state prior to osmolyte infusion.

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

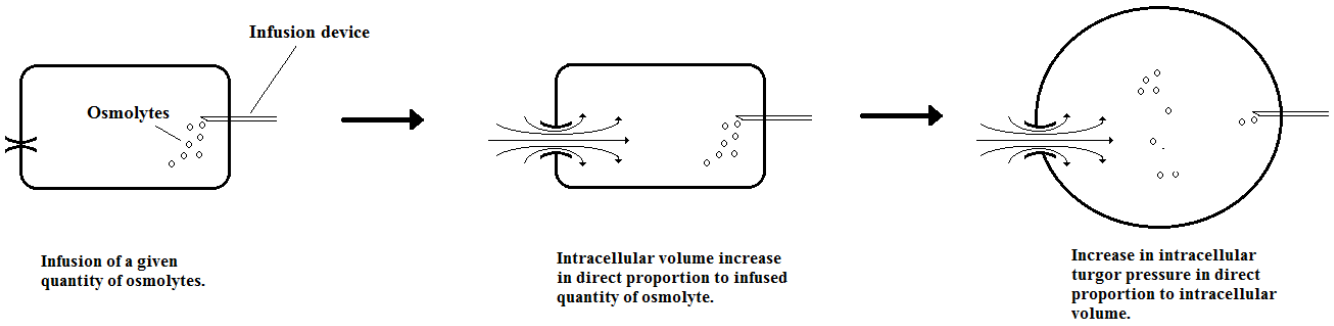

Figure 1.0. Depicts the drift path that follows from changes in osmolarity (primary property) as a result of free osmolyte (circles) infusion. In addition to changes in osmolarity, an increase in intracellular volume results from increased fluid influx (intracellular-facing arrows), and a concomitant increase in turgor pressure.

Infusion of free osmolytes would affect a concomitant net fluid influx, and consequently, an increase in fluid volume within the intracellular space of interest. If the encompassing cellular membrane were extremely rigid, then it would follow that a finite volume of fluid can be accommodated. Thus, eventually, both volume and net fluid changes will no longer occur. The increase in intracellular turgor pressure can therefore be said to occur with increasing intracellular volumes. If however, we suppose that the encompassing membrane undergoes distention (without loss of membrane integrity), then it should follow that with gradual increments in volume, an intracellular pressure would be reach at which point distention ensues. With further influx, we suppose that a point would be reached at which further distention would not occur, and further fluid influx would lead to loss of membrane integrity and rupture of membrane. In other words, with such increments in turgor pressure, membrane rupture can ensue after a *critical turgor pressure* is reached. We suppose that the integrity of the encompassing cellular membrane is the critical property of the system. Hence, of the properties stated, the property defined as membrane integrity is the greatest determinant of the aggregate measure of failure. Thus, we can approximate the point of failure as a point at which the encompassing cell membrane is ruptured.

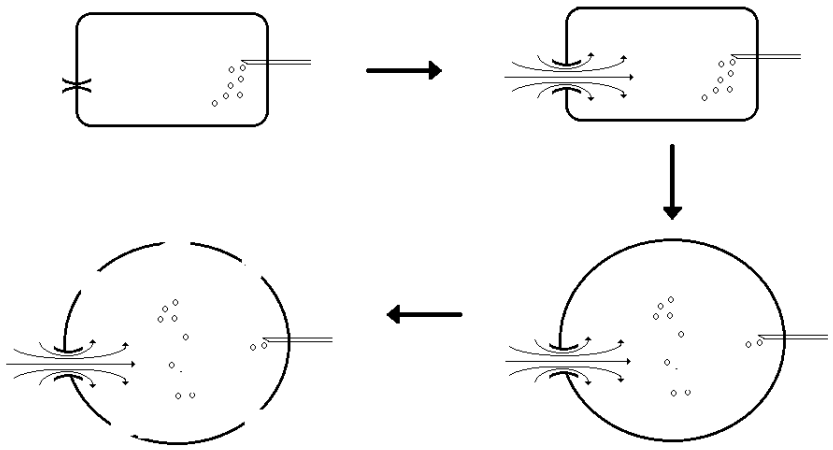

Figure 1.1. Illustrates the ultimate fate of a conformer system following an increase in intracellular osmolarity, in accordance with figure 1.0. With continuous free osmolyte influx, cell membrane integrity is affected (depicted as breaks along the cell outline), resulting in failure.

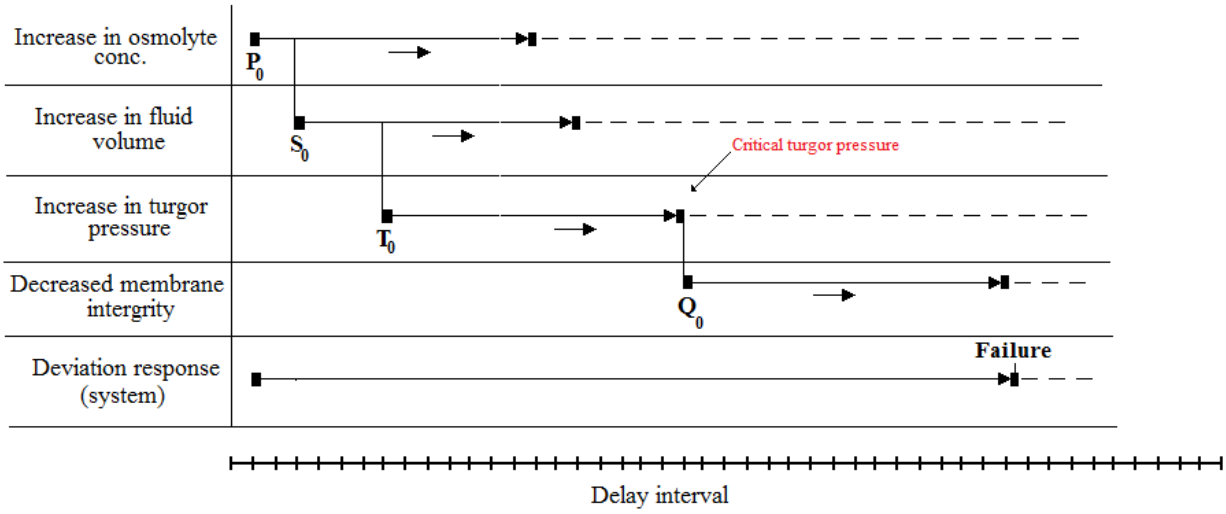

Figure 1.2. A gauge illustration of figure 1.1**.**

We suppose that both increments in fluid volume and turgor pressure occur along continua. Hence, we can define the spectrum of systemic states (from zero-point to failure) as a spectrum of an increasing tendency for cellular rupture.

In addition, we suppose the total intensity of ***n*** challenge pulses is such that, if presented – in tandem, with a uniform pulse interval – to an obligate conformer, it results in failure of the conformer system. A challenge pulse, as pertains to osmolyte infusion, is *a brief period of osmolyte infusion that has the same duration at every presentation*. We suppose that if the quantity of pulses is less than ***n,*** the system does not reach failure. Thus, ***n*** challenge pulses is required to achieve failure state. For an obligate regulator system, presentation of the same pattern of ***n*** challenge pulses can also affect a change in intracellular osmolarity, but unlike the conformer system, we suppose a functional response follows challenge. If appropriate, the **yield of functional response (YFR)** prevents attainment of failure state. For simplicity, we suppose that an appropriate YFR occurs for the functional response. Therefore, following challenge presentation, sufficient time is allowed (for availability of YFR) before subsequent challenge presentation. Lastly, we suppose that the YFR of interest affects the system only at the primary property.

Functions, mechanisms, and processes of biological responses:

Consider the defined primary property. The **function** of all functional responses to changes in this property can be said to involve decreasing the osmolarity of the intracellular space of interest. This is especially so considering that both [challenge and functional response] affect inverse changes to the intracellular osmolarity and can therefore be considered a natural stimulus-response pair. Here we define a **mechanism** as a specific means by which the function occurs. A mechanism therefore pertains to a single functional response. A **process,** as used here, is a specific sequence of steps for a given mechanism. Since we also consider a mechanism as being continuous, as opposed to discrete steps, it follows that the steps of a process are subjectively defined.

To illustrate these concepts, consider what occurs following infusion of free osmolytes. Functional responses are elicited and function to remove free osmolytes from solution, and the solution of interest is found within the intra-cellular environment. The following are a few possible mechanisms that may be elicited following challenge.

I. Removal of free osmolytes from cell interior by way of flux from intracellular space to cell exterior.

II. Removal of free osmolytes from cell interior by way of flux from intracellular space of interest to a second space also found within the cell. This requires that both spaces be separated by a barrier element, and hence can be thought of as separate compartments of the intracellular space.

III. Removal of free osmolytes from solution, without removing free osmolytes from compartment of interest. This can be done by incorporating osmolytes into larger structures, thereby limiting the degrees of freedom and extent of movement that would otherwise result when such osmolytes occur freely. Such mechanisms include:

a. Introduction of free osmolytes (via covalent bonds) into a larger structure.
b. Electrostatic interactions with a larger structure.

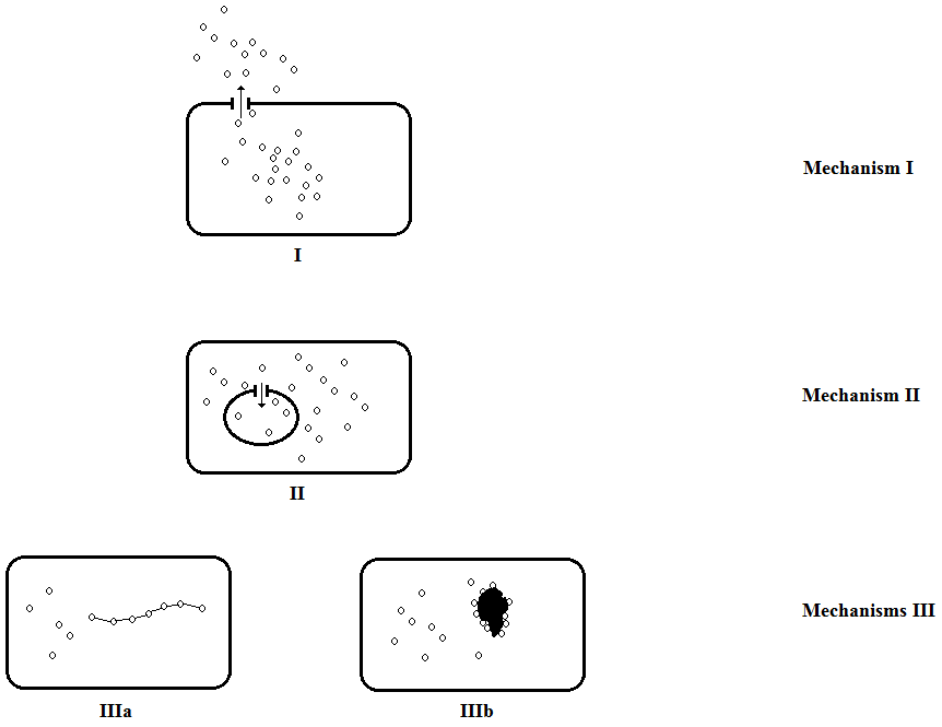

Figure 1.3.

For simplicity, we focus on a single mechanism, which in this case is mechanism (I). Let us now attempt to understand the stated mechanism in detail. For mechanism I, a decrease in free osmolyte content occurs via osmolyte efflux through the encompassing cellular membrane. This would require a channel element that traverses the membrane. In order to affect a decrease in solute concentration within cells via mechanism I, intracellular osmolytes must first interact with intracellular faces of these channels, with eventual detraction of solutes on the outer face (extracellular side).

The stepwise process of mechanism I involves: (1) diffusion of osmolytes to appropriate vicinity of channels; (2) interactions between osmolytes and channels at appropriate vicinity; (3) channeling of osmolytes from intracellular to extracellular space; (4) dissolution of osmolyte-channel interactions; and (5) diffusion of osmolytes away from vicinity of channels. We must also add that the lag interval for the given process is the sum time interval for initiation and completion of individual steps. For example, the lag interval for the process above is:

$$\Delta t_L = \sum_{a=1}^{5} \Delta t_a = \Delta t_1 + \Delta t_2 + \Delta t_3 + \Delta t_4 + \Delta t_5$$

Where,

Δt_a = The interval length for the a^{th} step of the process.

Also,

$$\Delta t_L = (t_{L_f} - t_{L_i})$$

For this work, the lag interval is the interval of time: from removal of a single osmolyte to removal of the quantity of infused osmolyte. Refer to figure 4 for illustration.

We define a **process element** as an entity that enhances the rate of a process for which it is involved with. Two examples of processing elements are enzymes and channels. For this discuss, we consider channels and pumps to serve equivalent ends –transfer of solutes across [otherwise] non-permeable membrane surfaces, and for this reason, we use them interchangeably. In addition, we suppose that under a given condition, a constant number of process elements exist for a given process.

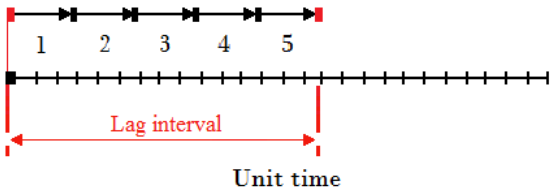

Figure 1.4. Shows the lag interval as a sum total of the length of individual processing steps.

Recapitulate on a "normal" condition:

We define a **normal condition** as one for which the quantity of osmolytes removed can equal the quantity of osmolytes infused. In addition, the time interval for efflux, lag interval $(t_{L_f} - t_{L_i})$, can equal the length of the time interval between infusions, pulse interval, $(t_{p_f} - t_{p_i})$.

$$(t_{p_f} - t_{p_i}) = (t_{L_f} - t_{L_i})$$

Where,

$\boldsymbol{t_{p_i}}$ = 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

$\boldsymbol{t_{p_f}}$ = 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

$\boldsymbol{t_{L_i}}$ = Moment of initiation of removal of a single osmolyte

$\boldsymbol{t_{L_f}}$ = Moment of removal of the last quantity of osmolyte(s)

Note that these all occur without changes to the cell's content of processing elements. That is, for a given quantity of processing elements, the cell can match the infusion frequency. Thus, under such a condition the infused osmolyte content is completely removed (for the given quantity infused) just as a subsequent pulse is initiated. We term the

functional response under such a condition, a **normal functional response.** We shall use the normal as a reference for comparison. It is important to note that we consider this a non-rectifying system (per gauge analysis). Hence, even though the property defined as osmolarity can return to its zero-point state, the system cannot be reverted via this lone mechanism. In addition we suppose the quantity of osmolytes removed from the cell interior over the lag interval cannot exceed the quantity infused over the pulse interval. We shall address this point when considering high output functional responses (and their resultant lag intervals) occurring at normal infusion intervals. Henceforth, we shall apply **infusion interval** in place of pulse interval.

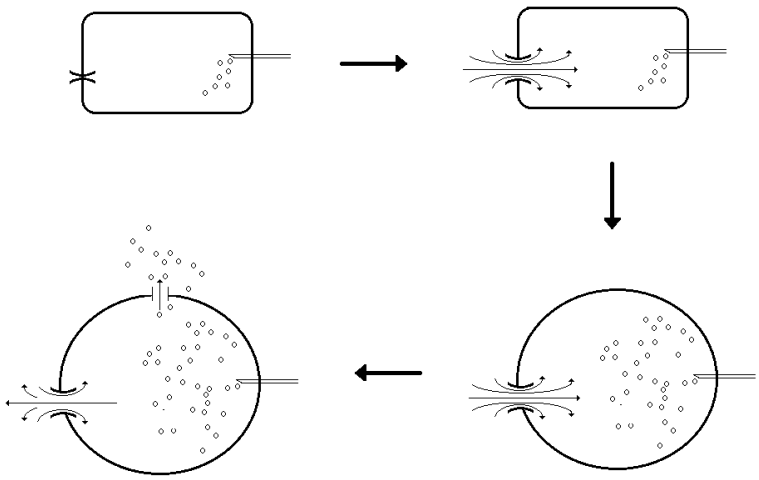

Figure 1.5. Illustrates the ultimate fate of an obligate regulator system following an increase in intracellular osmolarity, in accordance with figure 1.0. However, as opposed to the obligate conformer system, the obligate regulator can affect efflux of free osmolytes, hence prevents the sequelae that epitomizes the conformer system.

Dynamic nature of functional responses:

Effects of gradual reduction in infusion interval:

Now that we have somewhat of an understanding on both the challenge and corresponding functional response mechanism affecting and following from the cellular system, respectively. Let us now suppose a gradual reduction in infusion interval for a fixed lag interval, such that effects of preceding pulses are no longer corrected prior to onset of subsequent infusion events. Thus, the cumulative factor, C_f, increases, with resultant decrease in delay interval. In other words, the time to systemic failure will be decreased.

Where, delay interval, $(t_{d_f} - t_{d_i})$ is:

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

For the unicellular system, we define delay interval as equivalent to the interval from deviation of primary property (infusion of a given quantity of free osmolyte(s)) at $\boldsymbol{t_{d_i}}$, to rupture of the encompassing cell membrane at $\boldsymbol{t_{d_f}}$.

To explain this effect of gradual reductions in infusion interval, consider two cumulative factor values, C_{f_β} and C_{f_ε}, for a former infusion interval (β-interval) and the most current infusion interval (ε-interval) lengths, respectively, for a fixed lag interval, $(t_{L_f} - t_{L_i})_F$.

Where,

$$C_f = e^{-Q_{pL}}$$

And the **ratio of infusion (pulse) to lag interval, Q_{pL}**

$$Q_{pL} = \frac{(t_{p_f} - t_{p_i})}{(t_{L_f} - t_{L_i})} \;\; ; \quad (t_{L_f} - t_{L_i}) \neq 0$$

Thus,

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

And,

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

Where,

$$(t_{L_f} - t_{L_i})_F > 0$$

Since reduction in infusion interval occurs, it should follow then that the length of the ε-interval, $(t_{p_f} - t_{p_i})_\varepsilon$, is less than that of β-interval, $(t_{p_f} - t_{p_i})_\beta$:

$$(t_{p_f} - t_{p_i})_\varepsilon < (t_{p_f} - t_{p_i})_\beta \qquad Ineq.1$$

Thus, the cumulative factor, C_f must be greater for the ε-interval length, than for β-interval. That is,

$$C_{f_\varepsilon} > C_{f_\beta}$$

To demonstate how we came to this conclusion, let us analyze from a starting point of inequality 1.

Multiplying both sides of inequality 1 by $\frac{1}{(t_{L_f} - t_{L_i})_F}$

$$\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_F} < \frac{(t_{p_f} - t_{p_i})_\beta}{(t_{L_f} - t_{L_i})_F} \qquad Ineq.2$$

Multiplying both sides of inequality 2 by -1

$$-\left(\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_F}\right) > -\left(\frac{(t_{p_f} - t_{p_i})_\beta}{(t_{L_f} - t_{L_i})_F}\right) \qquad Ineq.3$$

Taking the inverse natural logarithm for both sides of inequality 3 to determine cumulative factor:

$$e^{-\left(\frac{(t_{p_f}-t_{p_i})_\varepsilon}{(t_{L_f}-t_{L_i})_F}\right)} > e^{-\left(\frac{(t_{p_f}-t_{p_i})_\beta}{(t_{L_f}-t_{L_i})_F}\right)} \qquad Ineq.4$$

Thus, we determine that:

$$C_{f_\varepsilon} > C_{f_\beta}$$

It should follow then that (with all else being constant) the delay interval –which was shown in equation 1 to be a [mathematical] function of the infusion interval– would be such that:

$$(t_{d_f} - t_{d_i})_\varepsilon < (t_{d_f} - t_{d_i})_\beta \qquad Ineq.5$$

Thus, as the infusion interval tends toward $(t_{p_f} - t_{p_i})_\varepsilon$, the delay interval tends toward a shorter interval length.

That is:

$$\lim_{C_{f_\beta}\to C_{f_\varepsilon}} \frac{\eta\cdot(\tilde{N}-N)}{k\cdot\left[Y+\left(Y(n-1)\left(C_{f_\beta}\right)\right)\right]} = (t_{d_f} - t_{d_i})_\varepsilon$$

For the preliminary work, (Jeff-Eke, 2015) it was shown that the **inverse likelihood of systemic failure,** T_1, is determined by the relative durations of both delay and lag intervals (as measured by the **quotient of delay-lag interval,** $\mathbf{Q_{dL}}$).

Where,

$$Q_{dL} = \frac{(t_{d_f} - t_{d_i})}{(t_{L_f} - t_{L_i})} \;\; ; \quad (t_{L_f} - t_{L_i}) \neq 0$$

Let us suppose that for both situations, the delay interval is greater than the lag interval. That is

$$(t_{d_f} - t_{d_i})_\varepsilon > (t_{L_f} - t_{L_i})_F$$

And

$$(t_{d_f} - t_{d_i})_\beta > (t_{L_f} - t_{L_i})_F$$

Multiplying both sides of inequality 5 by $\frac{1}{(t_{L_f}-t_{L_i})_F}$ in order to determine their respective Q_{dL} values

$$\frac{(t_{d_f} - t_{d_i})_\varepsilon}{(t_{L_f} - t_{L_i})_F} < \frac{(t_{d_f} - t_{d_i})_\beta}{(t_{L_f} - t_{L_i})_F} \qquad Ineq.6$$

We can thus conclude that Q_{dL} value is greater for ε-interval length than for β-interval length. However, since both $(t_{d_f} - t_{d_i})_\varepsilon$ and $(t_{d_f} - t_{d_i})_\beta$ are greater than $(t_{L_f} - t_{L_i})_F$,

And

$$T_1 = \begin{cases} 0, & Q_{dL} < 1 \\ 1, & Q_{dL} \geq 1 \end{cases}$$

it should follow that

$$T_{1_\varepsilon} = T_{1_\beta} = 1$$

Recall from Jeff-Eke, 2015 that we cannot resolve ambiguities that arise from two non-equal values for Q_{dL}, when both are greater than unity. Thus, we must also determine the **inverse predisposition to systemic failure**, T_2. We deduce from the pattern of changes to delay and lag interval lengths that the drift number value for the system, when the ε-interval length, N_ε, is greater than that for the β-interval length, N_β. To understand how we came to this conclusion, let us suppose that the system is initially at zero-point state ($N = 0$), prior to challenge presentation for both situations. Let us now suppose the inverse of delay intervals for either side for inequality 5.

$$\frac{1}{(t_{d_f} - t_{d_i})_\varepsilon} > \frac{1}{(t_{d_f} - t_{d_i})_\beta} \qquad Ineq.7$$

Multiplying both sides of inequality 7 by $(\tilde{N} - N)$ in order to determine the drift rate.

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\varepsilon} > \frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\beta} \qquad Ineq.8$$

where

$$\text{Drift rate} = \frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})}$$

Note that $\tilde{N} - N$ can also be considered the distance to or from systemic failure state, which occurs when drift number equals the property number, Ñ, (Jeff-Eke, 2015). Thus, when $N = \tilde{N}$, the distance from failure is zero. When $N = 0$, the distance is Ñ from failure. Thus, when at an intermediate value the distance depends on the specific value. Thus, we can determine N_ε for an ε-interval and N_β for β-interval.

Multiplying both sides of inequality 8 by Δt

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\varepsilon} \cdot (\Delta t) > \frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\beta} \cdot (\Delta t)$$

Where,

$$\Delta t < (t_{d_f} - t_{d_i})_\varepsilon$$

And

$$\Delta t < (t_{d_f} - t_{d_i})_\beta$$

If we suppose that:

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\varepsilon} \cdot (\Delta t) = N_\varepsilon - 0$$

And

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\beta} \cdot (\Delta t) = N_\beta - 0$$

From inequality 8, we deduce that:

$$N_\varepsilon - 0 > N_\beta - 0$$

It should follow then that:

$$N_\varepsilon > N_\beta$$

Thus, the **inverse predisposition to systemic failure** for ε-interval should be less than that for β-interval[2]. That is,

$$\left(1 - \frac{N_\varepsilon}{\tilde{\mathrm{N}}}\right) < \left(1 - \frac{N_\beta}{\tilde{\mathrm{N}}}\right)$$

Then,

$$T_{2_\varepsilon} < T_{2_\beta}$$

The aggregate measure of systemic failure, ב, is therefore greater for ε-interval, $ב_\varepsilon$ than for β-interval, $ב_\beta$.

Where:

$$ב = 1 - T_1 \cdot T_2$$

That is, since:

$$T_{1_\varepsilon} \cdot T_{2_\varepsilon} < T_{1_\beta} \cdot T_{2_\beta}$$

And

$$T_{1_\varepsilon} = T_{1_\beta} = 1$$

It should follow then that

$$1 - T_{2_\varepsilon} > 1 - T_{2_\beta}$$

$$ב_\varepsilon > ב_\beta$$

From this discussion, it should follow that, in order to prevent eventual deviation to failure –that may result from $(t_{p_f} - t_{p_i})_\varepsilon$, the lag interval must also decrease up to the minimum allowed. Let us now suppose that we nullify the requirement for a fixed lag interval. That is, variations to the lag interval can occur. Note, as stated earlier, that the minimum lag interval is equal in magnitude to $(t_{p_f} - t_{p_i})_\varepsilon$. That is, the lag interval at this new length (let us designate this $(t_{L_f} - t_{L_i})_\varepsilon$) must be:

$$(t_{L_f} - t_{L_i}) = (t_{p_f} - t_{p_i})_\varepsilon$$

Also, note that in order for this to still be considered a normal condition, the number of processing elements contained within the cell (for the given functional response) must be equal to that which defines the normal condition.

Since we suppose an isolated mechanism I, it should follow that reduction in lag interval is facilitated by an increase in processing frequency of currently utilized channel elements, or recruitment of additional channel elements;

[2] In the preliminary work we stated that the increasing drift and order numbers are analogous to a wave-like phenomenon. That is, following challenge, the change in drift and order values is such that both values increase in the direction away from zero-point (analogous to wave propagation from a single point of initiation). The faster the change in these values (corresponding to a shorter drift interval) the further they are from their respective zero point values for the given unit time observed. Thus, the drift number at which the corrected drift change, $\Delta \boldsymbol{N}'$, equals zero, $\boldsymbol{N}_{\mathbf{pr}}$; is greater for a shorter drift interval. Recall that $\boldsymbol{N}_{\mathbf{pr}}$ is the drift number value **prior** to YFR**.**

without increasing the processing element content of the cell. We shall discuss the latter in greater detail in a later work.

Functional response to further reductions to infusion interval length when at maximal processing element utilization:

Let us suppose that further [gradual] reductions to infusion interval eventually result in a state at which all processing elements of the cell are maximally utilized. That is, these elements are functioning at their possible maxima in order to affect a lag interval of equal length to infusion interval. It should follow then that further reductions past this infusion interval would most likely deviate the cellular system toward failure state. Again, in order to prevent the system from reaching failure state, reductions in lag interval must occur such that it [lag interval] equals the length of infusion interval. To satisfy this, the cell must have a means of introducing and utilizing the required quantity of processing elements. We suppose that the cell increases synthesis and organization of novel processing elements following further reductions in infusion interval. Since such a functional response involves utilization of more processing elements than under normal conditions, we refer to this as a **high output functional response**. We designate the greatest infusion interval length that just constitutes an increase in processing elements $(t_{p_f} - t_{p_i})_H$. Thus, $(t_{p_f} - t_{p_i})_H$ is less than $(t_{p_f} - t_{p_i})_\varepsilon$.

$$(t_{p_f} - t_{p_i})_H < (t_{p_f} - t_{p_i})_\varepsilon \qquad Ineq.\,9$$

Thus, it should follow that the required osmolyte channels constitute these newly synthesized and organized processing elements. **Figure 1.6** depicts utilization of a high output functional response involving mechanism I. Note the increased number of channel elements on the cell surface. It should also be noted that these processing elements are derived from carbon skeletons, and later we shall consider how this requirement for carbon skeletons affect the availability of these channels.

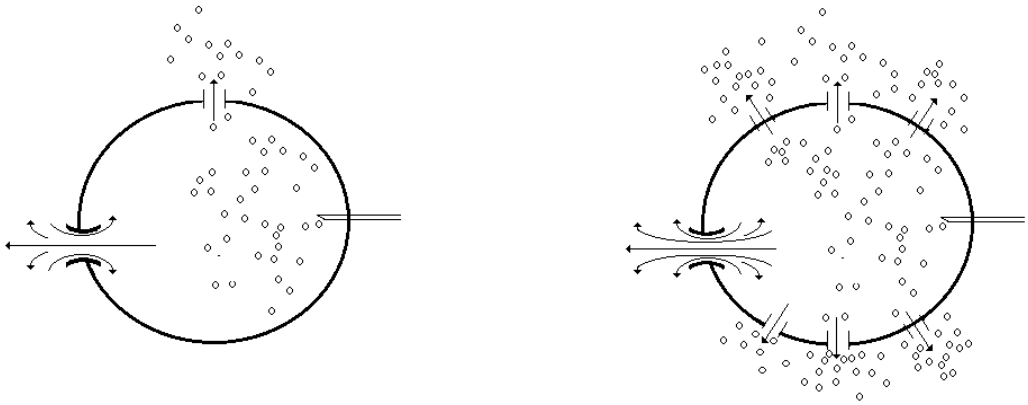

Figure 1.6. Shows two functional responses (normal and high output) of a cell following different infusion intervals. As opposed to the normal, the high output functional response can be seen to derive from an increase in the number of processing elements (channels) affecting an increased efflux of free osmolytes.

High output functional response at normal infusion interval:

Next, we attempt to determine what would happen if, while producing a high output functional response, we return the length of infusion interval to values that were previously attained under normal condition. Recall that in acquiring a high output functional response, the infusion interval length was reduced from values presented under

normal condition to a value at which functionality of the cell's constituent processing elements were exceeded. Since a high output functional response is to be maintained, it should follow that the lag interval must correspond to this high output state. We previously showed, for the case of reducing the length of the infusion interval from β to an ε-interval, that the lag interval must also decrease to equal the infusion interval at ε-interval. That is,

$$(t_{L_f} - t_{L_i})_\varepsilon = (t_{p_f} - t_{p_i})_\varepsilon$$

Thus, the lag interval at high output, $(t_{L_f} - t_{L_i})_H$, must also equal the magnitude of the infusion interval requiring a high output functional response.

$$(t_{L_f} - t_{L_i})_H = (t_{p_f} - t_{p_i})_H$$

In order to determine effects of a high output functional response occurring at a normal infusion interval we compare effects on the aggregate measure of systemic failure of occurrences of: lag intervals required for infusion intervals occurring under high output conditions to those [lag intervals] required for infusion intervals occurring under normal conditions. To accomplish this undertaking, we repeat the same initiatives previously utilized. Thus we begin with comparison cumulative factor values for an ε-interval, when the lag interval is of a normal condition, C_{f_ε}, to that when the lag interval is of a high output condition, C_{f_H}.

Rewriting inequality 9

$$(t_{p_f} - t_{p_i})_H < (t_{p_f} - t_{p_i})_\varepsilon$$

Substituting for $(t_{p_f} - t_{p_i})_H$ and $(t_{p_f} - t_{p_i})_\varepsilon$

$$(t_{L_f} - t_{L_i})_H < (t_{L_f} - t_{L_i})_\varepsilon \qquad Ineq.10$$

Taking the inverse of both sides of inequality 10

$$\frac{1}{(t_{L_f} - t_{L_i})_H} > \frac{1}{(t_{L_f} - t_{L_i})_\varepsilon} \qquad Ineq.11$$

Multiplying both sides of inequality 11 by $(t_{p_f} - t_{p_i})_\varepsilon$

$$\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_H} > \frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_\varepsilon} \qquad Ineq.12$$

Multiplying both sides of inequality 12 by -1

$$-\left(\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_H}\right) < -\left(\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_\varepsilon}\right) \qquad Ineq.13$$

Taking the inverse natural logarithm of each side of inequality 13

$$e^{-\left(\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_H}\right)} < e^{-\left(\frac{(t_{p_f} - t_{p_i})_\varepsilon}{(t_{L_f} - t_{L_i})_\varepsilon}\right)} \qquad Ineq.14$$

Thus the C_f is greater for a normal lag interval than for a high output lag interval. That is,

$$C_{f_H} < C_{f_\varepsilon}$$

If we are to input each C_f values into equation 1 we would get delay interval outputs such that the delay interval would be greater for a high output lag interval than for a normal lag interval. That is,

$$(t_{d_f} - t_{d_i})_H > (t_{d_f} - t_{d_i})_\varepsilon \qquad Ineq.15$$

To determine effects of delay interval lengths on the aggregate measure of failure, we first calculate the inverse likelihood of systemic failure and then the inverse predisposition to systemic failure. However, since we are comparing two [different] lag intervals (as opposed to the previous case where the lag intervals were identical) with two [different] delay intervals, we may fail to appreciate the difference between the high output and normal lag intervals. Instead, we compare the resultant drift number values over a given time interval, since this gives information on the time to systemic failure.

Let us now suppose the inverse of delay intervals for either side of inequality 15.

$$\frac{1}{(t_{d_f} - t_{d_i})_H} < \frac{1}{(t_{d_f} - t_{d_i})_\varepsilon} \qquad Ineq.16$$

Multiplying both sides of inequality 16 by $(\tilde{N} - N)$ in order to determine drift rate

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_H} < \frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\varepsilon} \qquad Ineq.17$$

Multiplying both sides of inequality 17 by Δt

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_H} \cdot (\Delta t) < \frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\varepsilon} \cdot (\Delta t) \qquad Ineq.18$$

Where,

$$\Delta t < (t_{d_f} - t_{d_i})_H$$

And

$$\Delta t < (t_{d_f} - t_{d_i})_\varepsilon$$

If we suppose that:

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_H} \cdot (\Delta t) = N_H - 0$$

And

$$\frac{(\tilde{N} - N)}{(t_{d_f} - t_{d_i})_\varepsilon} \cdot (\Delta t) = N_\varepsilon - 0$$

From inequality 18, we deduce that:

$$N_H - 0 < N_\varepsilon - 0$$

It should follow then that:

$$N_H < N_\varepsilon$$

What this translates to is that the distance from failure is greatest when a high output lag interval occurs under normal conditions of infusion interval, than it is for a normal lag interval occurring under similar conditions. Therefore we can conclude that the former is closest to an ideal regulator (in terms of maintaining the system closest to its zero-point state), than the latter. From the second assumption stated in the opening, maintaining a high output functional response, as opposed to a normal, should be of greater advantage to the cellular system. However, we shall discuss limitations to this conclusion. Before moving on to the next section, it is important that we state a caveat for this conclusion to hold. That is, for the high output functional response to affect a lower drift number value, N_H, than the normal, N_ε, it must have been initiated prior to challenge presentation. In other words, ***if present prior to challenge presentation,*** a high output functional response would affect the greater distance from failure state than would a normal functional response. We shall appreciate this in a subsequent section. Next we discuss the limitations of maintaining a high output functional response.

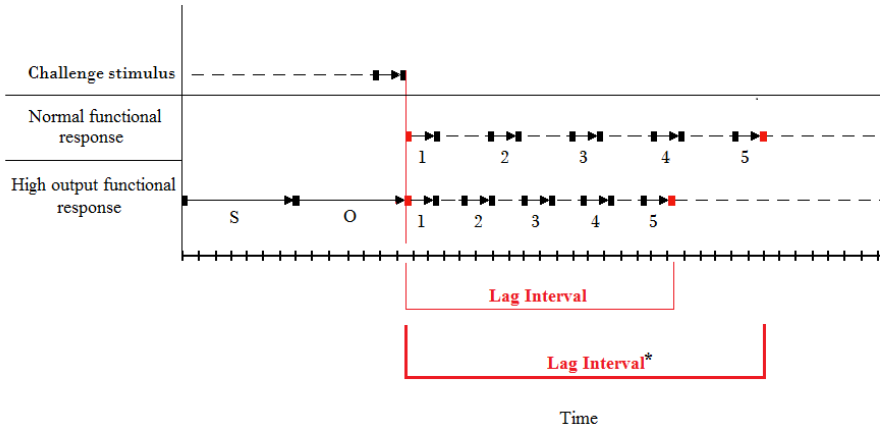

Figure 1.7. Compares the length of lag intervals of a normal functional response (asterisk) to a high output functional response. Note that the high output functional response has a shorter time interval to produce the appropriate YFR; than does the normal. We suppose that this results because the high output functional response is initiated prior to challenge presentation. Initiation of high output functional response requires synthesis **(S)** and organization **(O)** of processing elements, which, as shown in the figure, precedes presentation of stimuli. Note this figure is not drawn to scale, it only depicts a relationship between lag interval lengths for two conditions.

Effects of resource limitations on functional responses:

Let us suppose a second challenge (challenge 2) is presented to the cell. In addition, we suppose that similar to the free osmolyte challenge, challenge 2 affects a primary property, albeit different from that of the initial osmolyte challenge. We suppose that delta drift occurs upon deviation of state of property affected by challenge 2. Also, the intensity of a pulse of challenge 2 is such that, if presented to an obligate conformer, it results in attainment of failure state. Let us suppose that presentation of challenge 2 also affects deviation in state of an obligate regulator system, but that a functional response (functional response 2) exists, and affects a yield (YFR-2) appropriate enough to prevent the system from attaining a failure state. From our initial inclinations we can suppose that in the presence of both challenges, both response mechanisms must occur with respective lag intervals so as to prevent the system from reaching failure state.

Let us now suppose an initial normal condition, with normal challenge intensities for both the osmolyte challenge and challenge 2. In addition, we suppose an initial high output and a normal functional response for the osmolyte challenge and challenge 2, respectively. Subsequently, we suppose that the intensity of challenge 2 is increased such that it requires a high output functional response to decrease the aggregate measure of failure. It should follow then that the required carbon skeleton must be invested in attaining such functional response.

If on the other hand, all carbon skeleton are depleted from the cell while at an initial high output and normal functional response for free osmolyte challenge and challenge 2, respectively. Then further increments in intensity of either or both challenges is unlikely to affect a functional response, and can therefore increase the aggregate measure of failure. Thus, in order to prevent failure from a limited carbon skeleton content, it is important that:

1. The functional response is produced in proportion to the presented challenge intensity.
2. The change in functional response occurs in proportion to the change in challenge intensity.

Such channeling of resources between functional responses is in tune with the dynamic energy budget theory (DEB) (based on works by Nisbet et al, 2012; Pecquerie et al; 2010; Sousa et al, 2010), albeit at the level of a unicellular system.

A consequence of this limitation is that the system cannot maintain a high output functional response under normal conditions.

Disproportionate reverse-deviation of property states could lead to non-zero-point states:

In addition to limitations imposed by resource availability, high output functional responses cannot occur under normal conditions due to the possibility of over-reversion of the primary property state. To appreciate this, consider the infusion and efflux processes stated. If we suppose that under normal conditions the infusion interval, ε-interval, $(t_{p_f} - t_{p_i})_\varepsilon$, were to occur for the high output lag interval, $(t_{L_f} - t_{L_i})_H$. We deduce that:

Since,

$$(t_{p_f} - t_{p_i})_H < (t_{p_f} - t_{p_i})_\varepsilon$$

And

$$(t_{L_f} - t_{L_i})_H = (t_{p_f} - t_{p_i})_H$$

Then

$$(t_{L_f} - t_{L_i})_H < (t_{p_f} - t_{p_i})_\varepsilon$$

What this means is that since the lag interval that would normally occur under high output conditions is less than the infusion interval at normal, the system is corrected more rapidly than it is disturbed. In terms of the osmolarity example, this would mean that the frequency of osmolyte efflux is greater than the frequency of influx. Hence, the net effect is a lower osmolarity value than at zero-point state; which is also identical to a challenge defined as: removal of free osmolytes from intracellular space of interest. Thus, it is important that a high output functional response not occur under normal conditions.

Effects of rapid reductions in infusion interval:

Let the initial condition be normal. While at normal, we suppose a rapid reduction in infusion interval. Let us suppose that reductions are such that the system assumes a failure state, if in the absence of a high output functional response. It was previously stated that the means by which a cell assumes a high output functional response involves synthesis and organization of processing elements. In addition, we stated that the cell cannot maintain a high output functional response under normal conditions. Instead, the high output functional response must follow after challenge presentation at the affected property. Hence, synthesis and organization must follow challenge presentation at the affected property.

Although synthesis and organization may share a temporal overlap, time periods can also be defined during which no overlap can be observed; instead isolated parts of these processes occur. This is especially true in the case of

eukaryotic membrane proteins, such as these osmolyte channels/pumps. Here we refer to protein folding as the organization event. Channel proteins have been shown to follow the so-called "secretory pathway", which involves coupling of protein synthesis (by endoplasmic-membrane-bound ribosomal machineries) with translocation of these newly synthesized protein molecules, into the endoplasmic compartment. Both within this [endoplasmic] compartment and through to the adjacent Golgi system, further modification occur, but no data has shown incorporation of amino acids within these compartments. Thus, the initial synthesis and subsequent folding processes are clearly delineated in space and in time; with synthesis preceding organization (Lodish et al, 2008).

To minimize any added hindrances to the instantaneous functionality of novel processing elements (that result from such synthesis and organization events) we suppose that processing elements assume their respective functions immediately following organization. Even with such suppositions, the lag interval would be greater for a high output- than for a normal functional response. We reach this conclusion based on a presumption that the synthesis and organization steps are slower than the rate of the catalytic function of these channels. Hence, following rapid reductions in infusion interval, the aggregate measure of systemic failure will most likely be greater if a high output functional response is initiated, than if a normal functional response is initiated. Note how this differs from the situation wherein the high output functional response was initiated prior to challenge presentation. Refer to figure 1.8.

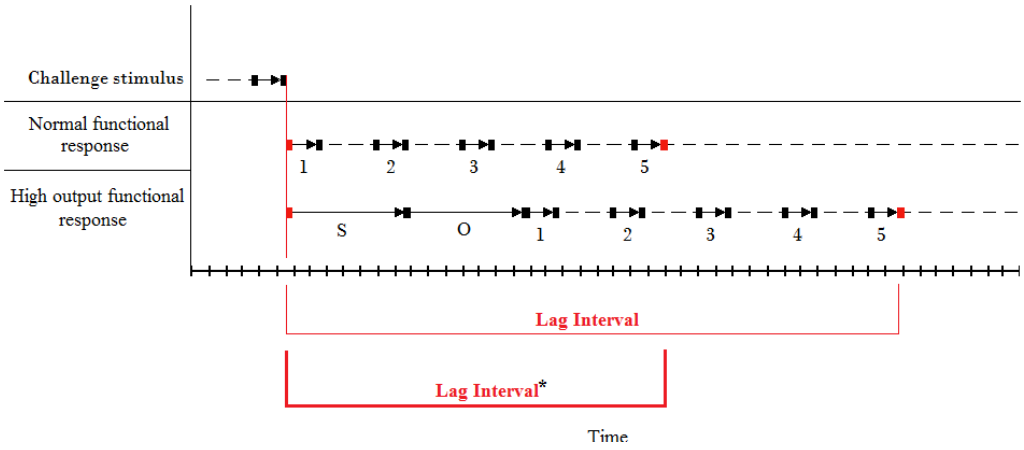

Figure 1.8. Compares the length of lag intervals of a normal functional response (asterisk) to a high output functional response. Note that the high output functional response has a longer time interval to produce the appropriate YFR; than does the normal. We suppose that this results from the requirement for synthesis **(S)** and organization **(O)** of more processing elements for the intended function. Compare both figures 1.7 and 1.8 to appreciate the temporal placement of the synthesis and organization events. Note this figure is not drawn to scale, it only depicts a relationship between lag interval lengths for two conditions.

A problematic effect of randomized infusion interval reductions on the aggregate measure of systemic failure:

Although we suppose that a system can affect a functional response to a change in its state, we also assume that it [system] has no influence on whether or not a challenge is presented. That is, the system is merely subjected to the dynamics of its surroundings, and cannot affect its experience(s) within surroundings. A consequence of this is that the nature and/or intensity of challenge that occurs at an immediate subsequent moment is not determined by the system.

In the context of the unicellular system, the question that arises is: *What functional responses (normal vs. high output) are recruited following a spontaneous, rapid, and extreme reduction in infusion interval?* We stated that with gradual reduction in infusion interval, there is ample time for production of an appropriate YFR. Hence, *failure*

can be evaded under such conditions. On the contrary, if such a rapid and extreme reduction were to spontaneously occur, such that a high output functional response is required at that immediate moment, then the propensity for failure increases. This is because under normal conditions the lag interval is normal, and in order to affect a spontaneous and rapid reduction in lag interval, these cells must produce a high output functional response (requiring both synthesis and organization) at a rate that exceeds their normal ability. In other words, the reduction in lag interval may not match that of the pulse interval. This indicates that the aggregate measure of systemic failure varies with the moment by moment variations in the intensity of the presenting challenge. Thus, under such extreme conditions, an obligate regulator is most likely to succumb as would its conformer counterpart. A solution to the problem may or may not exist.

References:

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

Lodish, H., A. Berk, C. Kaiser, M. Krieger, M. Scott, A. Bretscher, and H. Ploegh. "Moving proteins into membranes and organelles." *Molecular Cell Biology*. Sixth ed. New York: W.H. Freeman. 535-569. Print

Nisbet, R., Jusup, M., Klanjscek, T., & Pecquerie, L. (2012). Integrating dynamic energy budget (DEB) theory with traditional bioenergetic models. Journal of Experimental Biology, 215, 892-902. doi:10.1242/jeb.059675

Pecquerie, L., Nisbet, R., Fablet, R., Lorrain, A., & Kooijman, S. (2010). The impact of metabolism on stable isotope dynamics: A theoretical framework. Philosophical Transactions of the Royal Society B: Biological Sciences, 365, 3455-3468. doi:10.1098/rstb.2010.0097

Sousa, T., Domingos, T., Poggiale, J., & Kooijman, S. (2010). Dynamic energy budget theory restores coherence in biology. Philosophical Transactions of the Royal Society B: Biological Sciences, 365, 3413-3428. doi:10.1098/rstb.2010.0166.