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# What's in a name? Integrating homeostasis, allostasis and stress

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All organisms must adjust morphology, physiology and behavior as they go about their life cycles. For vertebrates, including humans, these adjustments occur as daily routines and in many cases, as seasonal routines as well. Superimposed on this predictable life cycle are unpredictable events, including many potential stressors, requiring immediate physiological and behavioral adjustments to cope. Additionally, infection, disease, age, old injuries, social status etc. may influence how an individual goes about its life cycle routines and responds to unpredictable perturbations. The classic concept of homeostasis (sensu Cannon, 1932) is fundamental to these adjustments. However, unless we have misinterpreted or overlooked something, homeostasis in its pure form does not incorporate adequately all of the processes involved and we believe that it is very useful to have supplemental terminology such as the allostasis concept in view of the many ambiguities of the uses of the words "homeostasis" as well as "stress".

For example, a cow that begins lactation undergoes morphological, physiological and behavioral changes so it can raise a calf. None of this is essential for the maintenance of homeostasis of the cow, although homeostatic set points will have changed from pre-lactation levels (Baumann, 2000). Another example is the migration of a songbird from Mexico to Alaska in spring and back again in autumn. Here again there are major changes in morphology, physiology and behavior that allow this animal to complete a journey of almost 5000 Km in less than a month. But none of this is essential for maintenance of homeostasis. In both examples, the process of preparing for lactation or migration involves regulation of gene expression. Furthermore, termination of lactation and migration involves turning off of many genes involved. Of course both the cow lactating and the songbird migrating must do so to reproduce successfully. But the adjustments in homeostasis that occur during these life cycle events are to accommodate changed physiology as part of the predictable life cycle, not simply responses to deviations from some set point that maintains life processes.

It is also important to bear in mind that changes in morphology, physiology and behavior associated with life cycle events such as lactation and migration also alter the responsiveness of the individual to unpredictable, and potentially stressful, events. Usually, a process such as lactation or migration results in the individual becoming more susceptible to perturbations of the environment, and adjustments in the stress response are made in anticipation of this. As far as we know, the classic concept of homeostasis does not incorporate all of these processes – homeostasis of daily routines, responses to perturbations, changed susceptibility to those

perturbations and anticipatory adjustments to cope with them for at least part of the life cycle. Furthermore, there is growing evidence that many organisms change their sensitivity to stresses temporarily (e.g. when breeding, Wingfield and Sapolsky, 2003) by adjusting secretions of mediators of allostasis that help maintain homeostasis (such as glucocorticoids). At first this seems counter intuitive, but temporary suspension of the classic stress response (and homeostatic adjustments in response to a perturbation) allows an individual to breed successfully, but the trade-off is potential permanent damage owing to the failure to show immediate responses that would normally promote adaptation. How do we model this apparently frequent strategy?

It is in this context that we offer some ideas and responses to the article by Romero and colleagues (2009) who present a different terminology and a new model for conceptualizing and describing the impact of stress on the body, combining traditional notions of stress and homeostasis with the more recent terminology of allostasis and allostatic load. It is our specific goal to point out where the concept of allostasis adds to the concept of homeostasis but also presents a framework by which to incorporate major events of the predictable life cycle (such as reproduction, migration etc.) with perturbations and the potential for stress. In our opinion, certain aspects of this formulation, summarized below, will be a useful addition to the ongoing discussion of this topic, but first some conceptual issues must be addressed that also involve semantics.

## What's in a name?

Related to the discussion of both types of allostatic load and overload, the key term that is at the heart of the controversy is the distinction between "homeostasis" and "allostasis" and the attempts to incorporate concepts of "allostasis" for those who prefer to deal solely with "homeostasis" (Dallman, 2003). McEwen and Wingfield (2007) define allostasis as achieving stability through change. A process that maintains homeostasis, defined as those physiological parameters essential for life, even though the set points and other boundaries of control may change with environmental conditions. Allostatic load is defined as the cumulative result of an allostatic state. It can be considered the result of the daily and seasonal routines organisms have to obtain food and survive, and extra energy needed to migrate, molt, breed etc. as well as deal with unpredictable perturbations (McEwen and Wingfield, 2007). If the energy required to fuel allostatic load exceeds the energy taken in (or that can also be mobilized from fat stores, see Korte et al., 2005) then allostatic overload type 1 occurs (McEwen and Wingfield, 2007).

As Romero et al. point out, allostasis can be defined as the active process of maintaining/re-establishing homeostasis, when one defines homeostasis as those aspects of physiology (pH, oxygen tension, body temperature for homeotherms) that maintain life. In that context, allostasis refers to the ability of the body to produce hormones (such as cortisol, adrenalin) and other mediators (e.g. cytokines, parasympathetic activity) that help an animal adapt to a new situation/challenge. This includes the predictable and unpredictable. Yet, some colleagues prefer to use homeostasis to mean the same as allostasis, in which case homeostasis refers to those aspects of physiology that keep us alive as well as those aspects of physiology that help us adapt. The advocates of "homeostasis only" say that this term has long been used to mean both things and to change it would be confusing, or worse, but they do not consider the following:

A cardinal feature of allostasis is that there are hugely different levels of activity of those mediators involved in adaptation – e.g. elevated heart rate, blood pressure, cortisol, or inflammatory cytokines - that may be needed in the short term to help us adapt, or which may occur chronically and lead to disease (e.g. hypertension, Cushing's disease, certain forms of depression, arthritis, metabolic syndrome). There is a key difference here: in contrast to the

mediators (of allostasis) that actively promote adaptation, those features that maintain life (using the restricted definition of homeostasis above) are ones that operate in a narrower range and do not change in order to help us adapt, i.e., they are not the mediators of change. Furthermore, the "homeostasis only" point of view does not incorporate anticipatory changes such as initiation of lactation prior to parental care, migration to a breeding ground, or reproductive development prior to seasonal breeding.

Although there have been many alternative concepts to explain these specific issues in detail (e.g. homeorhesis, poikilostasis etc., Moore-Ede, 1986; Mrosovsky, 1990; Kuenzel et al., 1999; Baumann, 2000), the concept of allostasis incorporates them all and provides a continuum from life cycle routines in relation to social status, body condition, age etc. and environmental perturbations (classic stresses). This in no way seeks to replace homeostasis concepts or to de-emphasize them. Rather, we see allostasis, allostatic load and allostatic overload as key concepts that incorporate classical homeostasis in the context of an organism's life cycle and in relation to individual experience and how they respond to their physical and social environments.

Table 2 of Romero et al. (2009) is a useful summary of terms and concepts building from Moore-Ede's (1986) original ideas. These terms are useful for "homeostasis only" arguments, but they do not incorporate everything – e.g. the anticipatory aspects of the life cycle that are not reactive (or enhance the capacity for adaptation). Allostasis does incorporate all of these. Because no individual experiences the environment (physical and social) in exactly the same way as another, these approaches allow "customization" of how individuals should respond and thus cope with their unique experiences in a changing environment (see also Korte et al., 2005; Landys et al., 2006).

It is also important to make note of the common use of the term "homeostasis" as in "homeostatic regulation", i.e., a self-limiting process involving negative feedback of some kind around a set-point. This is a term that crops up in many contexts. Moreover, the notion of a set point also highlights the concept (indeed, noted by Romero et al., 2009) that allostasis refers to the ability of a regulatory system to change a set point and operate at an elevated or reduced level (referred to as an "allostatic state", Koob and LeMoal, 2001) and similar to the use of the term "predictive homeostasis" by Romero et al., 2009). Indeed, the "homeostasis only" point of view notes that many, including Cannon (1932), think of homeostasis as being flexible, thus indicating no need for allostasis. Quoting from Romero et al., (2009): "*It has also become clear that a fair amount of the criticism of allostasis is due to the term itself, not the underlying concepts*".

As mentioned above, many physiologists and endocrinologists have had little difficulty using a definition of homeostasis that includes circadian and circannual changes. These researchers emphasize parts of Cannon's writings that seem to include circadian and seasonal changes. For instance, Cannon (1932: pg. 24) states: "*The coordinated physiological processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings – involving, as they may, the brain and nerves, the heart, lungs, kidneys and spleen, all working cooperatively – that I have suggested a special designation for these states, homeostasis. The word does not imply something set and immobile, a stagnation, it means a condition – a condition which may vary, but which is relatively constant.*" Quoting Romero et al. (2009) again, "*although allostasis may emphasize these concepts by stating them more explicitly, for many researchers the new term of allostasis is irrelevant at best, and at worst adds to the confusion surrounding the definition of stress (*Dallman, 2003)." Whereas the issue of how we define and use "homeostasis" is a really important one, the authors also imply that they choose their terms "*because certain authors don't like allostasis*". We are sure they agree

that getting at the underlying reasons for the schism is much more important, but we think Romero et al. (2009) are only part way there.

To illustrate this point, an interesting exercise would be to take the terms Predictive Homeostasis and Reactive Homeostasis and the terms Homeostatic Failure and Homeostatic Overload and substitute the word "allostasis": Predictive Allostasis, Reactive Allostasis, Allostatic Failure and Allostatic Overload. How does the meaning change and what is the gain or loss? For those who favor "homeostasis only", it is necessary to reconcile the contradiction that reactions and predictions involve those mediators that promote adaptation and do not pertain to those features that help the animal stay alive, e.g., pH, oxygen and temperature for a homeotherm. These parameters are not varied in an anticipatory way or as a means of adapting to seasonal changes or developing a migratory state, at least not in the way that cortisol or adrenalin are produced. As for '….failure" and "…..overload", it might be useful to think through differences in meaning with "homeostasis" or "allostasis" as alternate terms. The term homeostatic failure, i.e. the individual can no longer maintain essential physiological processes to support life, is a useful and important concept. But, we are not so sure about homeostatic load and overload because it highlights the confusion between those aspects of homeostasis that maintain life and those other mediators that help the individual adapt. We can see how an individual exposed to a stressor triggers classic homeostatic mechanisms to cope and maintain constancy, but are homeostatic load and overload appropriate in the context of anticipatory events such as reproductive development, migration etc.? Is gonadal development, or parental care, both of which contribute to increased energy demand, really homeostasis in the classic sense? This is where the term allostasis resolves the issue by incorporating all of this.

## The concepts of energy, energy demand, and levels of homeostasis/ allostasis

Central to the allostasis model, is the concept of energy. This has been presented in a very general sense – all of the energy and nutrients an organism needs to go about its daily and seasonal routines as the life cycle progresses, and to deal with unpredictable events from the physical and social environment that have the potential to be stressful (e.g. McEwen and Wingfield, 2003; Wingfield, 2004; Korte et al., 2005). They involve interactions of energy from food available in the environment (Eg – energy to be gained) and energy required for all aspects of the life cycle (Eo - the sum of energy for daily routines (Ee and Ei, and extra energy need to cope with social status, weather, avoidance of predators, age, injuries, infection etc.) in free-living animals (Fig. 1) and additional considerations in humans (Fig. 2). The potential interactions of energy demand of a free-living animal going about its daily and seasonal routines and coping with unpredictable perturbations, with the potential energy to be gained from food in the environment (Eg), is a key concept. In Fig. 1, if Eg declines below Eo then starvation is probable unless the organism can reduce allostatic load so energy demand, Eo, is below Eg. The boundary between Ee and Ei is also important because as Ee increases then the scope for Eo to increase in relation to Eg is decreased thus reducing the potential coping capacity (Wingfield, 2004)

If Eg is adequate to fuel all aspects of the life cycle (including fattening for migration or hibernation) and no severe perturbations occur, then the life cycle progresses normally. If Eg is higher and excess calories are thus available (i.e. above those required for fattening in life history stages such as migration and hibernation) then the individual may be able to store fat for future contingencies such as an unpredictable decline in Eg. In the latter scenario, an individual may then be able to mobilize these excess calories to fuel allostatic overload, at least temporarily, until environment conditions improve.

Although humans are also subject to the interactions of Eg and allostatic load (Eo) as outlined in Fig. 1, there are some additional considerations (Fig. 2). If Eg declines below that required for normal daily routines, then starvation may result – certainly a major issue in many human societies. However, adequate food, (but often regarded as restricted calories especially in societies of developed countries) may actually prolong life . In situations of prolonged excess calories, over consumption may lead to pathologies in the long term . This is true of non-human animals too especially in agriculture, zoos etc., but it is probably rare to non-existent in the wild because high Eg and availability of excess calories may not persist for long. Furthermore, there is extensive evidence from behavioral ecology that individuals with large fat stores tend to lose maneuverability and are more easily caught and eaten by predators (McNamara and Houston, 1990;Gosler et al., 2002). Thus there may be strong selection against individuals with too much fat in the wild. The allostasis model provides a useful framework for modeling these concepts within a mechanistic framework (McEwen and Wingfield, 2003;Wingfield, 2004;Korte et al., 2005).

Metabolic (energy) demands from the predictable life cycle (daily and seasonal routines) and the unpredictable can result in anabolism or catabolism depending upon available energy from food (Eg, Fig. 3). If Eg is high then the normal life cycle progresses and an individual may be able to store energy such as fat for future contingencies. If Eg is variable (in a temporal sense from day to day, or a spatial sense insofar as available food may be patchy in distribution, or both), then there may be complex shifts from anabolic to catabolic states over short time spans (minutes to hours). If Eg declines below Eo, resulting in allostatic overload type I (McEwen and Wingfield, 2003) then energy stores such as fat need to be mobilized until this allostatic overload is reduced to a manageable level or a new source of Eg is found.

Below the box in Fig. 3 are listed some mediators that are involved in energy management and metabolism in general. Note that this does not include mediators of allostasis such as cytokines that are involved with other, often related, processes particularly in relation to unpredictable events. A point to be made here is that although the relationship of allostatic load and overload to Eg varies in a fairly linear manner, the triggering of mediators of allostasis is not linear (McEwen, 2006) and forms a complex network depending upon condition of the individual (age, gender, phenotype, social status, injuries, infection etc.). In many cases the emergency life history stage may be triggered by this network allowing the individual to temporarily suspend the normal life history stage (e.g. breeding, migrating etc.), go into survival mode and reduce allostatic overload to a manageable level until environmental conditions improve and the normal life cycle can be resumed.

Summarizing so far, it is clear that depending on the experience of an individual in its environment, the energy taken in may be stored for future contingencies or may be used immediately to cope with current environmental conditions (Fig. 3). A crucial issue here is that Eg varies independently of Eo and it is the interaction of these two that determine whether an individual is exposed to allostatic overload type I or II (McEwen and Wingfield, 2003;Korte et al, 2005). This leads to some apparent paradoxes. For example, Eg changes seasonally allowing life history stages such as breeding and migration, to occur on schedule. However, in some years Eg is reduced by bad weather (or even changed permanently by human disturbances such as habitat degradation, urbanization etc.) and breeding becomes untenable because the potential allostatic overload accrued by reproductive activities cannot be sustained by Eg. In this scenario breeding activity may not be initiated at all thus avoiding allostatic overload. Is this homeostasis in the classic sense? We do not believe so. Similar responses may occur in humans when crops fail, natural disasters such as floods occur, or wars result in refugees fleeing their homes.

## Classification of the levels of mediators contributing to homeostatic/ allostatic state

Perhaps the most important contribution in the Romero et al. (2009) review is the classification of the levels of mediators – something McEwen and Wingfield (2003) did not address in depth. However, both approaches agree that the combined interactions of a suite of mediators changes from a basic level essential for existence (level A of McEwen and Wingfield, 2003; Landys et al., 2006) to level B. If activities of mediators fall below level A then homeostatic failure occurs (Romero et al., 2009). Between levels A and B, mediator action copes with daily and seasonal routines of the life cycle of McEwen and Wingfield (2003) and Landys et al. (2006). This is called predictive homeostasis by Romero et al. (2009). Superimposed on this is allostatic load incurred by unpredictable events (perturbations of the physical and social environments) resulting in overload at level C (reactive homeostasis of Romero et al., 2009). The allostasis models explore energy demand as a function of allostatic load and then predict that mediators, one example being glucocorticoids, may parallel allostatic load (McEwen and Wingfield, 2003; Landys et al., 2006) in relation to energy demand. In many cases, as allostatic load increases, then combinations of mediators may be activated in complex ways.

The Romero et al. (2009) model addresses changes in the network of mediators responding at each level and indeed, they have done an excellent job. But, it should be borne in mind that the relationship of allostatic load to networks of mediators involves changes in a non-linear manner as one might expect from Table 1 in their paper. Nonlinearity is due the biphasic actions of many of the mediators (now referred to as “hormesis”, Calabrese, 2008) as well as the ability of many of the mediators to regulate other mediators (e.g. sympathetic and parasympathetic regulation of each other; glucocorticoid and also parasympathetic inhibition of inflammation; (McEwen, 2006)). Landys et al. (2006) also suggest this by indicating that homeostasis processes interact in complex ways from levels A–C and are probably not simply linear.

We note that the allostasis model focuses on both why and how questions of the ways by which individuals respond to perturbations of the environment whereas Romero and colleagues (2009) almost entirely address the mechanisms of the response and the roles of mediators. The challenge now will be to integrate these more extensively and clarify terminology so that we avoid total confusion. Once we agree that the two concepts address different issues, integration should be possible. Furthermore, many aspects of how networks of mediators interact in often novel environmental situations remains to be tested fully and will only be done effectively once allostatic load can be measured independently. The latter is a major challenge for future research.

Whereas allostatic load can be conceived as a more or less linear increase in energy demand (Eo) balanced by energy availability (Eg), the levels of mediators involve a non-linear network, and contribute in highly variable ways depending upon the type of environmental and social situation an individual finds itself in. If Eo exceeds Eg, (overload type I) or if allostatic load persists at a level sustainable by Eg (overload type II) then actions of the mediators are designed to provide protection until allostatic overload declines and the individual can continue with normal daily and seasonal routines. However, if allostatic overload persists, then prolonged actions of the network of mediators results in wear and tear, pathophysiology and damage, rather than protection. Whether or not the relationship between allostatic load and energy demand is in fact linear will await accurate measurement of allostatic load in naturalistic settings.

## What causes allostatic load and overload?

At this point it is useful to discuss the issue of what causes allostatic load and overload because it is easy to confuse those environmental effects that contribute to allostatic load with the effects of prolonged actions of mediators. The latter do not contribute to allostatic load *per se* but are a consequence of allostatic load. For example, quoting from Romero et al. (2009) *"Note that none of the indices are energy based, so that allostatic overload must result from Type II, not Type I, overload. Consequently, the Allostatic Model is good at showing that allostatic overload results from accumulated allostatic load, but what causes allostatic load? In other words, the Allostatic Model does not help in understanding what drives increases in systolic and diastolic blood pressure, waist-hip ratio, etc. Instead, it relies upon the Traditional Model (i.e. repeated exposure to stressors) to explain changes in allostatic parameters. Furthermore, the Allostatic Model provides little help in predicting when allostatic load will become allostatic overload.*

We feel that this statement raises some important points about allostatic load and overload in the context of Eg discussed above. Furthermore, we think that confusion probably results from considering the actions of mediators (e.g, resulting in increases in systolic and diastolic blood pressure, waist-hip ratios etc.) as part of allostatic load. Rather, McEwen and Wingfield (2003), Wingfield (2004); Korte et al. (2005) and Landys et al. (2006) point out that allostatic load is the result of the cumulative metabolic (energy) demand of daily routines, seasonal routines and additional contributions such as age, gender, social status, disease, injury and not the action of the mediators themselves.

Whether or not overload occurs is determined by Eg. If type I allostatic overload cannot be ameliorated, or if type II allostatic overload becomes long term then the networks of mediators remain active resulting in wear and tear and various pathologies. Allostatic load itself does not result in these problems; rather, they are caused by the prolonged actions and dysregulation amongst the mediators of allostasis. In this case allostatic overload represents a transition to a perhaps somewhat arbitrary extreme state, as for example, when glucose dysregulation crosses a threshold designated as Type 2 diabetes. One pertinent example might be a good model to further distinguish dysregulation of mediators versus environmental contributors to allostatic load. This is the case of obesity in bears getting ready for hibernation (part of the predictable life cycle that the bears prepare for naturally) versus obesity in bears vegetating in zoos (where accumulated effects of captivity and excess food may result in eventual pathologies, including Type 2 diabetes). What are the differences in physiology that are associated with obesity in each situation – are they very different contributions to allostatic load and overload?

Another scenario, starvation, is discussed by Romero et al. (2009) and this also needs some clarification. Lack of food does not increase allostatic load per se, although other factors, such as predators, storms etc. that affect allostatic load will exacerbate the effects of starvation. The network of mediators released in response to onset of starvation tends to reduce allostatic load, thus conserving daily energy use and allowing mobilization of stored energy to cope. This has been modeled by the allostasis concept (Wingfield, 2004) using fat stores as a factor to buffer Eg and thus cope with allostatic overload when the individual is in negative energy balance (phase II of starvation). As fat stores become depleted, Eg is no longer buffered and the individual will enter starvation phase III. This is a good example of where the allostasis model and the reactive scope model differ as well as compliment one another, but in many ways address different issues. It is crucial to bear in mind that the allostasis models address actual energy demand AND what is available, whereas the reactive scope model addresses changes in concentrations of mediators of homeostasis that result.

To add to the confusion of what causes allostatic load there has been disagreement on the extent to which social interactions may be involved (e.g. Walsberg, 2003). Moreover, Day (2005)

argues that allostasis provides little help in understanding how the brain distinguishes stressful from non-stressful stimuli, nor does it provide a framework for identifying which are the important neural circuits underlying behavioral and cognitive responses. In answer to this, fear and anticipatory anxiety can have a powerful effect, e.g., determining when and for how long an individual may go out and forage because of the presence of a dominant conspecific or a predator. This effectively decreases Eg because that individual no longer has free access to food resources and thus is much more susceptible to allostatic overload. We agree that many behavioral and cognitive processes cost little or no energy. But the critical issue again is that they do affect access of the individual to resources such as food, mates, shelter etc. that, over time such as hours or days, reduces Eg and indirectly increases allostatic load relative to Eg.

Therefore, although some behavioral and cognitive processes may have trivial costs, the reduction of Eg as outlined above will result in allostatic overload more quickly in response to further perturbations, or the transition from one life history stage to another. The concept of allostasis addresses issues of access to Eg, shelter etc. that can have profound implications for homeostasis. These points have been modeled explicitly by Wingfield (2004), and Goymann and Wingfield (2004). Moreover, in many cases dominant individuals may actually expend more energy maintaining their status thus resulting in higher allostatic load than subordinates (reviewed in Goymann and Wingfield, 2004). Clearly it may not be the actual costs of behavioral traits themselves but the CONSEQUENCES of those behaviors (restricted access to food, shelter, mates) that require the individual to work harder. This emphasizes once more that the allostasis concept addresses energetic demand (allostatic load) and the energy available in food to fuel it (Eg).

## How best to measure allostatic load and overload?

A major question that arises repeatedly is “what is stress”. One very important conceptual issue in the allostasis model is that because allostatic load is a function of metabolic (energy) demand of daily and seasonal routines and unpredictable perturbations of the environment (and thus potentially stressful in the sense of exceeding the capacity of the individual to cope) one no longer needs to ask when stress begins (McEwen, 1998). However, we also acknowledge that the sustained elevation and dysregulation of mediators that normally turn on and then off and balance each other can also contribute to allostatic load. Eventually this may cross a threshold such as that referred to above for Type 2 diabetes and can be designated as allostatic overload. However, exactly what constitutes allostatic load and how to measure it remains unclear. Indeed, we agree with Romero et al. (2009) that a weakness of allostasis is the use of energy as the universal currency as Walsberg (2003) also points out. But this is not necessarily an inherent weakness of the model itself but in our understanding of what the components of allostatic load may be AND our inability to measure energy demand and availability in free-living animals.

There is no doubt that there will be great variation from one individual to another even among neighbors in similar habitat. It is reasonable to assume that no one individual experiences the environment in the same way as another. We do not see this as a weakness but rather a challenge to determine ways to measure all the variables that contribute to allostatic load. The allostasis model is currently very useful to guide us in this endeavor. The reactive scope model of Romero et al. (2009) focuses more on the mechanisms – concentrations of mediators of homeostasis (of allostasis, using our terminology) and becomes important once we are able to measure allostatic load meaningfully.

Romero et al. (2009) make a very good point about glucocorticoids and energy mobilization. Indeed Table 1 in their paper is timely and a very useful summary of mediators of allostasis that help maintain homeostasis as well as the effects that they have. This is another reason why

we need to develop ways of measuring components of allostatic load independently of the mediators themselves. So we agree with all the issues Romero et al. (2009) raise but consider them part of the research that is needed to resolve them and not a weakness of the model itself.

Future research should address the major components of allostatic load that should include not only energy demand (by measures of oxygen consumption) as an individual goes about its daily and seasonal routines and responds to unpredictable events such as weather, but also age and gender, quality of the territory (food available, shelters, exposure to weather etc.), disease (parasite load for example), body condition and presence of old injuries that might impair movement. This will be a challenge, but it is feasible to obtain measures of these sorts even in free-living animals (e.g. Porter et al., 2002; Ricklefs and Wikelski, 2002). Additionally, experimental manipulation of specific mediators and their effects on coping with allostatic load may also be determined. Considerable progress in this area can be expected in the next few years.

## What mediators are important to measure and how to separate mediators and outcomes?

It is important to note that when Romero et al. (2009) refer to mediators of homeostasis they are in fact referring to the same mediators we address for allostasis. Glucocorticoid effects have predominated in discussions of allostasis. Incorporation of other mediators is essential. For example, catecholamines and the autonomic nervous system are important (McEwen and Lasley, 2002; Schulkin, 2003), and there have been several discussions of the fight-or-flight response (part of the emergency life history stage) in the context of the life cycle of an animal (e.g. Wingfield et al., 1997; Wingfield and Ramenofsky, 1999). Attacks by predators or dominant individuals trigger a massive catecholamine response followed by glucocorticoids and other mediators of allostasis. However, it is important to bear in mind that these catecholamine responses may be over in seconds as the individual avoids a predator or attack from a dominant conspecific. Single ephemeral events such as these probably do not contribute significantly to extended allostatic load in the long term. However, increased frequency of these attacks or similar brief perturbations could contribute as pointed out by Boonstra et al. (1998), Cyr and Romero (2007) and Busch et al. (2008). Again, this is not a weakness of the allostasis model itself but a strength in that it can incorporate short-lived stresses by considering frequency of these events not just one in isolation. Clearly much more work is needed using the allostasis model as a guide.

Considering how to measure mediators of allostasis, there are many interacting mediators (McEwen, 2006). One way to approach this is the allostatic load battery, a broad ranging array of measures as outlined in Table 1

Some of the measures capture “mediators” but, at the same time, when those mediators are elevated there is potential to develop an “allostatic state” that under some conditions can contribute to allostatic load (especially if those mediators are elevated for long periods or reduced to low levels – e.g, too much or too little glucocorticoids are bad things to maintain). This can be measured in cumulative change in other measures (Koob and LeMoal, 2001). Yet not all of these mediators are easily measured in humans or in animals in the wild or in captivity, and there is a need to capture those “allostatic states” by measuring, for example, 24hr cortisol in urine or in feces, recognizing that what is measurable is only the “tip of the iceberg” as far as the other, interacting mediators of allostasis (or homeostasis, in the Romero et al., 2009 terminology) (McEwen, 2006).

Measurement of the glucocorticoids cortisol and corticosterone is one of the best ways of assessing mediators not only because they are accessible but also because they do many things

and are a key part of the network of allostasis. They are also easiest to measure in animals as well. There is a growing literature on fecal glucocorticoid levels in animals subjected to various measures of allostatic load - mostly from human disturbance, social status, disease, invasive species etc. (e.g. Bauchinger et al., 2005; Van Meter et al., 2009). It is the latter point that brings up the issue of allostatic overload type II in animals. This phenomenon could be a major cause of loss of biodiversity in recent decades and for the future. Animals under the additional pressure of human disturbance - recreational, urbanization, clear-cuts, introducing aggressive exotic species etc. may show many aspects of allostatic overload type II and could be good models for research. As for measuring other mediators, the same problems exist as for mammals. Catecholamine levels are difficult to interpret and central paracrine secretions even more so. For many cytokines we still do not have all the tools for comparative studies although genome sequencing in non-model species may take care of that for the future. Nonetheless, we always have to recognize that there are many other participant mediators even if we only measure one or two at a time.

## Developmental, including epigenetic, determinants of allostatic overload

Developmental issues raised by Romero et al. (2009) are an important addition to the discussion. This has been debated recently from the standpoint of allostatic overload Type II (McEwen 2006). Indeed, epigenetic and genetic factors interact with early life experiences to increase or decrease the behaviors and physiological factors that determine the rate of brain and body aging. This needs to be developed for Type I allostatic overload and for allostatic load in animals in the wild. Various genetic and epigenetic mechanisms that mould the developing phenotype are important evolutionary issues presumably to maximize fitness by development of a phenotype that will best cope with anticipated conditions. If those conditions fail to materialize, then that phenotype may have reduced fitness. This means there will be potentially great individual variation in homeostatic set points and allostatic load. Again, we see this as a weakness in the data collected not the model itself. It is a fascinating and important challenge to the allostasis model to incorporate these ideas.

Additionally, it is important to point out a very useful article by Monaghan (2007) who outlines a clear set of predictions and tests to integrate mechanisms and evolutionary ecology of developmental (maternal) effects. She proposes specific hypotheses about how early growth conditions, genetics and maternal effects affect development of a phenotype in relation to environmental change. Briefly, it is predicted that when environmental conditions, for example for breeding, are good then all phenotypes should do well but those developed under good conditions may do even better. However, if environmental conditions for breeding are poor then those phenotypes that developed under poor conditions should fare better (greater fitness) than those that developed under good conditions. Those that do not mach their environment may incur pathologies and reduced fitness (perhaps indicative of allostatic overload type II?). These predictions will be very useful in determining how mediators of allostasis may network under varying environmental conditions.

## Conclusion

Overall we feel that Romero et al. (2009) have raised some very important issues that need to be clarified so that the general reader can distinguish between the concepts of homeostasis and allostasis. However, we feel that those underlying allostasis need to be emphasized – particularly when an individual initiates a new life history stage that frequently incurs greater energy demand (reproduction, molting, migration). This is so much more than just maintaining basic life processes and thus we question whether homeostatic load is really a good substitute. This is where allostasis and allostatic load are so useful. They preserve the concept of homeostasis (i.e. within a life history stage homeostasis is still maintained – see Landys et al.

2006), but also encompass the anticipatory aspects of the life cycle. Certainly increased allostatic load elevates susceptibility to perturbations where homeostatic mechanisms may be exceeded thus triggering a stress response, but the strength of the allostasis concept is that it incorporates homeostasis unchanged and provides a framework to model how individual traits (body condition, infection, injury, age etc.), social status, daily and seasonal rhythms of food availability, predators, weather etc., as well as habitat differences and so on interact to contribute to overall allostatic load and thus energy demand to fuel it. Obviously variations in food availability and access to that resource will vary from individual to individual and are important components of the model proposed by McEwen and Wingfield (2003). We agree with Romero et al. (2009) that key issues for the future are how to measure allostatic load independently of glucocorticoid function, or for that matter any mediators of allostasis, so as to escape the circular arguments that result. An independent measure of allostatic load incorporating all of the above issues is key, and only then will the concept be tested objectively. It is here that the reactive scope model fits well and provides more predictions on how the mediators of homeostasis should change.

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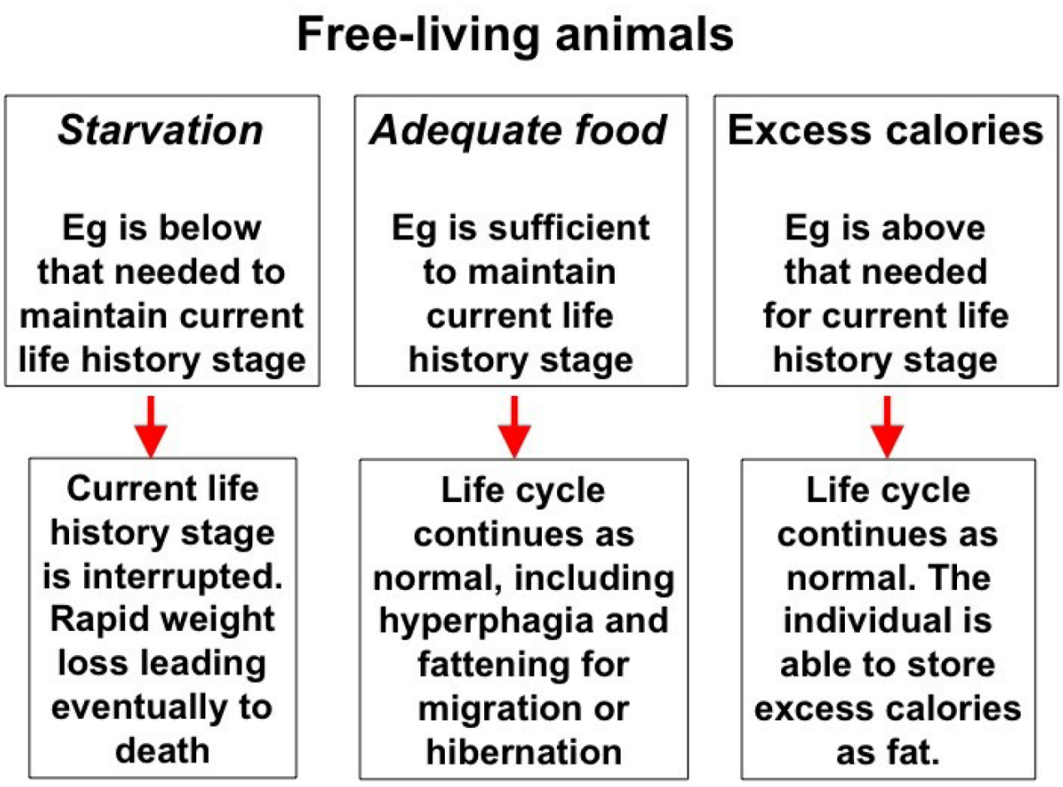


**Figure 1.**

The potential interactions of energy demand of a free-living animal going about its daily and seasonal routines, coping with unpredictable perturbations, and the potential energy to be gained from food in the environment (Eg). If Eg declines then starvation is probable unless the organisms can reduce allostatic load so energy demand is below Eg. If Eg is adequate to fuel all aspects of the life cycle (including fattening for migration or hibernation) and no severe perturbations occur, then the life cycle progresses normally. If Eg is even higher and excess calories are available (i.e. above those required for fattening in life history stages such as migration and hibernation) then the individual may be able to store fat for future contingencies such as an unpredictable decline in Eg. In the latter scenario, an individual may be able to mobilize these excess calories to fuel allostatic overload, at least temporarily, until environment conditions improve. Taken from McEwen and Wingfield (2003), Wingfield (2004), Korte et al. (2005).

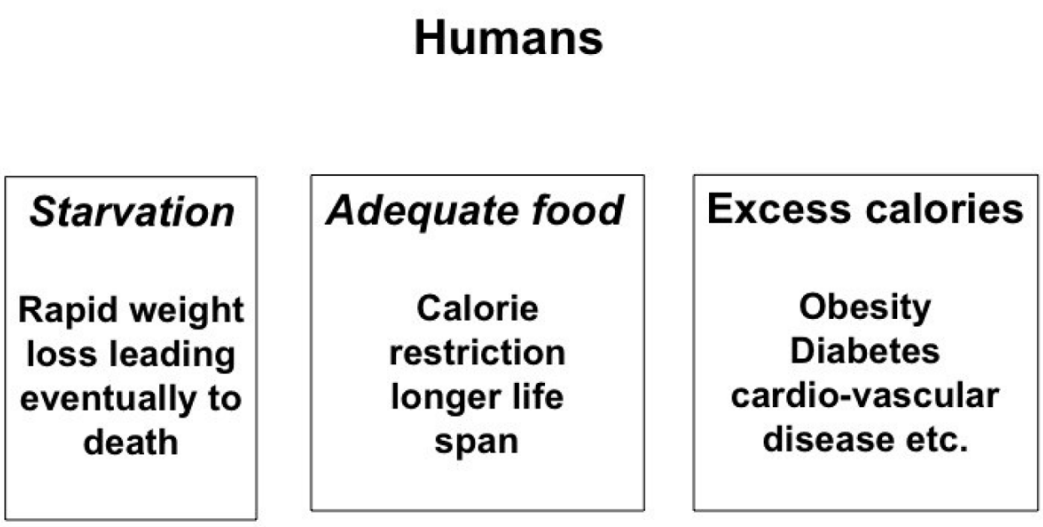


**Figure 2.**
Although humans are subject to the interactions of Eg and allostatic load as outlined in Fig. 1, there are some additional considerations given here. Declines of Eg below that required for normal daily routines may lead to starvation and is a major issue in many human societies. However, adequate food, but often regarded as restricted calories especially in societies of developed countries, may actually prolong life. Excess calories may lead to pathologies in the long term (McEwen, 2006). This is true of nonhuman animals too (especially in agriculture, zoos) etc. but is probably close to nonexistent in the wild because high Eg and availability of excess calories may not persist for long. The allostasis model provides a useful framework for modeling these concepts within a mechanistic framework

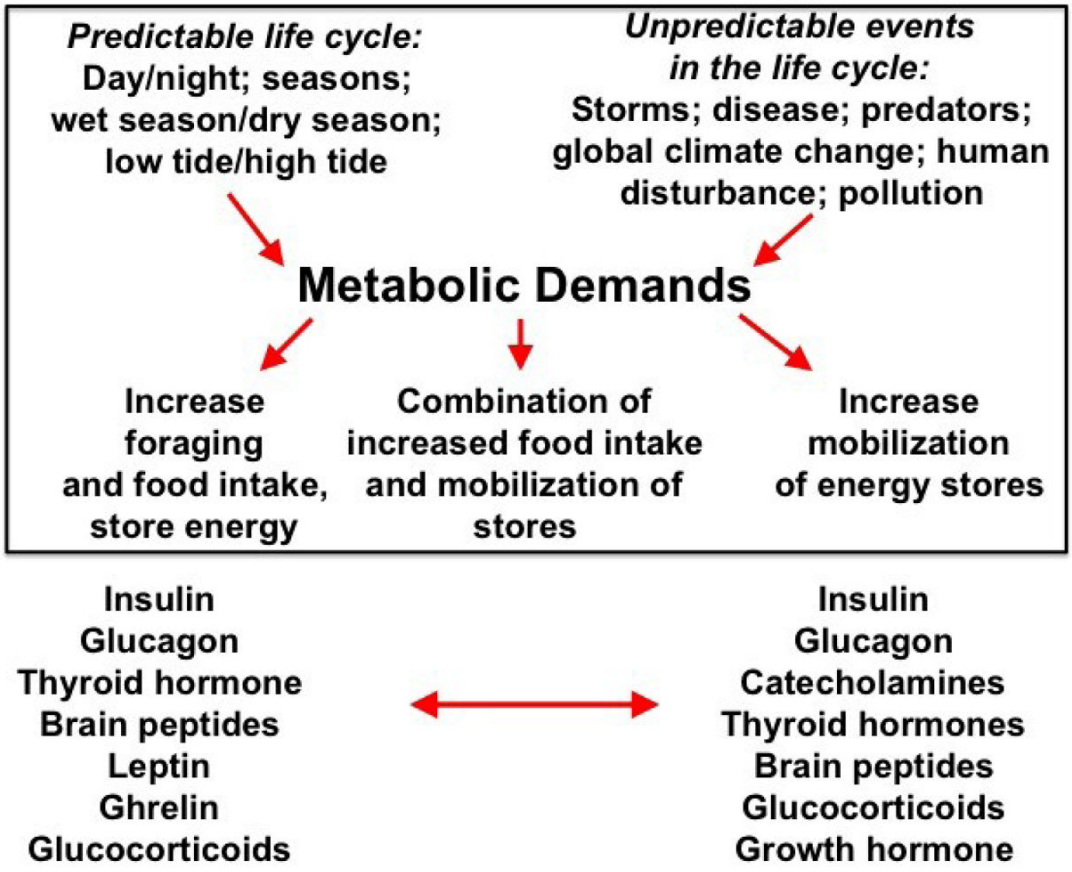


**Figure 3.**

The box summarizes how metabolic (energy) demands from the predictable life cycle (daily and seasonal routines) and the unpredictable can result in anabolism or catabolism depending upon available energy from food (Eg). If Eg is high then the normal life cycle progresses and an individual may be able to store energy such as fat for future contingencies. If Eg is variable (in a temporal sense from day to day, or a spatial sense insofar as available food may be patchy in distribution, or both), then there may be complex shifts from anabolic to catabolic states over short time spans (minutes to hours). If Eg declines below Eo (the sum of all metabolic demands of the individual – e.g. allostatic overload type 1) then energy stores such as fat need to be mobilized until allostatic load is reduced to a manageable level or a new source of Eg is found. Below the box are some mediators that are involved in energy management and metabolism in general. Note that this is not a complete list and does not include other mediators of allostasis such as cytokines that are involved with other, often related, processes particularly from unpredictable events. A point to be made here is that although the relationship of allostatic load to Eg varies in a fairly linear manner, the triggering of mediators of allostasis is not linear and forms a complex network depending upon condition of the individual (age, gender, phenotype, social status, injuries, infection etc.). In many cases the emergency life history stage may be triggered by this network allowing the individual to temporarily suspend the normal life history stage (e.g. breeding, migrating etc.), go into survival mode and reduce allostatic load to a manageable level until environmental conditions improve and the normal life cycle can be resumed.

**Table 1**

Allostatic load battery in CARDIA

| |
|---|
| Urine -- 12hr overnight |
| 1. Ur. Norepinephrine |
| 2. Ur. Epinephrine |
| 3. Ur. free cortisol |
| Saliva -- 6 saliva samples over one day -- assayed for cort |
| The outcomes of these mediators are: |
| Blood |
| 1. total and HDL cholesterol |
| 2. glycosylated hemoglobin |
| 3. IL-6 |
| 4. CRP |
| 5. fibrinogen |
| Other |
| 1. Waist-hip ratio |
| 2. Systolic and diastolic BP - seated/resting |
| 3. heart rate variability |