***Damage-Fitness Model: The missing piece in integrative stress models***

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**Appendix: Existing models of stress responses**

*Allostasis Model*

Allostasis Model describes how animals’ energetic requirement changes within a day and across seasons and physiological mediators constantly rework to meet the demand (Landys, Ramenofsky, & Wingfield, 2006; McEwen & Wingfield, 2003; McEwen & Wingfield, 2010; Wingfield, 2005). Allostasis is a process that maintains a stable level of vital physiological parameters, such as blood pressure, body temperature, blood pH levels, and plasma glucose levels (homeostasis) as the surrounding environment and life history stage change. Physiological mediators such as glucocorticoids, neurotransmitters, and cytokines fluctuate as energetic demands to maintain life-history-adjusted homeostasis changes (McEwen & Wingfield, 2003). Allostatic State refers to altered levels of the mediators due to predictable and/or unpredictable events, which over time incurs costs to the body (Allostatic Load) (McEwen & Wingfield, 2003; McEwen & Wingfield, 2010) (Fig. 6). Type 1 Allostatic Overload occurs when energy demand surpasses energy obtained from the environment. This is likely to occur when an unpredictable event occurs on top of energetically demanding predictable events (McEwen & Wingfield, 2003). For example, when a cold weather hits while insectivores are raising their young, it decreases the amount of available insects and increases energy to maintain body temperature. As a result, female pied flycatchers (*Ficedula hypoleuca*)lost body mass and fat stores, and had a lower fledging success than during the warm period (Eeva, Lehikoinen, Rönkä, Lummaa, & Currie, 2002). Type 2 Allostatic Overload occurs when altered levels of mediators are persistent for a prolonged period of time and mediators themselves cause pathology in the body as in the case of type II diabetes (McEwen & Wingfield, 2003; McEwen & Wingfield, 2010). This can occur even when food supply in the environment is abundant. The Allostasis Model departs from the notion that physiological parameters are kept within a narrow range, as described the classical model of homeostasis. Instead, the model incorporates fluctuations in energetic demands within a day, across seasons, and between life-history stages and how physiological mediators modify to maintain internal stability (McEwen & Wingfield, 2003). Furthermore, the model addresses a biphasic nature of consequences of mediators. For instance, adrenaline and noradrenaline boost memory consolidation and glucocorticoids facilitate this effect of adrenaline and noradrenaline (Roozendaal, McEwen, & Chattarji, 2009). However, an excess dose of glucocorticoids inhibits working memory. Thus, these mediators help and protect the body at a moderate dose but become harmful when the levels are chronically elevated or becomes dysfunctional (McEwen & Wingfield, 2003). The description of the dynamic economy of the external and internal environments is one of the strengths of the Allostasis Model.

*Reactive Scope Model*

Reactive Scope Model is an extension of Allostasis Model to address its weaknesses, including a heavy focus on energy input, energy consumption, and glucocorticoids, and no incorporation of how the developmental environment affects future stress responses (Romero, Dickens, & Cyr, 2009). Reactive Scope Model describes a change in physiological mediators over time, such as glucocorticoids, heart rate, cytokines, locomotion, and neurogenesis (Romero et al., 2009). Predictive Homeostasis is a range of mediator values in response to predictable events, such as a range of glucocorticoids to facilitate feeding behavior within a day and across non-breeding and breeding seasons (Fig. 6). In contrast, Reactive Homeostasis is a range of mediator values in response to unpredictable events such as a storm. Animals require certain concentrations of physiological mediators to survive, below which is referred to as a Homeostatic Failure (not shown in Fig. 6). Above the Reactive Homeostasis range is referred to as Homeostatic Overload. This is a range where the physiological mediator becomes harmful to the body. For instance, heart rate increases as animals wake up in the morning and slows down when animals lay down (Predictive Homeostasis). These changes are necessary to deliver an adequate amount of blood to organs depending on activity levels. Heart rate also increases suddenly if you are startled as a part of the fight-or-flight response, shunting blood to the heart and skeletal muscles so an individual can escape a stressor (Reactive Homeostasis) (Romero et al., 2009; Sapolsky, Romero, & Munck, 2000). An example of the Homeostatic Overload is when repeated or prolonged stimulation of the fight-or-flight response results in cardiovascular disease (Romero & Butler, 2007; Romero et al., 2009). One of the significant differences between Allostasis and Reactive Scope Models is what is on the y-axis: energy levels in Allostasis Model and physiological mediator levels in Reactive Scope Model. Like the Allostasis Model, Reactive Scope Model incorporates the biphasic effect of physiological mediators – they are beneficial at one level while harmful at another. The model also describes how thresholds between Reactive Homeostasis and Homeostatic Overload can change with developmental stages, acclimation to a stressor, and maternal and developmental environments. For instance, wear and tear reduces the threshold between Reactive Homeostasis and Homeostatic Overload, meaning a smaller increase in heart rate, glucocorticoid, or cytokine levels is needed to become pathological when the same increases in absence of wear and tear would not.

*Physiological Regulatory Networks*

Physiological regulatory networks place its importance on examining connections among physiological functions of an organism that act together to maintain homeostasis (Cohen, Martin, Wingfield, McWilliams, & Dunne, 2012). Physiological Regulatory Network state refers to levels of all the physiological integrators such as glucocorticoids, sex hormones, and cytokines that respond to changes in internal demands or external environment in order to maintain stability in phenotypes (Cohen et al., 2012). Integrators influence functional subnetworks such as stress responses, immune responses, and energy metabolism (Fig. 6, green arrows). The key idea is that each integrator is involved in more than one subnetwork, and subnetworks are interconnected to each other. For instance, testosterone and glucocorticoids are each examples of integrators (Cohen et al., 2012). In a simple term, testosterone promotes territorial behavior, maintenance of male sexual function, as well as suppresses immune function (Wingfield, Jacobs, & Hillgarth, 1997). Glucocorticoids also suppress immune function at high concentrations by inhibiting synthesis of lymphocytes and cytokines and lower testosterone levels through reducing gonadotropin releasing hormone and luteinizing hormone levels (Sapolsky et al., 2000). In birds, they both bind to the same binding globulins, influencing the other’s free hormone levels (Deviche, Breuner, & Orchinik, 2001). Thus, testosterone and glucocorticoids are integrators of the reproductive system, immune system, and energy metabolism subnetworks and those integrators and subnetworks are connected to each other which ultimately determine health of an individual (Fig. 6). Subnetworks feedback negatively onto integrators. The more negative feedback there is to regulate integrator levels, the less flexible for the organism to adapt to a change in the environment (Cohen et al., 2012) but also the less likely for an animal to suffer from Homeostatic Overload. Physiological Regulatory Networks also incorporate changes in internal needs and condition as well as responses to external environment throughout the day, season, and lifetime. The concept proposes that related molecules, such as testosterone, androgen receptor, and sex steroid binding globulin, are under natural selection and as a result, will evolve together to minimize excess components and improve efficiency (Cohen et al., 2012). While it describes realistic, complex interconnections among physiological systems, it will likely take a considerable amount of time to untangle all connections.

*Control Theory*

In recent years, physiologists have applied an engineering approach to map out physiological feedback systems to maintain homeostasis (Bechhoefer, 2005; Stear, 1975; Zhang & Andersen, 2007; Zhang, Pi, Woods, & Andersen, 2009, 2010). In this homeostatic control system, there is a transducer which senses deviations in controlled variable (e.g., ROS) from a set point, a controller which receives and integrates inputs from the transducer (e.g., transcription factor), and actuators which directly help correct deviations in controlled variables (e.g., antioxidants). The strength of this approach is that once the cellular or physiological events for a particular functional module are determined, one can simulate changes in levels of transducers, transcription factors, actuators in response to a stressor using a mathematical model. For instance, Zhang et al. (Zhang et al., 2009) simulated temporal, dose-dependent changes in antioxidant enzymes after an exposure to polycyclic aromatic hydrocarbons, an environmental toxin from burning organic matter. This depicted a) a rapid elevation of the toxin in a cell, followed by a decline to steady, low levels with b) a gradual persistent increase in antioxidant enzymes, and c) a rise and a fall of ROS (Zhang et al., 2009). This illustrates a non-linear, temporal change in these 3 parameters. The Control Theory also incorporates a feedforward loop to the controller. This loop regulates the controller directly, independent of the controlled variables by sending the stressor and activating the actuator (Zhang et al., 2010). In the example of oxidative balance after an exposure to xenobiotics, the xenobiotics directly induce transcription of antioxidant enzymes (feedforward loop). This results in a dose-dependent hormetic response where at low levels of the xenobiotics, the compensatory mechanisms with antioxidant enzymes overcompensate due to the feedforward loop, resulting in ROS levels that are lower than baseline. On the other hand, at high level of xenobiotics, feedback and feedforward mechanisms cannot keep up with defusing the stressor, elevating ROS production higher than the baseline. A mathematical simulation shows that a J-shaped, hormetic change in ROS levels appears only with a feedforward mechanism (Zhang et al., 2009).

Bechhoefer, J. (2005). Feedback for physicists: A tutorial essay on control. *Reviews of Modern Physics, 77*, pp. 783-836.

Cohen, A. A., Martin, L. B., Wingfield, J. C., McWilliams, S. R., & Dunne, J. A. (2012). Physiological regulatory networks: ecological roles and evolutionary constraints. *Trends in Ecology and Evolution, 27*, pp. 428-435.

Deviche, P., Breuner, C., & Orchinik, M. (2001). Testosterone, corticosterone, and photoperiod interact to regulate plasma levels of binding globulin and free steroid hormone in Dark-eyed Juncos, *Junco hyemalis*. *General and Comparative Endocrinology, 122*, pp. 67-77.

Eeva, T., Lehikoinen, E., Rönkä, M., Lummaa, V., & Currie, D. (2002). Different responses to cold weather in two pied flycatcher populations. *Ecography, 25*, pp. 705-713.

Landys, M. M., Ramenofsky, M., & Wingfield, J. C. (2006). Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes. *General and Comparative Endocrinology, 148*, pp. 132-149.

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior, 43*, pp. 2-15.

McEwen, B. S., & Wingfield, J. C. (2010). What is in a name? Integrating homeostasis, allostasis and stress. *Hormones and Behavior, 57*, pp. 105-111.

Romero, L. M., & Butler, L. K. (2007). Endocrinology of stress. *International Journal of Comparative Psychology, 20*, pp. 89-95.

Romero, L. M., Dickens, M. J., & Cyr, N. E. (2009). The reactive scope model -- A new model integrating homeostasis, allostasis, and stress. *Hormones and Behavior, 55*, pp. 375-389.

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews: Neuroscience, 10*, pp. 423-433.

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21*, pp. 55-89.

Stear, E. B. (1975). Application of control theory to endocrine regulation and control. *Annals of Biomedical Engineering, 3*, pp. 439-455.

Wingfield, J. C. (2005). The concept of allostasis: coping with a capricious environment. *Journal of Mammalogy, 96*, pp. 248-254.

Wingfield, J. C., Jacobs, J., & Hillgarth, N. (1997). Ecological constraints and the evolution of hormone-behavior interrelationships. *Annals of the New York Academy of Sciences, 807*, pp. 22-41.

Zhang, Q., & Andersen, M. E. (2007). Dose response relationship in anti-stress gene regulatory networks. *PLoS Computational Biology, 3*, p e24.

Zhang, Q., Pi, J., Woods, C. G., & Andersen, M. E. (2009). Phase I to II cross-induction of xenobiotic metabolizing enzymes: a feedforward control mechanism for potential hormetic responses. *Toxicology and Applied Pharmacology, 237*, pp. 345-356.

Zhang, Q., Pi, J., Woods, C. G., & Andersen, M. E. (2010). A systems biology perspective on Nrf2-mediated antioxidant response. *Toxicology and Applied Pharmacology, 244*, pp. 84-97.