Why understanding the nonlinear properties of human behavior is important …

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This work was done as a private venture and not in the author's capacity as an employee of the Jet Propulsion Laboratory, California Institute of Technology.

Outline

- Cortisol rhythmicity in the HPA-axis
- Stress response
- Nonlinear system modeling
- Conclusions

Main message: *There is a need for a computer model of the cortisol cycle to understand stress response*

Cortisol rhythmicity displays identifiable nonlinear properties, which suggests the operation of a nonlinear system

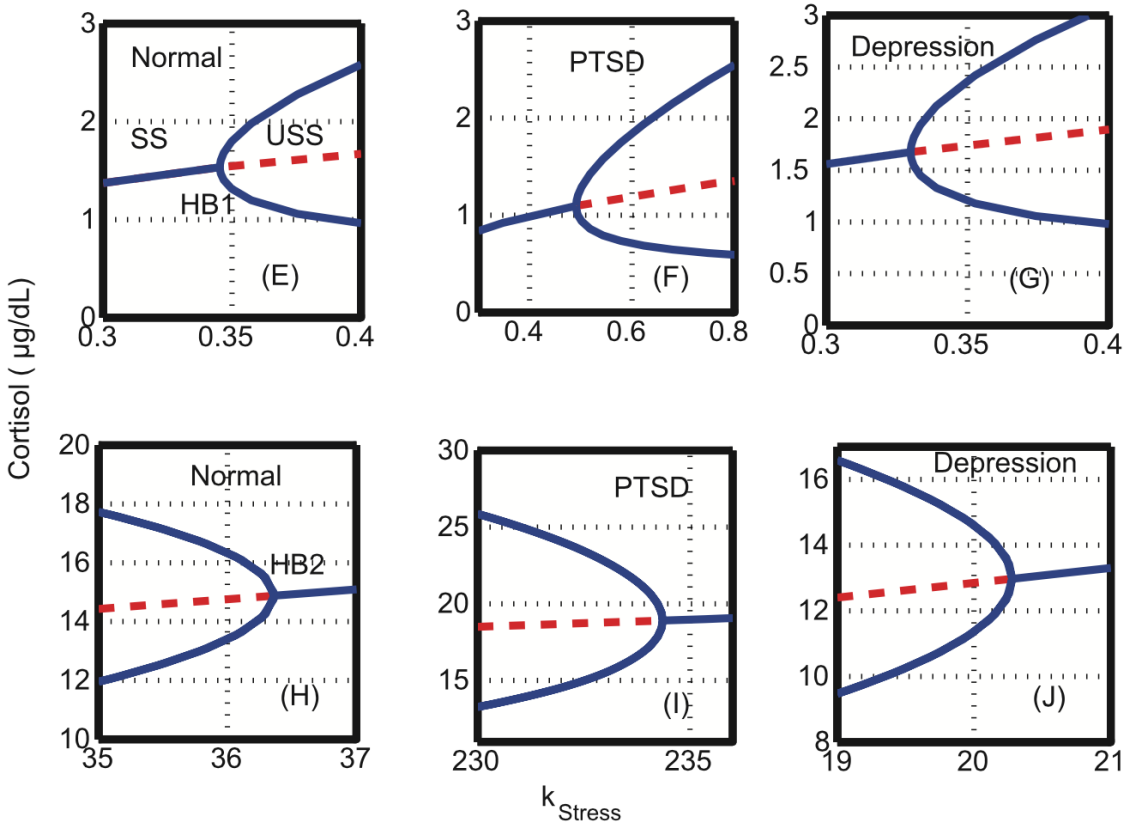
This means that researchers have begun to apply analytical strategies to study cortisol rhythmicity. These are strategies that have helped us understand other complex problems.

- These strategies include the use of powerful mathematical tools and related concepts that JPL and NASA apply to space flight, astrophysics, and high-level engineering problems.

- Also, nonlinear systems can be modeled in a computer, allowing us to study how they work.

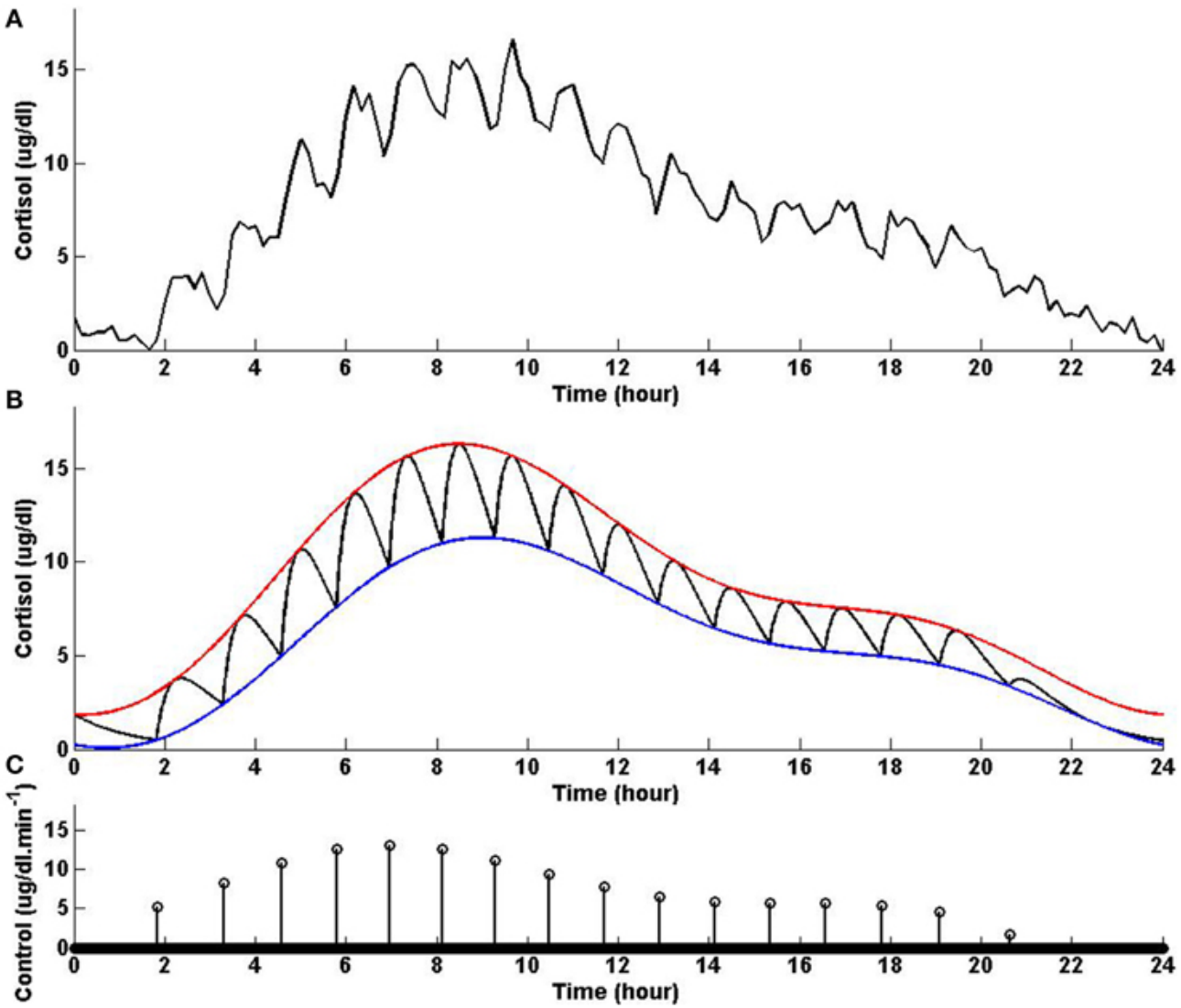
So, what is nonlinear about the human stress response?

- For our purposes “nonlinear” describes the cortisol cycle’s rhythmic pulse (see diagram), where the rhythm’s stability is determined by regulatory influences.



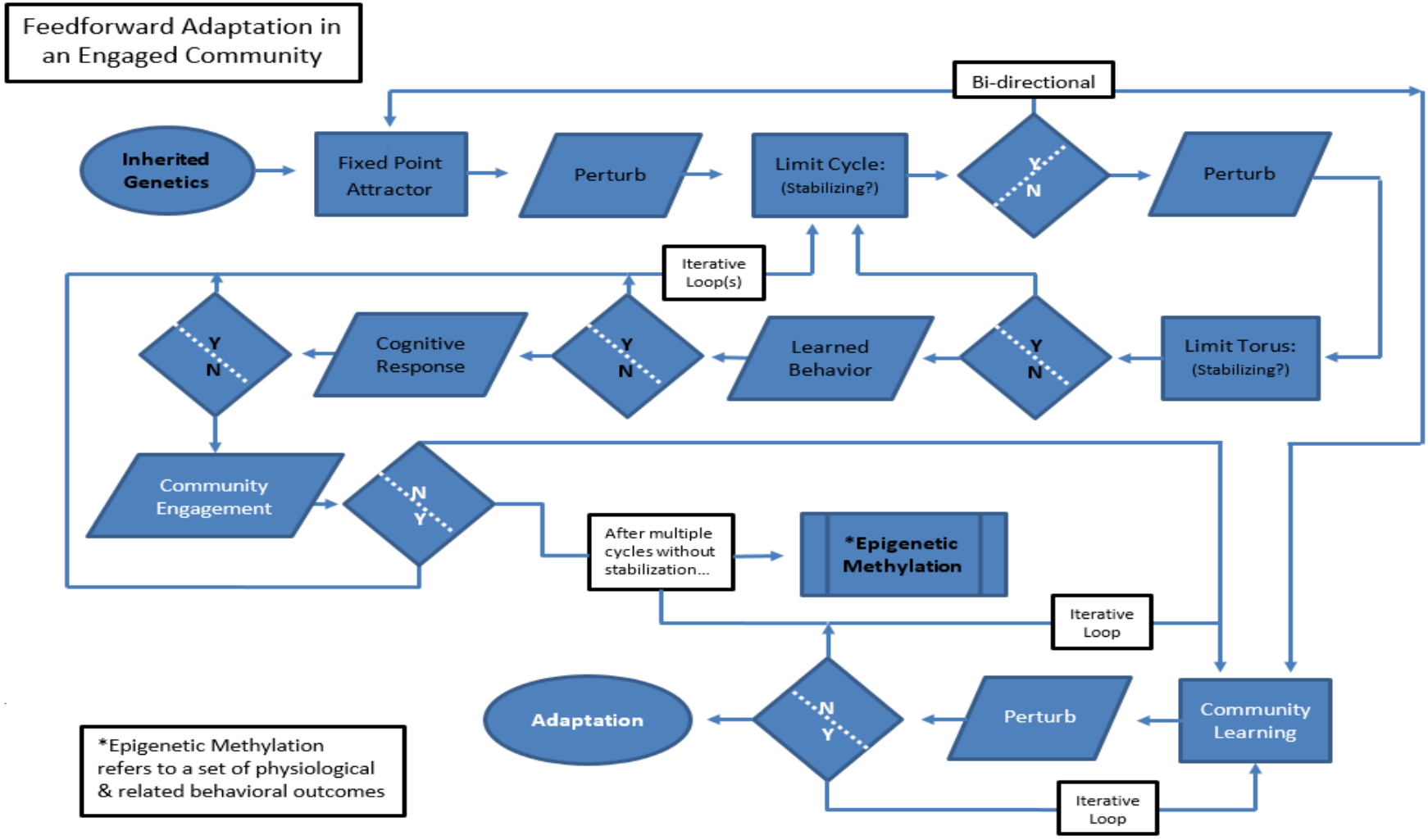
Sriram, K. et al: *Modeling cortisol dynamics in the neuro-endocrine axis distinguishes normal, depression, and post-traumatic stress disorder (PTSD) in humans*, PLoS Computational Biology, Feb. 2012, vol. 8, issue 2

Computer Generated Model of Cortisol Rhythmicity

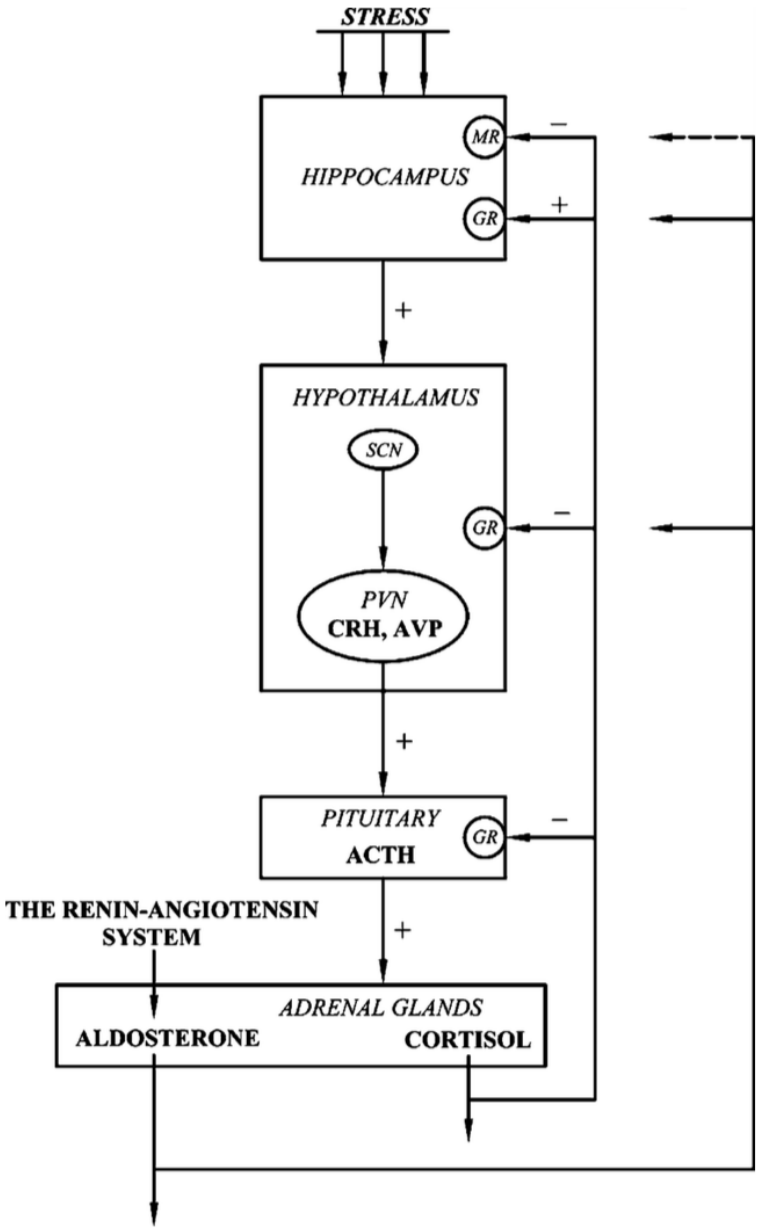


Faghih et al: An optimization formulation for characterization of pulsatile cortisol, Front. Neurosci., 11 August 2015

Human cortisol rhythmicity stabilization flow diagram



HPA-axis Feedback and feedforward loops



Savic et al.: A mathematical model of stress reaction: individual differences in threshold and duration, Psychobiology, 2000, 28, (4), 581-592.

Fig. 1. The hypothalamic–pituitary–adrenal system feedback and feedforward loops. Hypothalamic corticotrophin-releasing hormone (CRH) and arginin-vasopressin (AVP) stimulate secretion of ACTH from the pituitary, followed by cortisol secretion from adrenal cortex. A cortisol negative feedback mechanism, mediated through hypothalamic and pituitary glucocorticoid receptors (GR), as well as hippocampal mineralocorticoid receptors (MR), is responsible for the basal activity maintenance, as well as the termination of stress-induced activity of this system, but there is also a positive feedback of cortisol on CRH secretion, exerted by cortisol acting at the hippocampal GR.

So, what is nonlinear about the human stress response?

- For our purposes “nonlinear” describes the cortisol cycle’s rhythmic pulse (see diagram), where the rhythm’s stability is determined by regulatory influences.

- **How and why this rhythm remains stable or becomes unstable and what happens as a result has up to this point been difficult to understand because it involves nonlinear behavior acting across many different scales… from the cellular molecular level, to the level of individuals’ behavior in community, or even including national and geopolitical influences… which is the reason why we need these more powerful tools**

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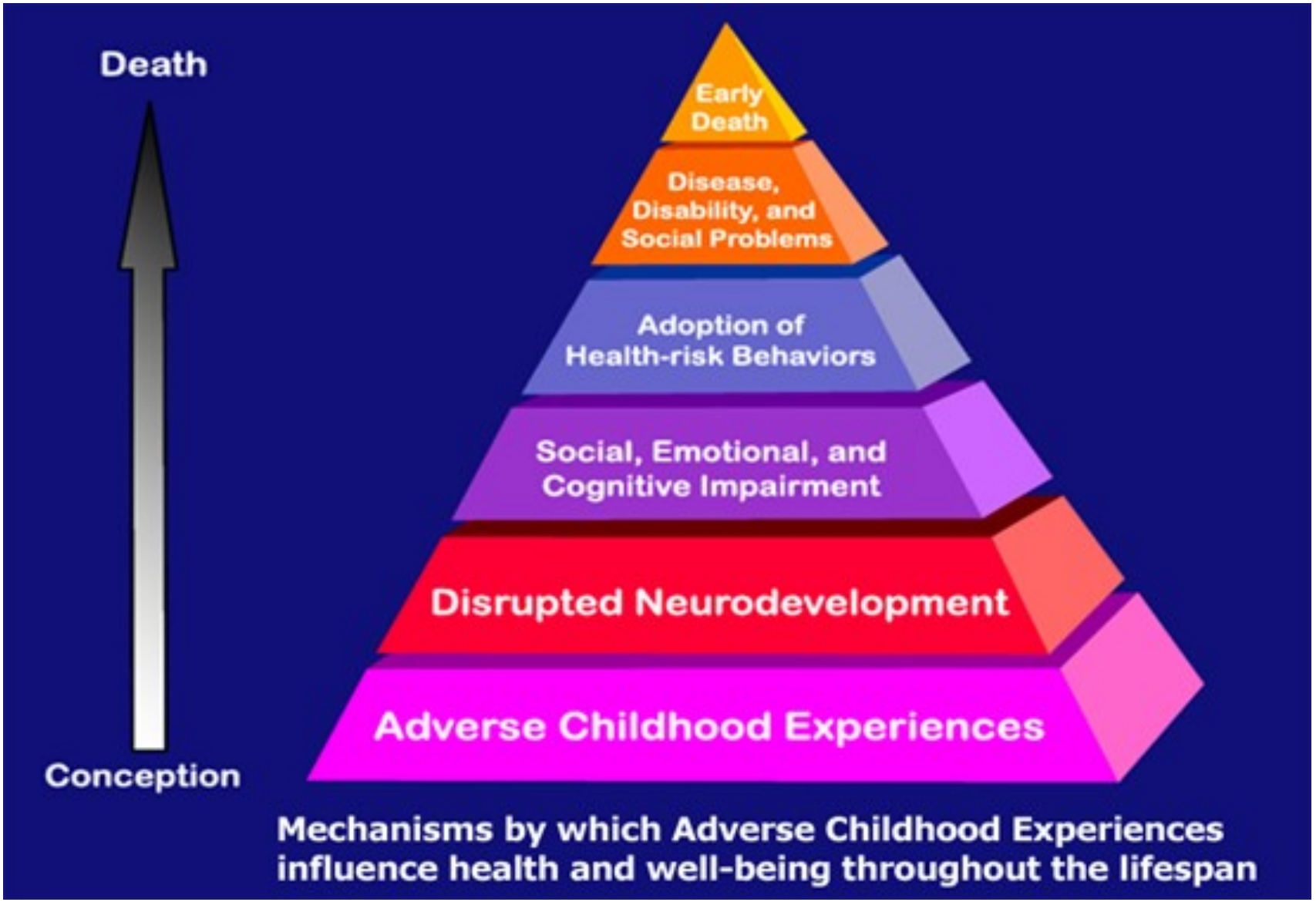
Connection between cortisol rhythmicity and health care



ACE Study – CDC-Kaiser – 17,000 patients - http://www.cdc.gov/violenceprevention/acestudy/about.html

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- **This makes some people more stress reactive than others.**

Even moderate instability in cortisol's rhythmic pulse can cause problems

- Clinicians refer to this as chronic stress. When stress response is chronically unstable, then people have higher risk for disease because instability triggers the immune system to produce inflammatory agents. These contribute to heart disease, cancer, and other chronic diseases that lead to early death.

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- **Instability in cortisol's rhythmic pulse is known to trigger impulsive behavior, which often means high risk behavior, like drugs, violence, and promiscuity, which can feed a vicious cycle of escalating stress.**

Onset of depression

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Onset of depression, from individual to societal response

- When people have felt stressed for too long, they may become depressed. This is another kind of instability where the brain over regulates the stress response, reducing the level of cortisol that is produced by the rhythmic pulses.

- **Each of these different kinds of instability in the cortisol cycle's rhythmic pulse is physically unhealthy as a chronic condition and can also lead to social behavior that is counterproductive.**

Stress causes humans to change the world

- Not only do our experiences in life affect our stress response, but the human stress response affects the world around us. The relationship is bi-directional and reciprocal. This means that not only does our stress response adapt to stress, but also that, for humans, the experience of stress causes us to adapt the world in reaction to our stress response, i.e., the experience of stress causes us to make our world less stressful.

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- **It means that the nonlinear properties of human stress response are also likely to be mirrored in the collective behavior of humans. If so, then the powerful tools that we can use to study cortisol rhythmicity can also be used to understand the dynamics of cooperative human behavior.**

There must be regulating influences that stabilize cooperative behavior

- This means that we should be able to identify the regulatory influences that are operating on the scale of cooperative behavior because just as regulatory influences stabilize cortisol rhythmicity, similarly, there must be regulating influences that stabilize cooperative behavior. This implication follows naturally once we determine that human behavior is a significant part of the nonlinear dynamics that regulates cortisol rhythmicity.

- This is what we will use computer modeling to study.

The nonlinear ODE equations for the cortisol cycle in the HPA-axis (hypothalamo-pituitary-adrenal)

$$\frac{d[CRH]}{dt} = k_{stress}\frac{K_i^{n2}}{K_i^{n2}+[GR]^{n2}} - V_{S3}\frac{[CRH]}{K_{m1}+[CRH]} - K_{d1}[CRH] \quad (1)$$

$$\frac{d[ACTH]}{dt} = K_{P2}[CRH]\frac{K_i^{n2}}{K_i^{n2}+[GR]^{n2}} - V_{S4}\frac{[ACTH]}{K_{m2}+[ACTH]} - K_{d2}[ACTH] \quad (2)$$

$$\frac{d[CORT]}{dt} = K_{P3}[ACTH] - V_{S5}\frac{[CORT]}{K_{m3}+[CORT]} - K_{d3}[CORT] \quad (3)$$

$$\frac{d[GR]}{dt} = K_b[CORT]([G_{tot}]-[GR]) + V_{S2}\frac{[GR]^{n1}}{K1^{n1}+[GR]^{n1}} - K_{d5}[GR] \quad (4)$$

$$G_{tot} = G + GR \quad (5)$$

CRH, ACTH, CORT, GR, and Gtot are the corticotrophin-releasing hormone, adreno-corticotrophin hormone, cortisol, glucocorticoid receptor complex, and total glucocorticoid receptor, respectively. kstress is the bifurcation parameter that drives the system by initiating the CRH production, Ki is the inhibition constant that regulates the strength of the negative feedback loop, $V_{S3,S4,S5}$ are the rates at which the hormones CRH, ACTH, and CORT are degraded enzymatically through saturation kinetics, Km1,m2,m3 are the Michaelis constants, Kd1,d2,d3,d5 are the autonomous degradation constants, KP2,P3,b are the rates of production of ACTH, CORT, and GR respectively, n1, n2 are the Hill constants, and K1 is the activation constant.

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Conclusions

- Cortisol rhythmicity displays identifiable nonlinear properties, which suggests the operation of a nonlinear system
- Effective regulation is important to keep the rhythm stable
- Multiscale modeling and simulation of cortisol rhythmicity can be accomplished by nonlinear dynamical system techniques
- It is important to develop a better understanding of how all of the above works because a lot of cost to healthcare and society is riding on our ability to develop solutions.

References

[1] Jadi, M.P., Sejnowski, T.J.: *Regulating cortical oscillations in an inhibition-stabilized network,* Proc. of the IEEE, vol. 102, no. 5, May 2014.

[2] Brown, E.N. et al: *A stochastic differential equation model of diurnal cortisol patterns*, Am. J. Physiol. Endocrinol. Metab., 280, E450-E461, 2001.

[3] Sriram, K. et al: *Modeling cortisol dynamics in the neuro-endocrine axis distinguishes normal, depression, and post-traumatic stress disorder (PTSD) in humans*, PLoS Computational Biology, Feb. 2012, vol. 8, issue 2.

[4] Keenan, D.M., et al: *A feedback-controlled ensemble model of the stress-lresponsive hypothalamo-pituitary-adrenal axis*, PNAS, March 27, 2001, vol. 98, no. 7, pp. 4028-4033.

[5] Young, E. A., et al: *Cortisol pulsatility and its role in stress regulation and health*, Frontiers in Neuroendocrinology, 25, 2004, pp. 69-76.

[6] Kim et al: Timing and bistability in the hypothalamic-pituitary-adrenal axis: a model for onset and exposure therapy of stress disorders, PNAS, 2015.

[7] Farhy, L.S.: Modeling of Oscillations of Endocrine Networks with Feedback.

[8] Vinther, et al: The minimal model of the hypothalamic-pituitary-adrenal axis, J. Math. Biol., (2011), 63-633-690.

[9] Ben-Zvi, A., Vernon, S. D., Broderick, G.: Model-based therapeutic correction of hypothalamic-pituitary-adrenal axis dysfunction, Computational Biology, Jan. 2009, vol. 5, issue 1.

[10] Zarzer et al.: Differentiation between genomic and non-genomic feedback controls yields an HPA axis model featuring hypercortisolism as an irreversible bistable switch, Theoretical Biology and Medical Modelling, 2013, 10-65.

[11] Kyrylov, et al.: Modeling robust oscillatory behavior of the hypothalamic-pituitary-adrenal axis, IEEE Transactions of Biomedical Engineering, vol. 42, no. 12, Dec. 2005.

[12] Savic et al.: A mathematical model of stress reaction: individual differences in threshold and duration, Psychobiology, 2000, 28, (4), 581-592.

[13] Jelic et al.: Mathematical modeling of the hypothalamic-pituitary-adrenal system activity, Mathematical Biosciences, 197, 2005, 173-187.

[14] Andersen et al.: Mathematical modeling of the hypothalamic-pituitary-adrenal gland (HPA) axis, including hippocampal mechanisms, Mathematical Biosciences, 246, (2013), 122-138.

[15] Gupta et al.: Inclusion of the glucocorticoid receptor in a hypothalamic pituitary adrenal axis model reveals bistability, Theoretical Biology and Medical Modelling, 2007, 4:8.