

Ben-Zvi A *et al*, "Model-Based Therapeutic Correction of Hypothalamic-Pituitary-Adrenal Axis Dysfunction," *PLoS Comput Biol* 5(1)(2009): e1000273.

**Abstract:** The hypothalamic-pituitary-adrenal (HPA) axis is a major system maintaining body homeostasis by regulating the neuroendocrine and sympathetic nervous systems as well modulating immune function. Recent work has shown that the complex dynamics of this system accommodate several stable steady states, one of which corresponds to the hypocortisol state observed in patients with chronic fatigue syndrome (CFS). At present these dynamics are not formally considered in the development of treatment strategies. Here we use model-based predictive control (MPC) methodology to estimate robust treatment courses for displacing the HPA axis from an abnormal hypocortisol steady state back to a healthy cortisol level. This approach was applied to a recent model of HPA axis dynamics incorporating glucocorticoid receptor kinetics. A candidate treatment that displays robust properties in the face of significant biological variability and measurement uncertainty requires that cortisol be further suppressed for a short period until adrenocorticotrophic hormone levels exceed 30% of baseline. Treatment may then be discontinued, and the HPA axis will naturally progress to a stable attractor defined by normal hormone levels. Suppression of biologically available cortisol may be achieved through the use of binding proteins such as CBG and certain metabolizing enzymes, thus offering possible avenues for deployment in a clinical setting. Treatment strategies can therefore be designed that maximally exploit system dynamics to provide a robust response to treatment and ensure a positive outcome over a wide range of conditions. Perhaps most importantly, a treatment course involving further reduction in cortisol, even transient, is quite counterintuitive and challenges the conventional strategy of supplementing cortisol levels, an approach based on steady-state reasoning.

*[Note: Without seeing the entire article, we can't be sure-but this appears to be a report of the predictions of a mathematical model, probably one utilizing dynamical systems processes. Such a model always involves simplifying assumptions—both because the computational complexity is too great and because to date no one truly understands all of the subtle signaling processes and interactions involved in any complex biological system. It is possible this counterintuitive prediction will turn out to be a usable therapy to restore the known disturbances in the HPA axis of CFS/CFIDS/ME patients, who are already known to have low cortisol levels. However, the effects of further lowering cortisol in a patient with low cortisol levels and an over-active immune system, who possibly also has an active subclinical viral infection, could be quite dire. So we strongly recommend no one try this until very careful randomized, placebo-controlled, double-blind studies are carried out.]*