Modeling the Biological Mechanisms That Determine the Dynamics of Stress Response of the Human Body

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Stimuli threatening the homeostasis is conceptualized as stress by Walter Cannon (Cannon, 1932). A complex set of physiological mechanisms is activated as a stress response to a stressor perturbing the balanced system. The evolutionary function of the response is to enable the body to cope with stress. However, depending on the level, duration, and frequency of the stressors, the mechanism may lose its function and the body can go into a pathological state.

The stress response involves whole of the body, but is primarily centered around three subsystems: endocrine, immune, and neural systems. Five balancing and three reinforcing feedback loops are hypothesized to play the most crucial roles at hour-level maintenance of the homeostasis against stressors (Figure 1).
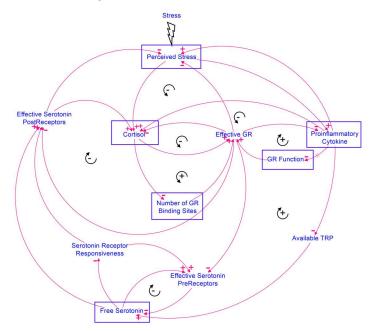

Figure 1: Causal loop diagram

In this study, we construct a simulation model of these three subsystems to imitate the stress response dynamics under different types of external stimuli. Cortisol, glucocorticoid receptors, proinflammatory cytokines, serotonin, and serotonin receptors are the main variables of the model. Considering the purpose of this study, time unit of the model is chosen as hour, and therefore, variables of the model stand for the hourly average levels, not the instantaneous levels.

The model is tested and validated under four different settings: no stressor, single-minor stressor, repetitive-minor stressor with low frequency, and repetitive-minor stressor with high frequency. The dynamic outputs of the model show a high resemblance with available

qualitative and quantitative real-life data (Figure 2). Moreover, the model provides a quantitative representation of some highly acknowledged qualitative hypotheses about the stress response of the body, such as allostatic load construct of Bruce S. McEwen (McEwen, 1993).
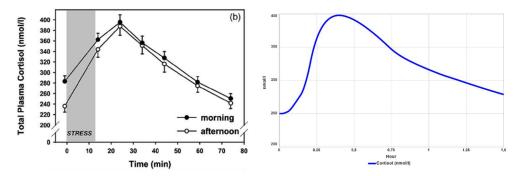

Figure 2: Cortisol response to a single-minor stressor: real data (Kudielka et al., 2004) vs. model output
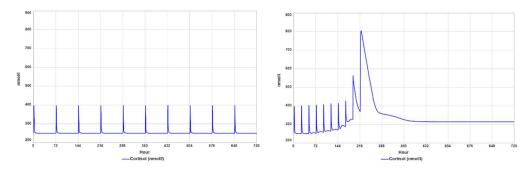

Figure 3: Cortisol response to a repetitive-minor stressor with low frequency vs. high frequency

Model's capability of capturing the role of internal interactions in the system is authenticated with sensitivity analysis (as in Figure 3), some runs revealing bifurcations with respect to stress stimulus level and duration parameters.

Ultimately, we have used the model to replicate stress-caused abnormalities. First, we have applied a single but major stress, and consequently, the model can successfully generate one-month dynamics of depression-like abnormalities. Secondly, we have experimented with an additional mild stress to a body that experienced a single major stress approximately one month ago. The model reveals an interesting fact: a body with past experience reacts more sensitive to a mild stress than a body without a stress history (Figure 4). The last scenario we have analyzed is the cytokine-induced sickness behavior. In this case, an immune stimulator (as cytokine) is externally applied to the model instead of a psychological stressor. The model demonstrates the
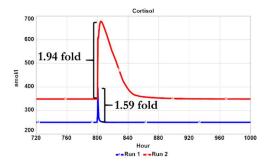

Figure 4: Comparison of cortisol responses of the body with (Run 2) and without (Run 1) earlier stress experience to a single-minor stressor

abnormality dynamics of the stress measures of the body, following a sickness behavior period.

Overall, the model serves well our purposes in this study: it provides us with a theoretically grounded tool to observe, understand, and experiment with the stress response mechanisms. The model can present quantitative representation of very well acknowledged hypotheses about the stress response of the body. This is a novel quantitative step towards the comprehension of stress response in relation with other disorders, and it provides us with a tool to design and test treatment methods. The ultimate aim of such research would be to provide a comprehensive systemic framework to the body's relations with external environment and use this framework to design and test treatment strategies, with or without drugs.

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