

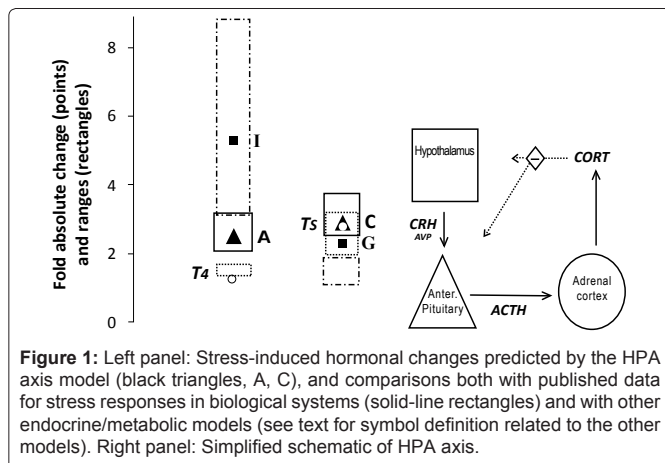


Towards Validation of an Endocrine Simulation Model

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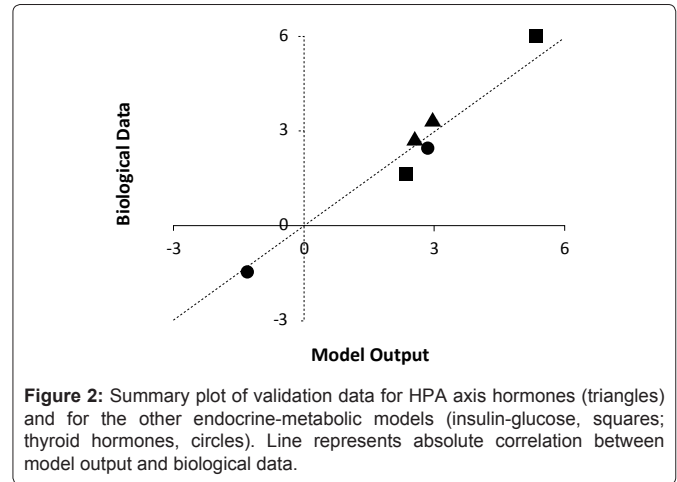
From a biomedical engineering point of view, the body's endocrine network can be considered as a high-order feedback control system based on chemical signals-hormones-produced by endocrine glands and endocrine cells embedded in other body tissues. A large number of mathematical models have been developed to simulate subsystems of the body's endocrine-metabolic network. These models, as with many other 'in silico' representations of biological phenomena, require validation before they can be expanded in their core applications, and applied to novel biological simulations and response predictions. Such validation is normally done through comparisons with data obtained directly in the related biological systems.

We have previously reported [1] modeling of the hypothalamus-pituitary-adrenal (HPA) axis with three main hormones (Figure 1, right panel), corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, as well as protein-bound cortisol parameters, based on a system of five differential equations. We have more recently worked on validation of the model to include further simulation of circadian rhythms and induction of stress parameters (manuscript in preparation). In figure 1 (right panel), for example, a stress response output of the model (triangles) in terms of fold increases in ACTH (A) and cortisol (C, or corticosterone) levels is compared to the range (solid lines) of responses obtained directly from different biological systems. These ranges include a variety of



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different behavioral and physiological of stresses [2-10], and are represented by the mean +/- s.e.m of the data reported in these studies.

For comparison with the HPA, results reported for two other models involving (a) thyroid hormones [11] and (b) insulin [12] were estimated as follows:

(a) fold-increases of TSH levels (Ts, thyroid stimulating hormone), and decreases of T4 levels (free T4), after iodine-loading simulation, (white circles)

(b) fold-increases in glucose levels (G, 30:120 minute ratios for G-loading simulation), and in insulin activity (I, 30 minute response after G-loading simulation), (black squares)

These values are also plotted in figure 1 (left panel) along with the respective data ranges (single-dash lines for thyroid hormones, multi-dash lines for insulin and glucose) obtained directly from different biological systems: glucose and insulin ranges refer to levels after G-loading tests [12-14]; TSH and T4 ranges refer to levels after iodine supplementation [11,15]. Figure 2 shows a correlation composite of all three models-refer to respective original articles [1,11,12] for their mathematical constructions; there is good correlation ($R^2=0.98$) between biological data (mean response values) and model output data. In these examples representing different modeling approaches for the simulation of endocrine-metabolic subsystems, model response data for the given parameters are within, or close to, the range calculated from experiments on biological systems.

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