

Measurement Identification and Robustness Analysis of the Fathead Minnow Steroidogenesis Model

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The ability to effectively manipulate complex, biochemical networks in a predictable fashion is limited by the lack of understanding of network robustness and fragility. Biochemical systems are highly connected, dynamic networks whose manipulation without detailed understanding of network signaling and performance often leads to unwanted and potentially detrimental side effects. Understanding the fundamental mechanisms allowing for robust performance will allow for more highly potent therapeutic approaches which minimize secondary interactions [6]. Here, steroidogenesis in the male fathead minnow (FHM) provides a model system to study network response, compensation, and failure upon exposure to environmental stressors in the form of endocrine disrupters. Sensitivity analysis is used to quantify the robust performance of the male FHM model and to identify states (proteins, genes, *etc.*) which optimize information content during future experimentation and model validation.

There are several ways to evaluate robustness (and its counterpart, fragility). Sensitivity analysis (the instantaneous response of the system's states to infinitesimal perturbations in parameter value [5]) is used to identify the portions of a network whose manipulation will have the greatest effect on the behavior of the system and has been applied to many biological systems [2, 3] but sensitivity analysis is intrinsically local and often difficult to apply with performance criteria. The MatLab BioSens [4] Toolbox is employed to calculate sensitivities as well as perform measurement selection. BioSens uses the Fisher Information Matrix (FIM) which weights the significance of the sensitivity measurement by the variance in the data. Furthermore, BioSens is equipped with a measurement selection tool which can identify the states whose measurement optimizes parameter accuracy and identifiability.

The male FHM model quantifies the relationship between the environmental stressor, 17 α -ethynylestradiol (EE₂), and testosterone (T) and 11-ketotestosterone (KT) production in the testes. The model consists of 5 compartments, the gill, the brain, the gonad, the liver compartment of all "other" tissues (See Fig. 1). A mass balance of all the steroid hormones of interest produces a model of 32 states and 74 parameters. In general, interactions are

depicted as simple, first order mass action kinetics, but both T production and vitellogenin (Vtg) production are assigned Hill kinetics.

Preliminary results indicate that Vtg production is highly sensitive to perturbations in the Hill kinetics describing the formation of Vtg from the concentration of bound estrogen receptor, and, pending experimental results, these interactions may have to be expanded upon. Steroid production is also fragile to disturbances of diffusion of EE₂ between the blood and the gills, but quite robust to disturbances in diffusion elsewhere in the endocrine system. Of the 74 parameters, 24 are practically identifiable, and this number may increase by varying the exposure patterns. The results from the male FHM model will be used to optimize experimentation for the female system, and current results suggest measurements of EE₂ in the gonad and brain and Vtg in the liver will optimize information content.

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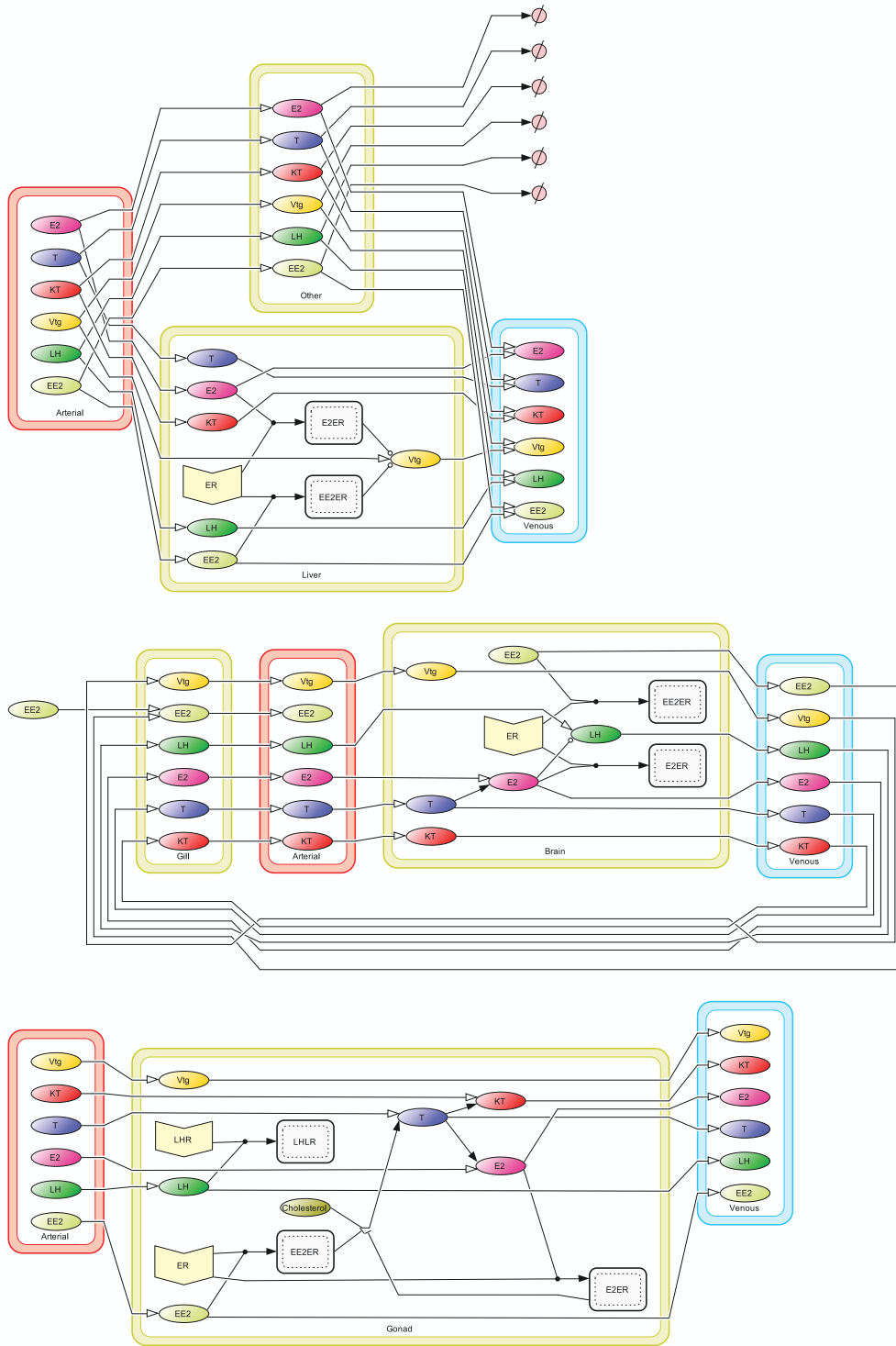


Figure 1: A schematic of the FHM system. 17α -ethynylestradiol (EE2) enters the system through the gills into the arteries. Testosterone (T), luteinizing hormone (LH), 11-ketotestosterone (KT), vitellogenin (Vtg), and EE2 enter the brain, liver, and gonads from the arteries, interact, and are recycled by the venous blood flow. Induction and degradation of the estrogen receptors (ER) and LH receptors (LHR) are assumed to be at equilibrium. Please see CellDesigner for greater description of reaction symbols [1].