

# Mass action kinetics applied to ODE models of the pituitary-ovarian axis: Multiple stable periodic solutions simulate normal and acyclic clinical observations.

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Mathematical models developed on clinical correlation and in-vitro causation were first applied to endocrine regulation of the pituitary-ovarian axis in women by Schlosser and Selgrade in 1999. The resulting model used biochemical properties of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Estradiol (E2), Progesterone (P4) and Inhibin (INH) for stable, periodic in-silico representation. With successful parameter estimation the Schlosser/Selgrade models accurately reflected mean serum levels and oscillatory behavior as reported by McLachlan et al. (1990). Subsequent incarnations of Harris et al. (2000) and Pasteur (2011) merged the pituitary and ovarian sub-systems and expanded the model to represent both Inhibin A (INH-A) and Inhibin B (INH-B) respectively. Thorough analysis of these models revealed an additional stable periodic solution in the five-hormone model that resembles hormone levels of patients with Polycystic Ovarian Syndrome (PCOS). As PCOS is seen as primarily a hyper-androgenic disorder, the inclusion of Androgens into the Schlosser/Selgrade model seems necessary to produce accurate simulations of serum pituitary-ovarian hormones in women with PCOS. As Testosterone (T) is the dominant female androgen and is significantly increased in PCOS patients, we focus our efforts on modeling pituitary feedback and inter-ovarian follicular growth properties as functions of circulating free T levels reported by Sinha et al.. Structurally based on in-vitro findings of Yasin et al. and Weiss et al., parameters have been identified that simultaneously simulate LH, FSH, E2, P4, INH-A and INH-B of Welt et al. and free T levels of Sinha et al.. The resulting model expands that of Selgrade et al. to a system of sixteen ordinary differential equations that applies mass action kinetics to follicular phase growth. Bifurcation analysis reveals multiple periodic solutions that approximate clinical observations of circulating hormones in normal and PCOS patients with increased accuracy. The new model will allow investigators to study potential hormone interventions to return acyclic patients to regular ovulatory cycles.