Abstract

Mathematical modelling of thyrotropic regulatory pathway provides important understanding on the working of hypothalamus-pituitary-thyroid axis. An ordinary differential equation (ODE) model based on an existing model for euthyroid condition is used and the model parameters are estimated to fit the available individual subject data using genetic algorithms. A cosinor model for the circadian variation of thyroid hormones is used to obtain more reliable results. This parameter determination method is tested on groups of subjects with similar observations of thyrotropin (TSH), free tri-iodothyroine (FT_3) and free thyroxine (FT_4), identified through clustering, to determine their parameter values jointly to estimate parameter sets with lower variation than parameters determined independently.

The regulatory behaviour in case of hypothyroidism is also modelled where the circadian variations in TSH in central and extreme primary hypothyroidism significantly differ from that of euthyroidism. An ODE model for thyrotropic regulatory system, inspired by existing models, encompassing both euthyroid and hypothyroid behaviours of thyroid hormones is presented. This extended model is validated with clinical data from multiple sources for general observable behaviours of thyroid hormones and TSH, data related to TSH circadian variations, levo-thyroxine (LT_4) and lio-thyronine (LT_3) administration effects and TRH tests. A methodology for detecting personalised model for hypothyroid subject data is developed to determine optimal drug dosage range using satisfiability modulo theories (SMT) based approach. A regression based initial drug dosage estimation scheme based on subject specific information is also presented. The results are validated through available data set of hypothyroid subjects before and after treatment.

The identifiability of the model parameters is also considered. SMT based parameter space exploration approach to determine parameter identifiable combination is introduced for structurally unidentifiable models. For higher dimensional systems and for larger parameter space, computationally intractability of this method is mitigated to a large extent by heuristically limiting the parameter space to be explored using Gaussian process regression and gradient based approaches. This method is validated on multiple examples.

***Keywords*:** *Mathematical model, Thyrotropic regulation pathway, Hypothyroidism, Genetic algorithms, Dosage estimation, Parameter estimation, Parameter identifiability, Satisfiability modulo theories (SMT)*