

# Time Delay Analysis

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Bayesian Inference and Markov Chain Monte Carlo methods have been advocated for the estimation of model parameters from ODEs by Rogers et al. (*Bayesian model-based inference of transcription factor activity*, BMC Bioinformatics, 8(2), 2006). We look at some of the issues involved in extending Bayesian inference methods to systems containing time delays. Verdugo and Rand (*Hopf bifurcation in a DDE model of gene expression*, Communications in Nonlinear Science and Numerical Simulation, 13:235-242, 2008) apply Lindstedt's method to the nonlinear system of delay differential equations proposed as a model by Monk (*Oscillatory Expression of Hes1, p53 and NF- $\kappa$ B Driven by Transcriptional Time Delays*, Current Biology, 13:1409-1413, 2003) for the Hes1 feedback loop, resulting in closed form approximate expressions for the amplitude and frequency of oscillation. Analysis shows that oscillatory solutions can arise through Hopf bifurcation in the delay parameter. We extend the work of Verdugo and Rand to the more realistic case where the decay parameters of hes1 mRNA and Hes1 protein, key components of the feedback, are not equal, focusing on oscillatory behaviours. We aim for results that explain how the model parameters affect the system dynamics and hence could be used to inform a parameter estimation from expression data. We illustrate our results by applying Bayesian inference to some real biological data.

It has been observed that mRNAs for Notch signalling molecules such as the bHLH factor Hes1 oscillate with 2-hour cycles during somite segmentation. Hirata et al. (*Oscillatory Expression of the bHLH Factor Hes1 Regulated by a Negative Feedback Loop*, Science 298, 840-843, 2002) investigated the molecular mechanism behind observed oscillations of mRNAs for Notch signalling molecules. They examined the time course of hes1 mRNA in detail. Hirata et al. measured the half lives of hes1 mRNA and Hes1 protein and identified the proteases for Hes1 protein degradation. Their experiments show that the degradation of Hes1 protein is required for Hes1 mRNA increase and that de novo production of the protein is required for reduction of hes1 mRNA. These facts together support their theory that Hes1 is an essential component of a two hour cycle clock and not just an output of a primary clock. The Hirata data comprises scaled hes1 mRNA expression level every 30 minutes over a 12 hour period. Monk's model was able to explain, via numerical simulations, the oscillation of hes1 mRNA and Hes1 protein in cultured cells observed by Hirata et al. We use a Bayesian approach to the parameter fitting problem which takes into account the inherent uncertainty in the data and uses our a priori bifurcation analysis to inform the choice of priors.