

Time Delay Analysis LICSB 2008

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Introduction

- Motivation
- Model
- Mathematical Analysis
- Biological Data
- Bayesian Inference
- Conclusions

Motivation

Genes **downregulated** by their protein products: Hes1, p53, NF- κ B

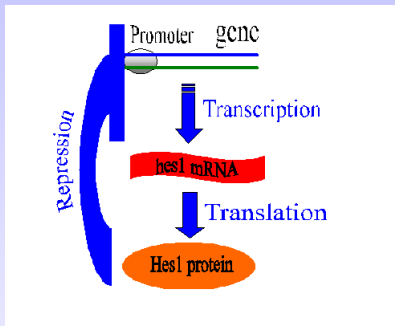
Hirata et al. (*Science*, 2002) presented data and a mathematical model (ODE).

Monk (*Current Biology*, 2003) showed observed oscillatory behaviour can be explained by incorporating a time delay.

Verdugo and Rand (*Comms in Nonlin. Sci. and Num. Sims*, 2008) analysed Monk's model in the case where $\mu_m = \mu_p$.

Rogers et al. (*BMC Bioinformatics*, 2006) **Bayesian inference** used for parameter estimation in ODEs – we will extend this to the delay case.

Monk's Model



$$\dot{m} = \frac{1}{1 + (p(t - \tau)/p_0)^n} - \mu_m m$$
$$\dot{p} = m - \mu_p p$$

Mathematical Analysis

Verdugo and Rand (*Communications in Nonlinear Science and Numerical Simulations*, 2008) analysed oscillatory solutions in Monk's model in the case where $\mu_m = \mu_p$.

Our aims are

- extend the analysis to $\mu_m \neq \mu_p$
- use the analysis to inform the choice of prior for Bayesian parameter inference
- test systematically whether Monk's model can explain Hirata et al.'s data

Mathematical Analysis Summary

- ★ Linearize around the equilibrium
- ★ Show that with no delay equilibrium is stable
- ★ Increasing delay gives rise to Hopf Bifurcation
- ★ Nonlinear system exhibits periodic solution
- ★ Lindstedt's Method approximates periodic solutions

Linearize around the equilibrium

Set $\dot{m} = 0$ and $\dot{p} = 0$ and obtain expressions for p^* and m^* :

$$\begin{aligned}(p^*)^{n+1} + p_0^n p^* - \frac{p_0^n}{\mu_m \mu_p} &= 0 \\ m^* &= \mu_p p^*\end{aligned}$$

Define ζ and η to be deviations from the equilibrium:

$$\zeta(t) = m(t) - m^*, \eta(t) = p(t) - p^*, \text{ and } \eta_d = \eta(t - \tau)$$

This results in a linear system:

$$\begin{aligned}\dot{\zeta} &= -\mu_m \zeta - \mathbf{K} \eta_d \\ \dot{\eta} &= \zeta - \mu_p \eta\end{aligned}$$

Show that with no delay equilibrium is stable

Looking for solution $\eta = e^{\lambda t}$ gives

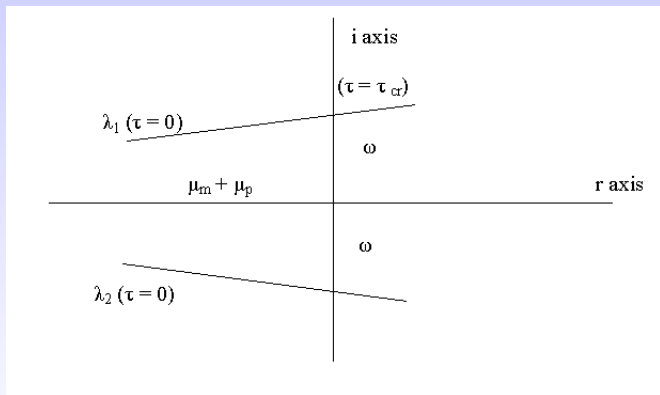
$$\lambda^2 + (\mu_m + \mu_p) \lambda + \mu_m \mu_p + K e^{-\lambda \tau} = 0$$

For $\tau = 0$, we can show that:

- if $\mu_m = \mu_p$, we always have a stable spiral
- if $\mu_m \neq \mu_p$, we have a stable spiral for $|\mu_m - \mu_p|$ sufficiently small and stable fixed point otherwise

Increasing delay gives rise Hopf Bifurcation

Look for a periodic solution emerging through
Hopf bifurcation



Nonlinear system exhibits periodic solution

For values of delay τ close to τ_{cr} the nonlinear system is expected to exhibit a periodic solution (limit cycle) which can be written

$$\zeta(t) = B \cos(\omega t + \phi)$$

$$\eta(t) = A \cos \omega t$$

Substituting above solutions into into equations

$\dot{\zeta} = -\mu_m \zeta - K \eta_d$ and $\dot{\eta} = \zeta - \mu_p \eta$ and matching time dependent terms results in explicit formulae

Explicit Formulae

$$\frac{\text{Amplitude}_{\text{mRNA}}}{\text{Amplitude}_{\text{protein}}} = \sqrt{\omega^2 + \mu_p^2}$$

$$\text{Critical time delay} = \frac{1}{\omega} \arctan \left(\frac{\omega \mu_p + \omega \mu_m}{\omega^2 - \mu_m \mu_p} \right)$$

$$\text{Phase angle} = \frac{\omega}{\mu_p}$$

Lindstedt's Method

- Technique for uniformly approximating periodic solutions to ODEs when regular perturbation approaches fail
- Regard the frequency ω as unknown in advance
- Solve by demanding that an appropriate series expansion contains no secular terms
- Result: closed form approximate expressions for the amplitude and frequency of oscillation

Summary of new mathematical results

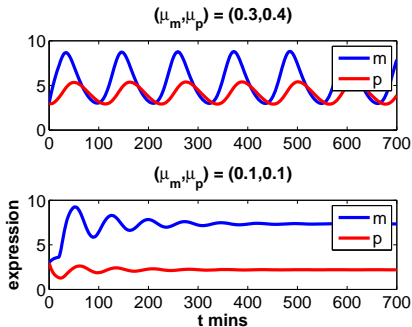
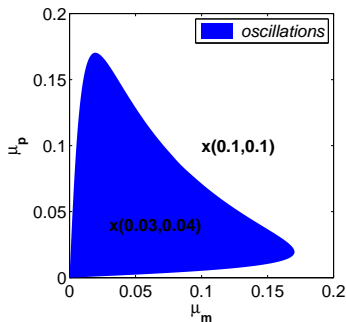
Using bifurcation theory and Lindstedt's method

- ratio of amplitude of mRNA and protein has a simple characterisation, and the individual amplitudes can be approximated
- frequency of oscillation takes a maximum that can be explicitly defined in terms of the model parameters
- oscillatory solutions arising from Hopf bifurcation occur only when the difference between decay constants is sufficiently small
- regarding μ_m and μ_p as unknowns, there is a computable, finite region in the μ_m - μ_p plane where oscillatory solutions exist

Illustration: bounds on μ_m and μ_p

$$\omega^2 > \mu_m \mu_p$$

$$\omega \mu_m + \omega \mu_p < K$$



Parameter Estimation Bayesian Inference

What we would like to know:

- probabilities for the values of unknown parameters, given the data

What we can assign:

- probability of the data arising, given parameter values
- initial probabilities for the parameter values

Bayes' Theorem:

posterior probability \propto likelihood function \times prior probability

Likelihood and Priors

Likelihood

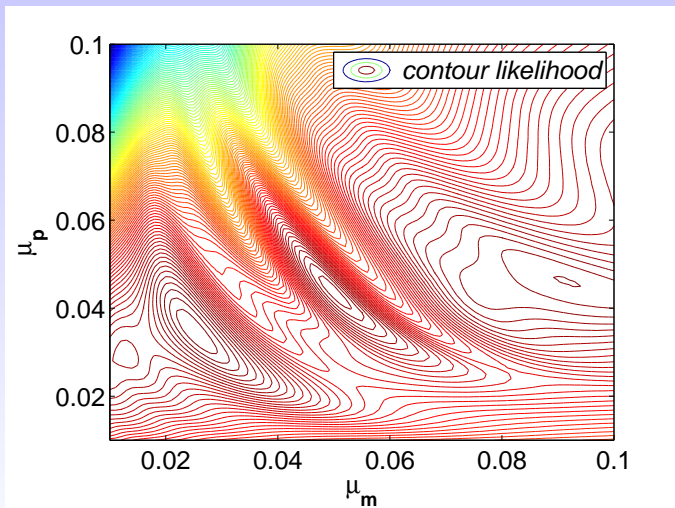
Assume errors are normally distributed:

$$N(f(\theta, t_k), \sigma^2)$$

Priors

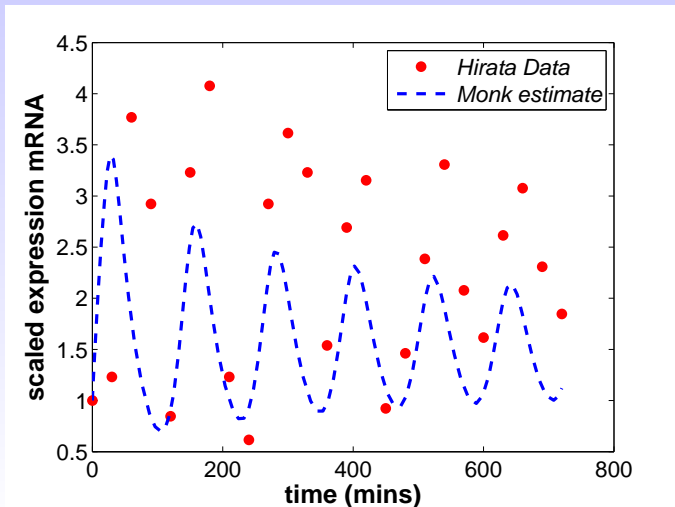
- Some parameters experimentally measured
- Some informed by mathematical analysis

Inference Challenge



Biological Data

Hirata et al. data comprises scaled *hes1* mRNA expression levels every 30 minutes over a 12 hour period



From bio literature and a *a priori* analysis:

| Priors | | |
|----------|--------|---------|
| θ | mean | std dev |
| ρ_0 | 100 | 10 |
| n | 5 | 1 |
| μ_m | 0.0288 | 0.002 |
| μ_p | 0.0311 | 0.004 |
| τ | 19 | 1 |
| k_s | 2.2 | 0.1 |

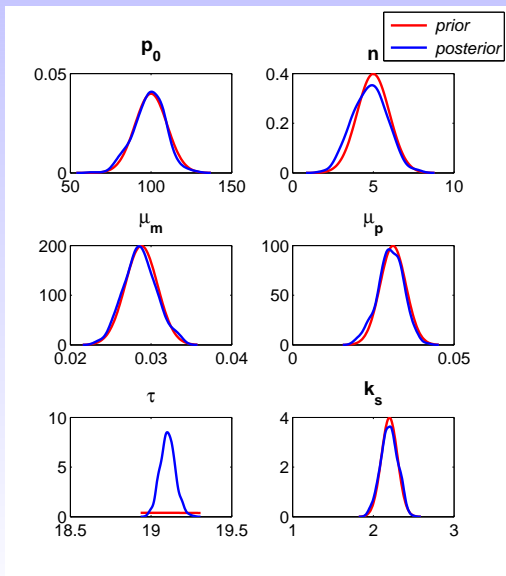
Markov Chain Monte Carlo

Computational technique to sample from the p.d.f.

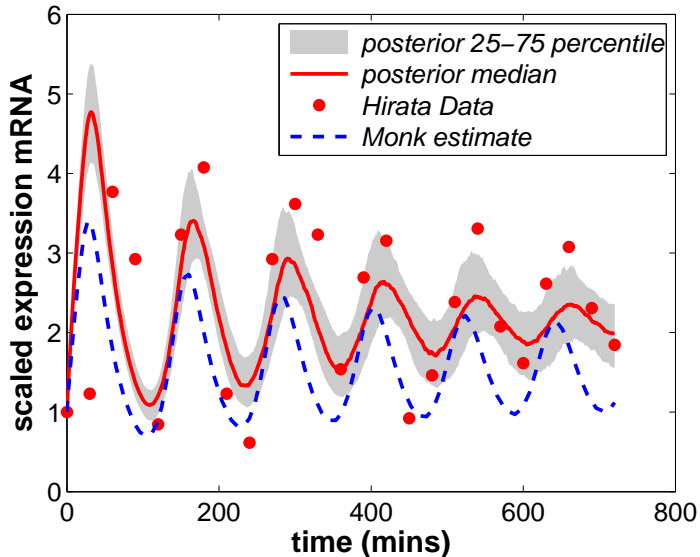
- Candidate values chosen randomly: proposal function
- Samples are binned, normalized and smoothed
- Practical issues include choice of burn in period and test for convergence

| MCMC | | | | |
|----------|-------------------|----------|----------|-----------|
| θ | st pts | σ | acc rate | \hat{R} |
| p_0 | 105,99,90 | 0.55 | 21 | 1.0002 |
| n | 5.5,5,5 | 0.7 | 34 | 1.0002 |
| μ_m | 0.03,0.028,0.032 | 0.4 | 23 | 1.0000 |
| μ_p | 0.028,0.028,0.032 | 0.5 | 31 | 1.0000 |
| τ | 18,18,19 | 0.005 | 22 | 1.0005 |
| k_s | 2,2.5,2.2 | 0.2 | 27 | 1.0001 |

Results: Posterior p.d.f.



Results



Summary and Conclusions

- Mathematical analysis can give insights into the possible dynamical behavior of gene expression models
- This analysis can also inform the choice priors when parameters are inferred using Bayesian inference
- A full Bayesian MCMC computation improves on Monk's conclusions, giving $\mu_m \neq \mu_p$ and a longer time delay