Modelling RNA Oscillatory Circuits

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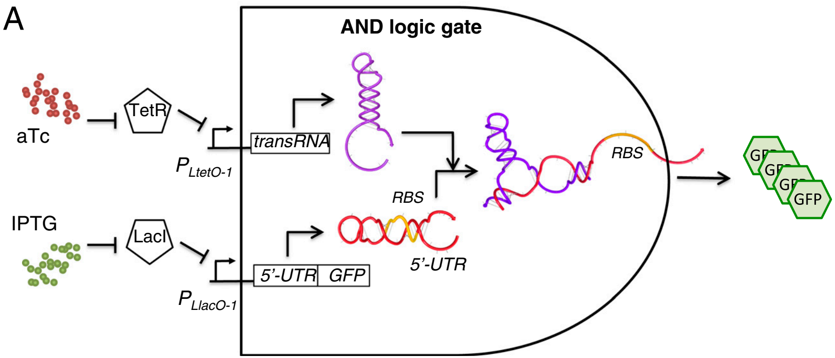
September 22, 2015

Outline

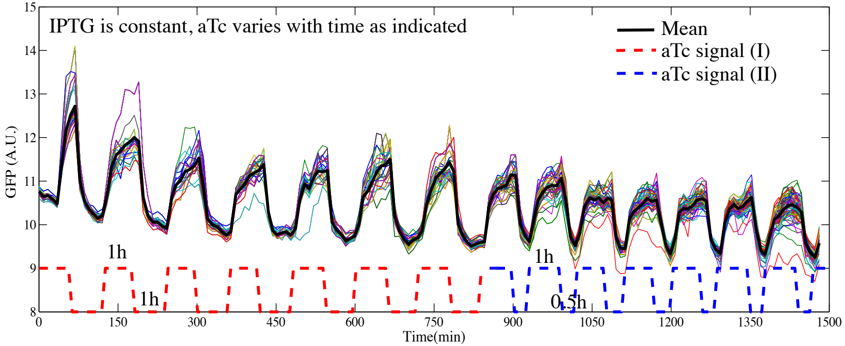
1. Description of RNA Oscillatory system
   - Recent Experimental data
   - ODE Model for system
2. Parameter Estimation in ODE Model
   - Methodology - least squares error minimisation
   - Results - Inestimable parameters, model simplifications
   - Future Work

The RNA Oscillatory System



- mRNA produced 'self repressed' - tail folded over the RBS
- sRNA binds to it - new complex has RBS uncovered.

Recent Experimental data



- Time series of individual cell fluorescence, forced with aTc.

ODE Model for system (1)

$$\frac{ds}{dt} = \frac{N\alpha_T}{f_T}y(t) - (\mu + \delta_s)s - k_{\mathrm{on}}sm + k_{\mathrm{off}}s:m$$

$$\frac{dm}{dt} = \frac{N\alpha_L}{f_L}x(t) - (\mu + \delta_m)m - k_{\mathrm{on}}sm + k_{\mathrm{off}}s:m$$

$$\frac{ds:m}{dt} = k_{\mathrm{on}}sm - (k_{\mathrm{off}} + k_{\mathrm{hyb}})s:m - (\mu + \delta_{sm})s:m$$

$$\frac{dc}{dt} = k_{\mathrm{hyb}}s:m - (\mu + \delta_c)c$$

- Hybridization of sRNA(s) and mRNA (m), into unstable complex ($s:m$) then stable one (c).

ODE Model for system (2)

$$\frac{dp}{dt} = \beta m + f_s \beta c - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g}$$

$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g}$$

$$z = z_0 + \frac{g}{\Theta}$$

- Translation of stable complex (c) into immature GFP (p).
- maturation of GFP (g), machine calibration giving measured fluorescence (z).

Parameter Estimation in ODE Model

Goal

Estimate unknown parameters in model using time series data.

- Least squares error minimization approach

$$\arg\min_{\theta} \sum_{i=1}^{n} (z_{\mathrm{exp,mean}}(t_i) - z(t_i, \theta))^2.$$

- Used evolutionary algorithm, CMA-ES, to perform minimisation.

Parameters to be estimated in our model

$$\frac{ds}{dt} = \frac{N\alpha_T}{f_T}y(t) - (\mu + \delta_s)s - k_{\text{on}}sm + k_{\text{off}}s:m$$

$$\frac{dm}{dt} = \frac{N\alpha_L}{f_L}x(t) - (\mu + \delta_m)m - k_{\text{on}}sm + k_{\text{off}}s:m$$

$$\frac{ds:m}{dt} = k_{\text{on}}sm - (k_{\text{off}} + k_{\text{hyb}})s:m - (\mu + \delta_m)s:m$$

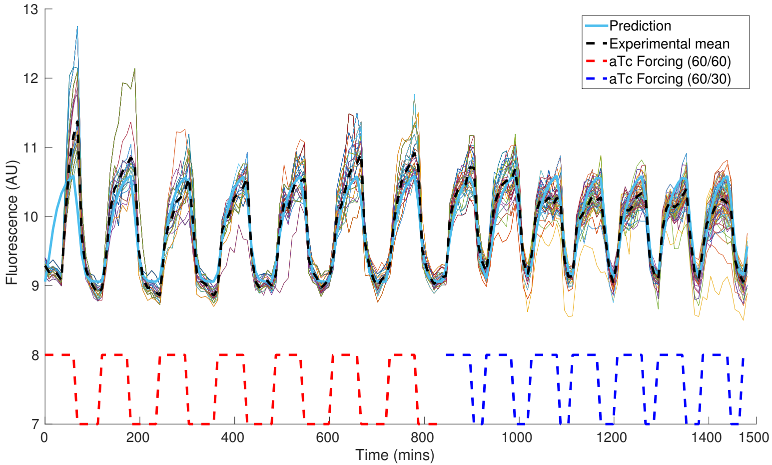
$$\frac{dc}{dt} = k_{\text{hyb}}s:m - (\mu + \delta_m)c$$

$$\frac{dp}{dt} = \beta m + f_s\beta c - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g}$$

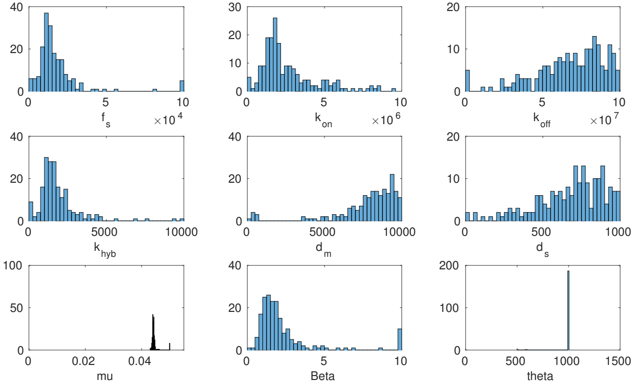
$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g}$$

$$z = z_0 + \frac{g}{\Theta}$$

Initial Estimation Results

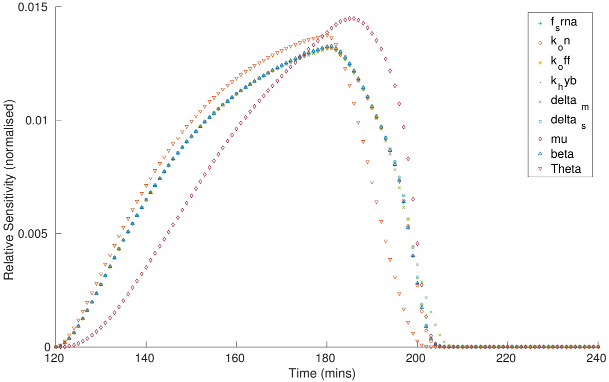


Initial Estimation Results



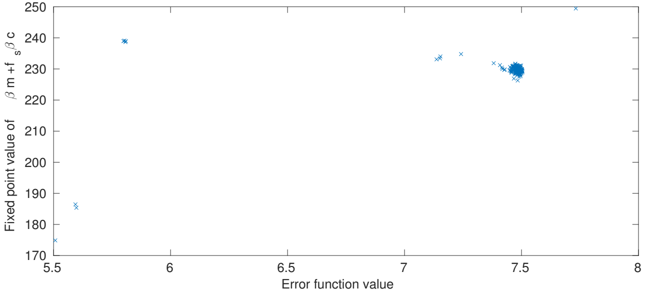
- Many parameters poorly estimated.

Sensitivity Analysis



- Sensitivity analysis suggests perturbations of several parameters all give similar effects on model output - hard to resolve

Model fixed point for estimated parameters



- Similar fixed point values of translation forcing term, $\beta m + f_s \beta c$, across estimated parameter sets.
- Suggests translation may be rate limiting step.

Simplified Model (1)

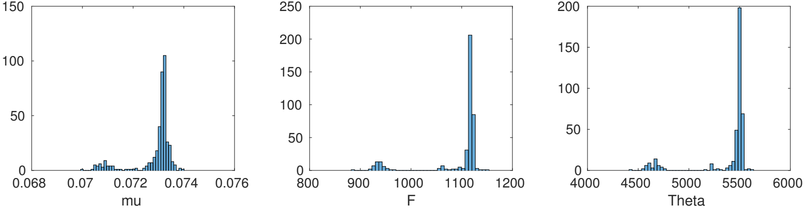
$$\frac{dp}{dt} = Fy(t) - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g}$$

$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g}$$

$$z = z_0 + \frac{g}{\Theta}$$

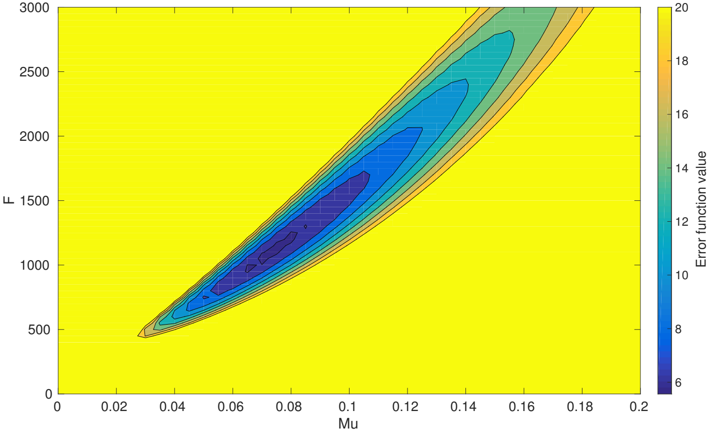
- Model only rate limiting steps - force translation term directly.
- 3 unknown parameters

Simplified Model Results (2)



- Error values as low as full model
- Clearer parameter estimation results
- Two peak structure due to local minima

Simplified Model Results (3)



- Error landscape, $\Theta = 1000$.

Future Work

- Fluorescence data not enough to estimate all unknown parameters
    - Further experiments ?
    - Bounds on unknown parameter values.
- Improve modelling of translation step
- Change methodology - Bayesian Methods?