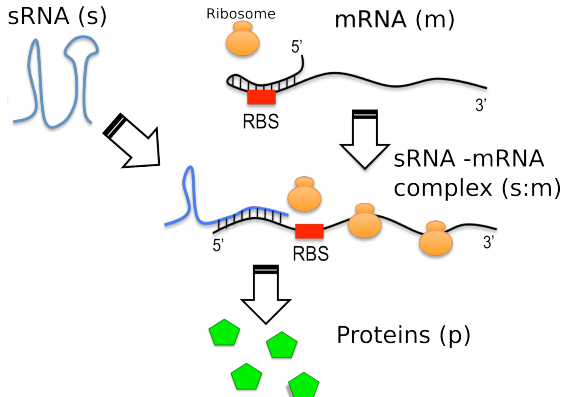# Modelling RNA Oscillatory Circuits

J. Binysh[1]

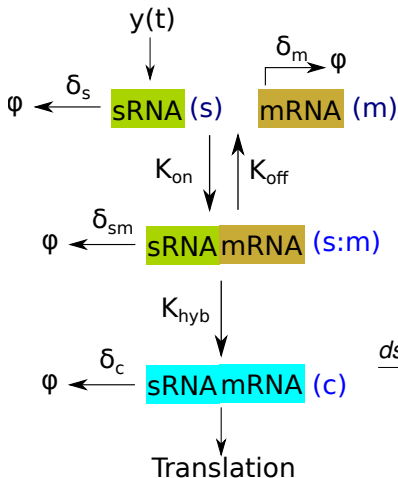[1] Centre for Complexity Science
University of Warwick

September 23, 2015

The RNA Oscillatory System

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

ODE Model for system (1) - Complex Formation

- Hybridization of sRNA (s) and mRNA (m), into unstable complex ($s : m$) then stable one (c).
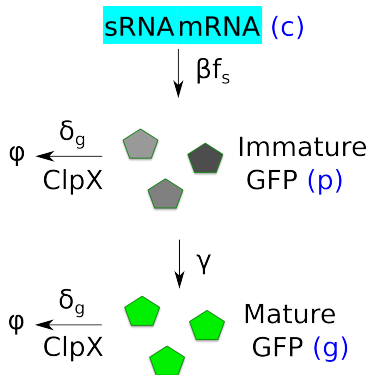
$$\frac{ds}{dt} = \frac{N\alpha_T}{f_T} y(t) - (\mu + \delta_s)s - k_{on}sm + k_{off}s : m$$

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

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

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

ODE Model for system (2) - Translation

sRNAmRNA (c)

$\downarrow \beta f_s$

$\varphi \xleftarrow[\text{ClpX}]{\delta_g}$ Immature GFP (p)

$\downarrow \gamma$

$\varphi \xleftarrow[\text{ClpX}]{\delta_g}$ Mature GFP (g)

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

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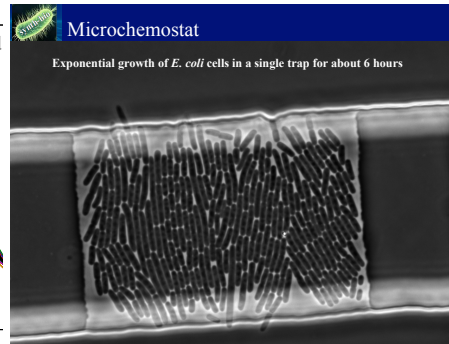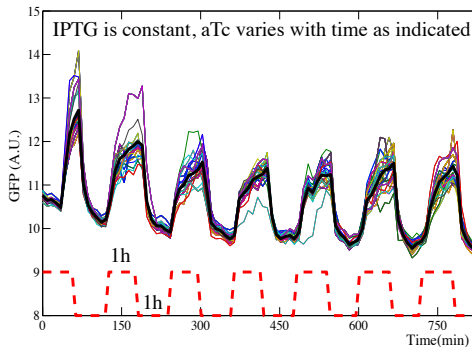
$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g}$$

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

Description of RNA Oscillatory system
Parameter Estimation in ODE Model

Methodology - least squares error minimisation
Results - Inestimable parameters, model simplifications
Future Work

Parameters to be estimated in our model

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

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

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

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

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

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

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Recent Experimental Data

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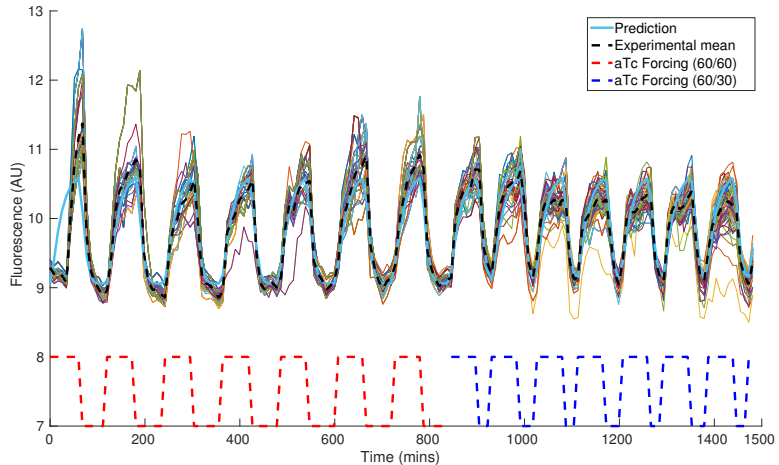## Parameter Estimation in ODE Model

Goal

Estimate unknown parameters in model using time series data.

- Least squares error minimization approach

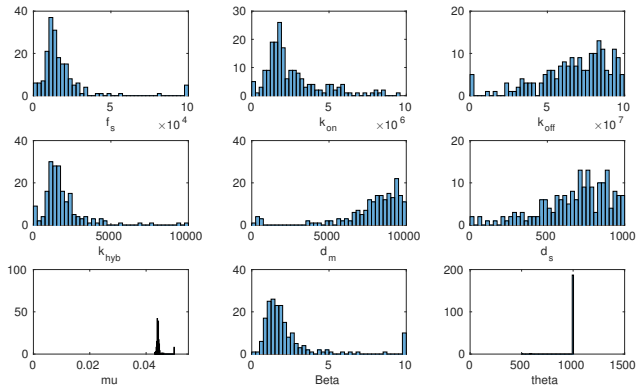$$\arg\min_{\boldsymbol{\theta}} \sum_{i=1}^{n} (z_{\mathrm{exp,mean}}(t_i) - z(t_i, \boldsymbol{\theta}))^2.$$

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

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Initial Estimation Results

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Initial Estimation Results

- Many parameters poorly estimated.

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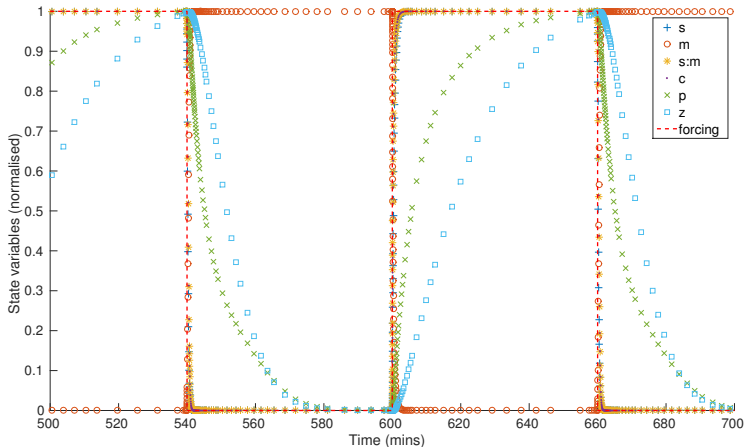Future Work

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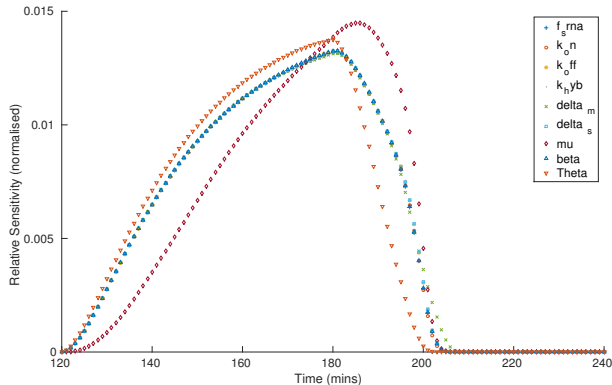
- Sensitivity analysis suggests perturbations of several parameters all give similar effects on model output - hard to resolve

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Model output for all state variables

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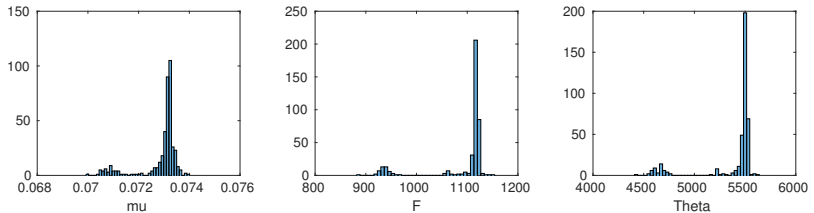
Model fixed point for estimated parameters
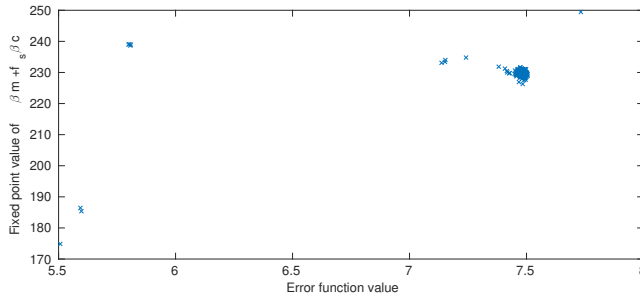
- Similar fixed point values of translation forcing term, $\beta m + f_s \beta c$, across estimated parameter sets.
- Suggests translation may be rate limiting step.

Description of RNA Oscillatory system
Parameter Estimation in ODE Model

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Future Work

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

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Simplified Model Results (2)

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

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Simplified Model Results (3)

- Error landscape, $\Theta = 1000$.

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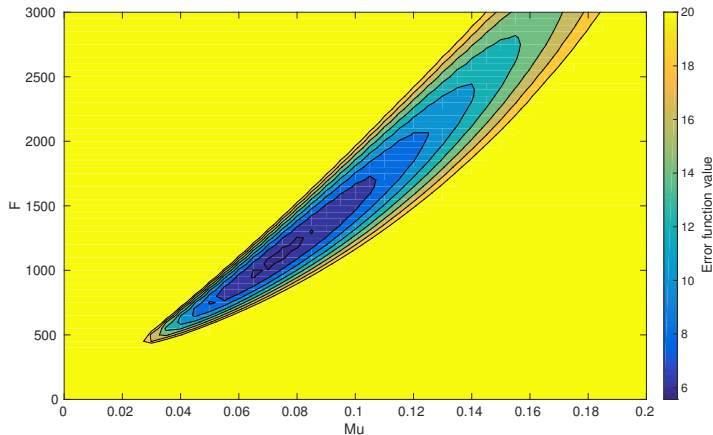
Future Work

- 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?