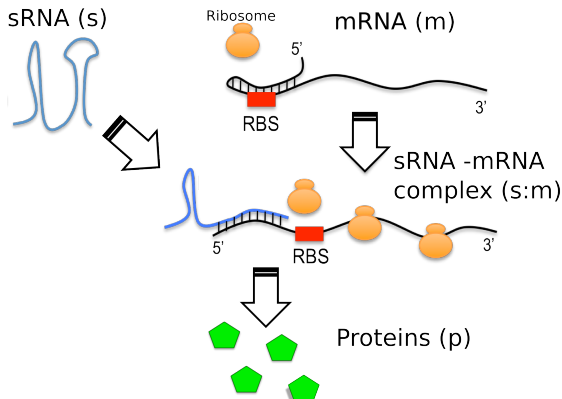# Modelling RNA Circuits

J. Binysh[1]
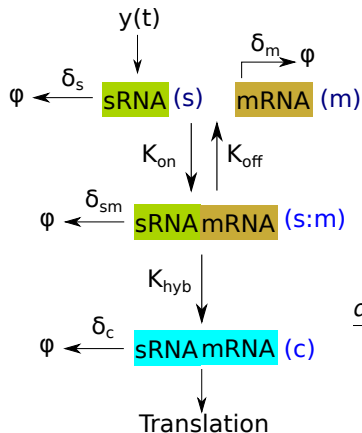
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University of Warwick

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The RNA 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

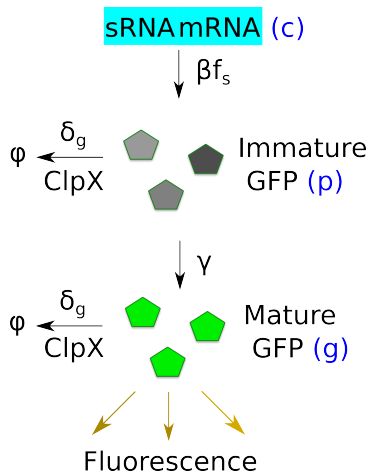- ▶ Hybridization of sRNA (s) and mRNA (m), into unstable complex ($s : m$) then stable one (c).

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

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

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

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

ODE Model for system (2) - Translation

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

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

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

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

Full model, with Parameters to be estimated

$$\frac{ds}{dt} = \frac{N\alpha_T}{f_T}y(t) - (\mu + \delta_s)s - k_{\text{on}}sm + k_{\text{off}}s:m \tag{1}$$

$$\frac{dm}{dt} = \frac{N\alpha_L}{f_L}x(t) - (\mu + \delta_m)m - k_{\text{on}}sm + k_{\text{off}}s:m \tag{2}$$

$$\frac{ds:m}{dt} = k_{\text{on}}sm - (k_{\text{off}} + k_{\text{hyb}})s:m - (\mu + \delta_m)s:m \tag{3}$$

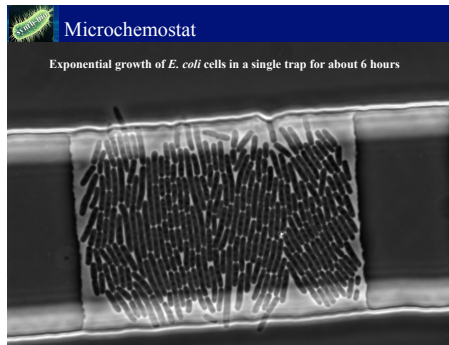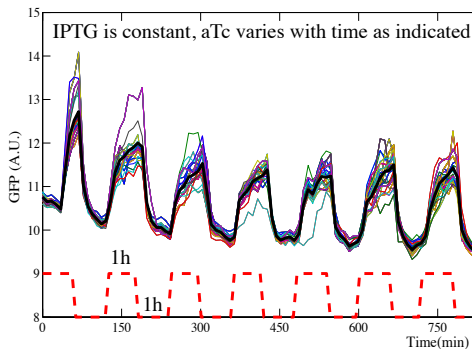$$\frac{dc}{dt} = k_{\text{hyb}}s:m - (\mu + \delta_m)c \tag{4}$$

$$\frac{dp}{dt} = \beta m + f_s\beta c - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g} \tag{5}$$

$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g} \tag{6}$$

$$z = z_0 + \frac{g}{\Theta} \tag{7}$$

Recent Experimental Data

- Single cell fluoresence time series data (Jaramillo Lab, unpublished).
- Data records $z = z_0 + \frac{g}{\Theta}$

Method for Parameter Estimation in ODE Model

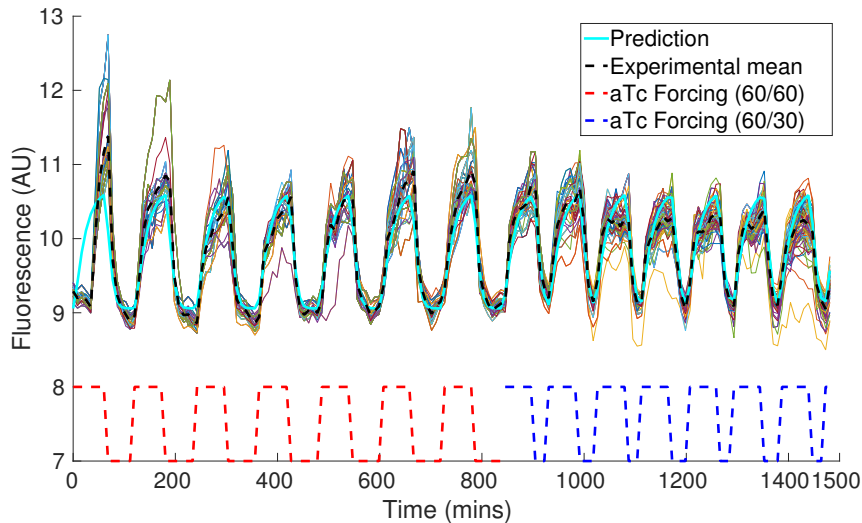### Goal

Estimate unknown parameters in model using time series data.
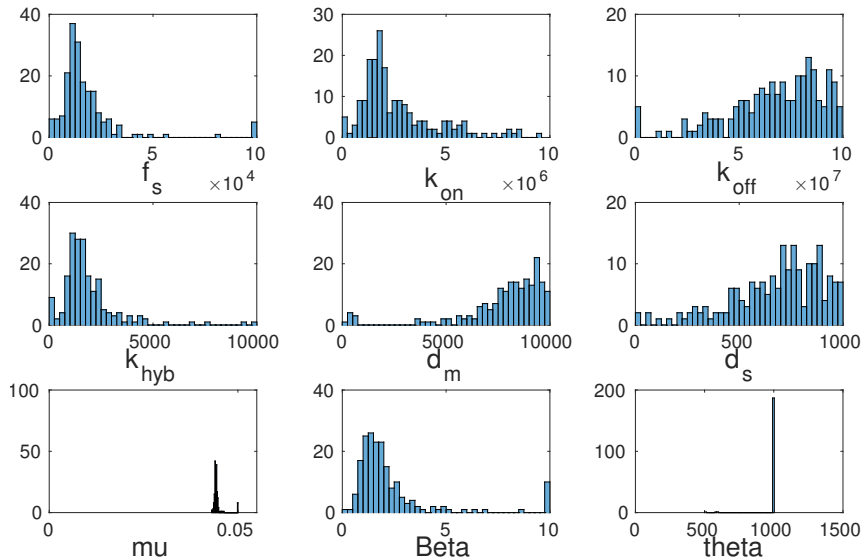
- Least squares error minimization approach

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

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

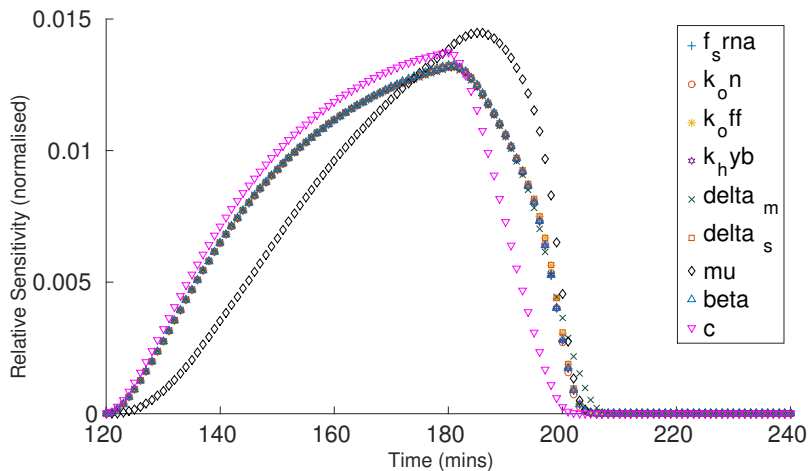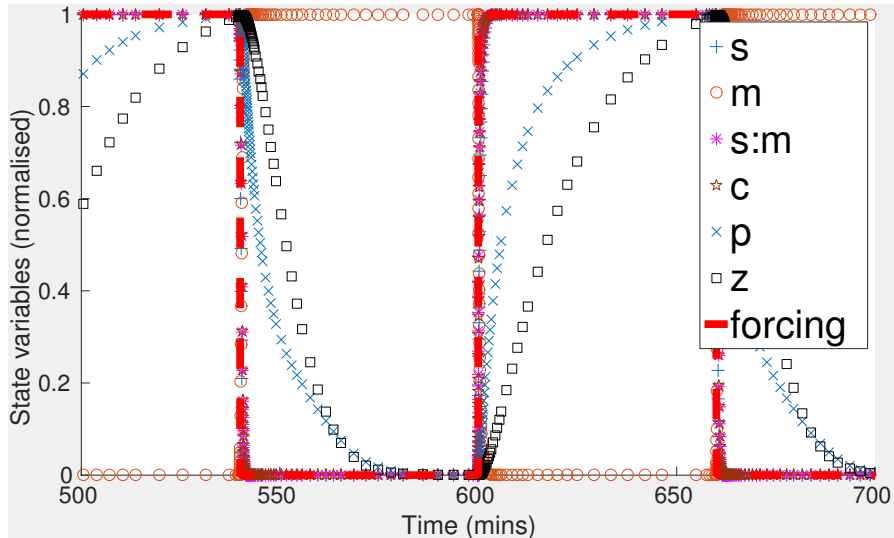# Initial Estimation Results

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 output for all state variables

Full model again

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

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

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

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

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

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

Simplified Model

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

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

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

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

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

$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g}$$
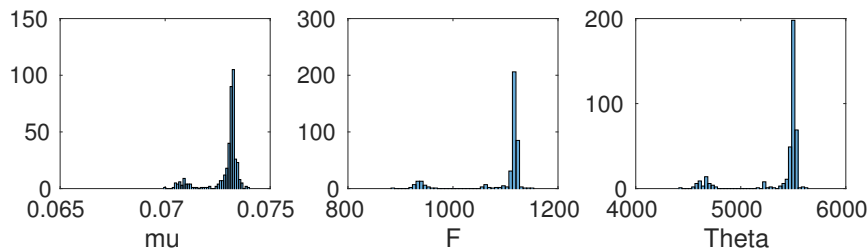
$$z = z_0 + \frac{g}{\Theta}$$

Simplified Model

$$\frac{dp}{dt} = Fy(t) - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g} \tag{8}$$

$$\frac{dg}{dt} = \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g} \tag{9}$$
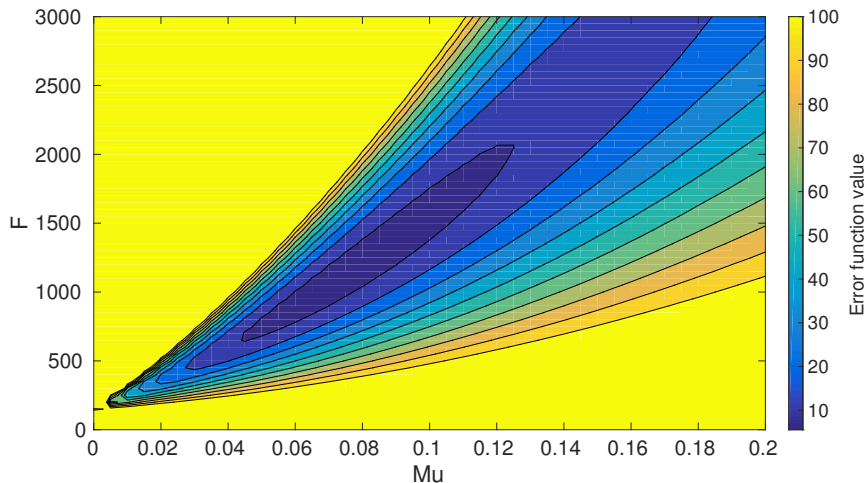
$$z = z_0 + \frac{g}{\Theta} \tag{10}$$

► Model only rate limiting steps - force translation term directly.

► 3 unknown parameters

Simplified Model Results (1)

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

Simplified Model Results (2)

- Error landscape, $\Theta = 5400$.

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?