

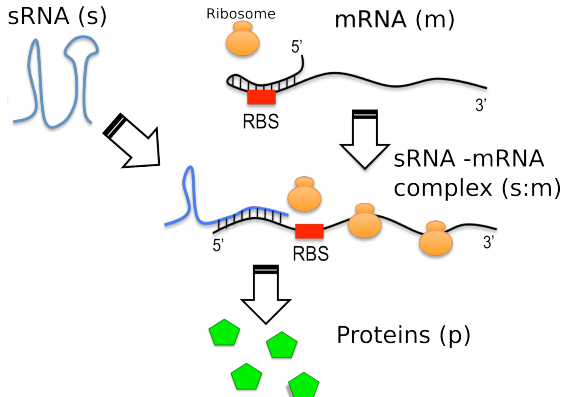
Modelling RNA Oscillatory Circuits

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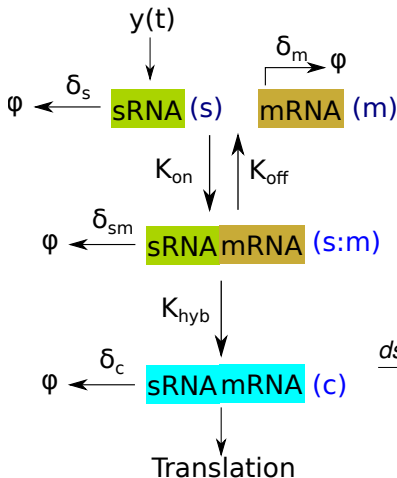
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The RNA Oscillatory System



- 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).

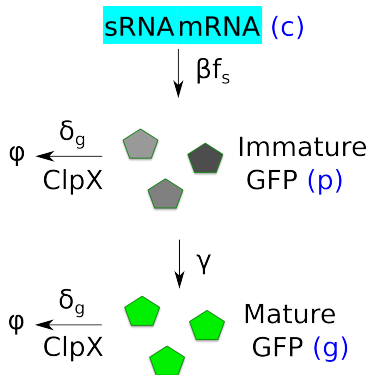
$$\frac{ds}{dt} = \frac{N\alpha_T}{f_T} y(t) - (\mu + \delta_s)s - k_{on}sm + k_{off}s : m$$

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

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

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

ODE Model for system (2) - Translation



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

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

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

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

Parameters to be estimated in our model

$$\begin{aligned}\frac{ds}{dt} &= \frac{N_{\alpha_T}}{f_T} y(t) - (\mu + \delta_s)s - k_{\text{on}}sm + k_{\text{off}}s : m \\ \frac{dm}{dt} &= \frac{N_{\alpha_L}}{f_L} x(t) - (\mu + \delta_m)m - k_{\text{on}}sm + k_{\text{off}}s : m \\ \frac{ds : m}{dt} &= k_{\text{on}}sm - (k_{\text{off}} + k_{\text{hyb}})s : m - (\mu + \delta_m)s : m \\ \frac{dc}{dt} &= k_{\text{hyb}}s : m - (\mu + \delta_m)c \\ \frac{dp}{dt} &= \beta m + f_s \beta c - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g} \\ \frac{dg}{dt} &= \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g} \\ z &= z_0 + \frac{g}{\ominus}\end{aligned}$$

Parameter Estimation in ODE Model

Goal

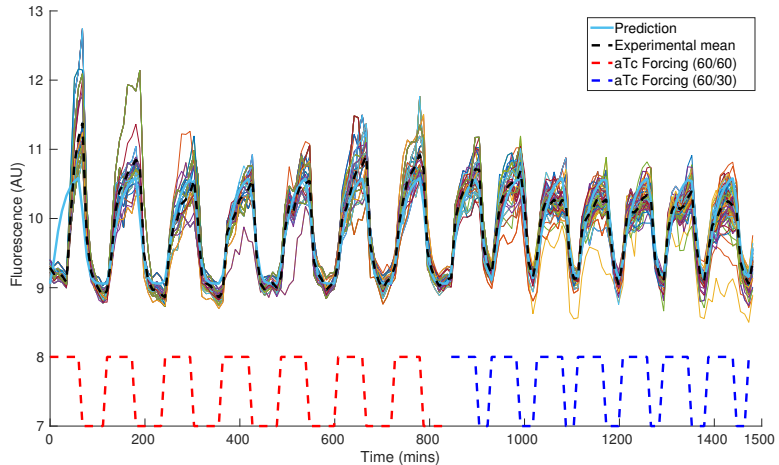
Estimate unknown parameters in model using time series data.

- Least squares error minimization approach

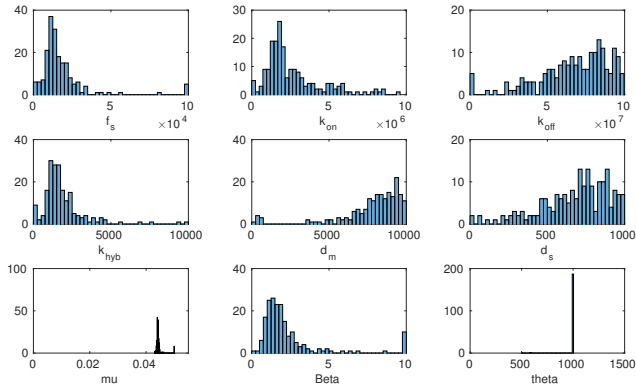
$$\arg \min_{\theta} \sum_{i=1}^n (z_{\text{exp,mean}}(t_i) - z(t_i, \theta))^2.$$

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

Initial Estimation Results

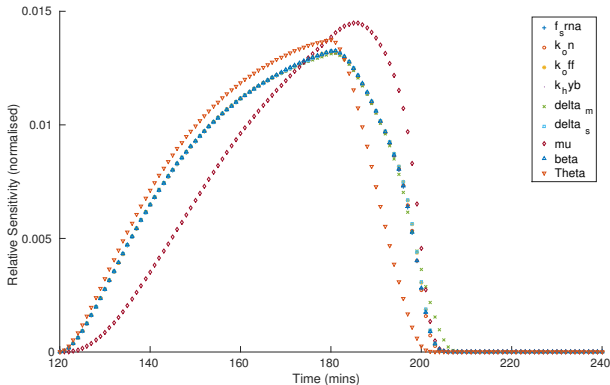


Initial Estimation Results



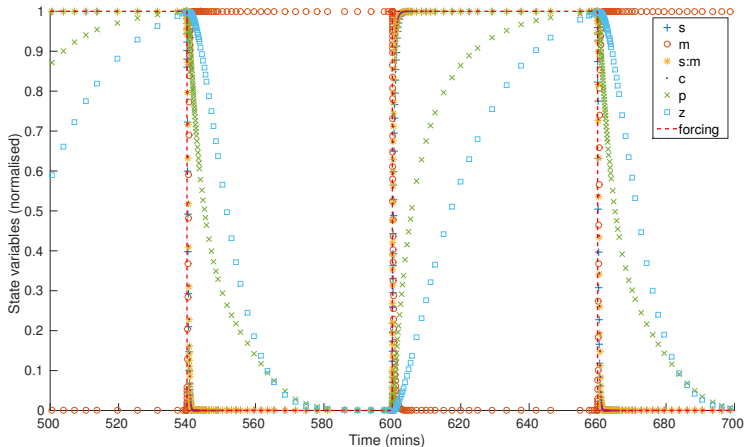
- Many parameters poorly estimated.

Sensitivity Analysis

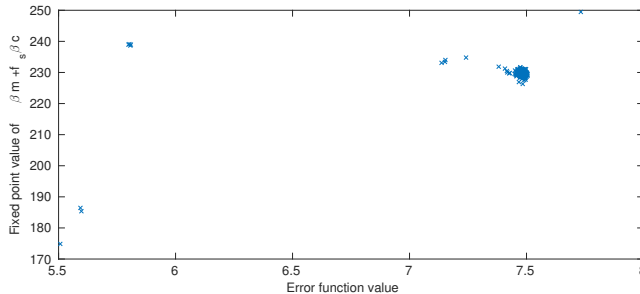


- Sensitivity analysis suggests perturbations of several parameters all give similar effects on model output - **hard to resolve**

Model output for all state variables



Model fixed point for estimated parameters



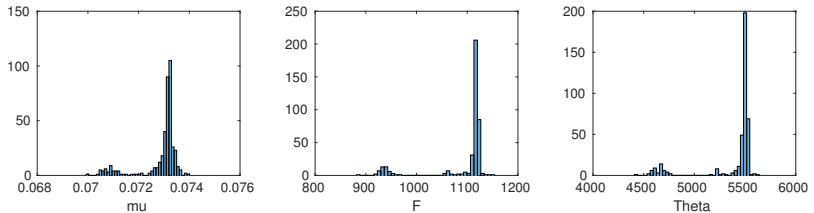
- Similar fixed point values of translation forcing term, $\beta m + f_s \beta c$, across estimated parameter sets.
- Suggests translation may be rate limiting step.

Simplified Model (1)

$$\begin{aligned}\frac{dp}{dt} &= \textcolor{red}{F}y(t) - (\gamma + \textcolor{red}{\mu} + \delta_g)p - \frac{v_z p}{K_z + p + g} \\ \frac{dg}{dt} &= \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g} \\ z &= z_0 + \frac{g}{\textcolor{red}{\Theta}}\end{aligned}$$

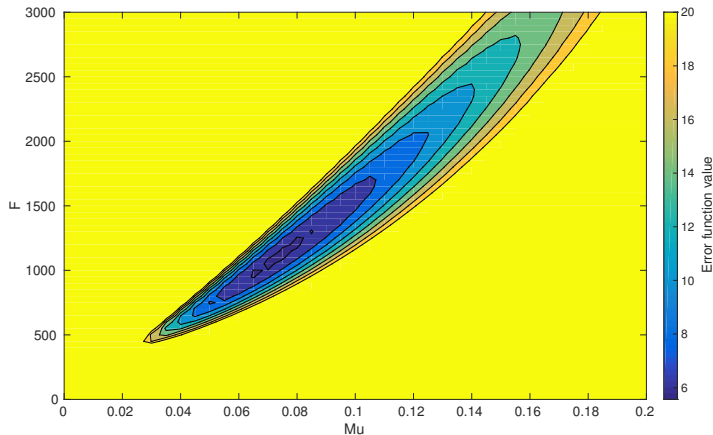
- Model only rate limiting steps - force translation term directly.
- 3 unknown parameters

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?