Modelling RNA Oscillatory Circuits

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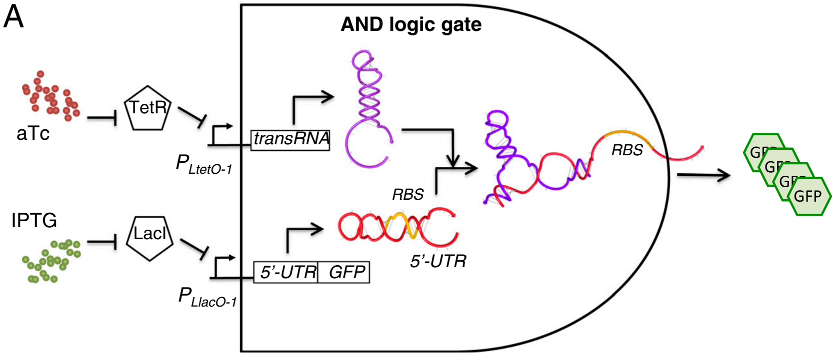
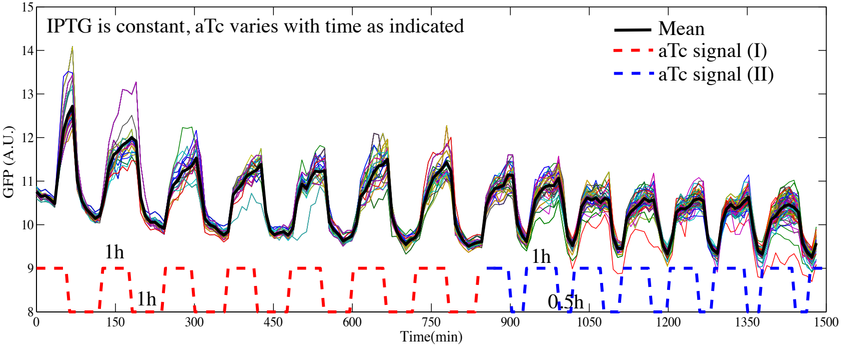
Outline

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

$$\frac{ds}{dt} = \frac{N\alpha_T}{f_T} y(t) - (\mu + \delta_s)s - k_{\mathrm{on}} sm + k_{\mathrm{off}} s:m$$
$$\frac{dm}{dt} = \frac{N\alpha_L}{f_L} x(t) - (\mu + \delta_m)m - k_{\mathrm{on}} sm + k_{\mathrm{off}} s:m$$
$$\frac{ds:m}{dt} = k_{\mathrm{on}} sm - (k_{\mathrm{off}} + k_{\mathrm{hyb}})s:m - (\mu + \delta_{sm})s:m$$
$$\frac{dc}{dt} = k_{\mathrm{hyb}} s:m - (\mu + \delta_c)c$$

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

ODE Model for system

$$
\begin{aligned}
\frac{dp}{dt} &= \beta m + f_s \beta c - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g} \\
\frac{dg}{dt} &= \gamma p - (\mu + \delta_g)g - \frac{v_z g}{K_z + p + g} \\
z &= z_0 + \frac{g}{\Theta}
\end{aligned}
$$

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

Parameter Estimation in ODE Model - Methodology

Goal

Estimate unknown parameters in model using time series data.

- Least squares error minimization approach

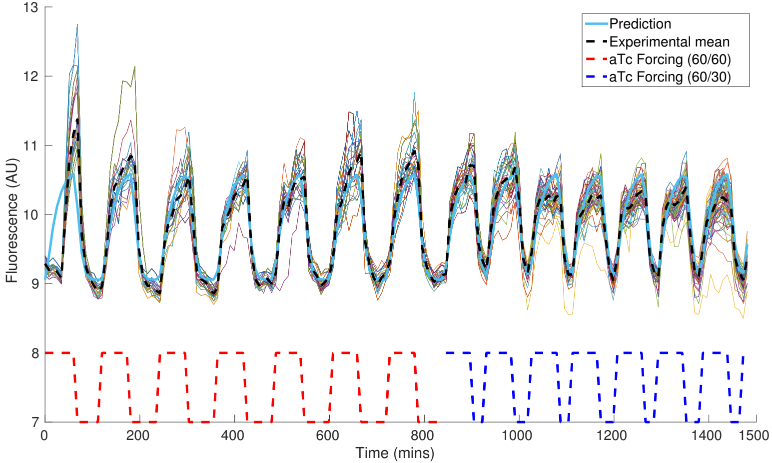
$$\arg\min_{\theta} \sum_{i=1}^{n} (z_{\mathrm{exp,mean}}(t_i) - z(t_i, \theta))^2.$$

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

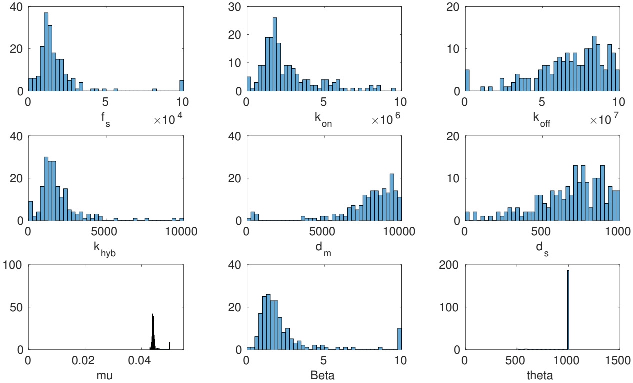
Parameters to be estimated in our model

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

Initial Minimization Results

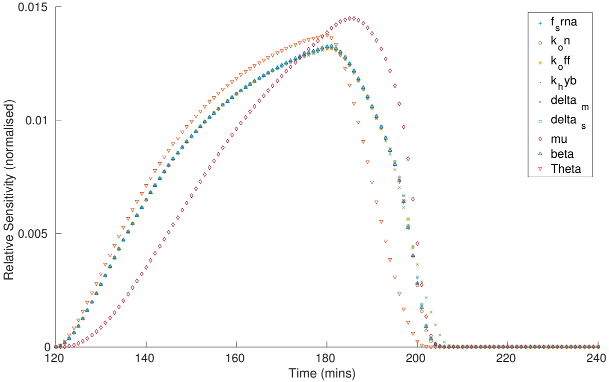


Initial Minimization Results



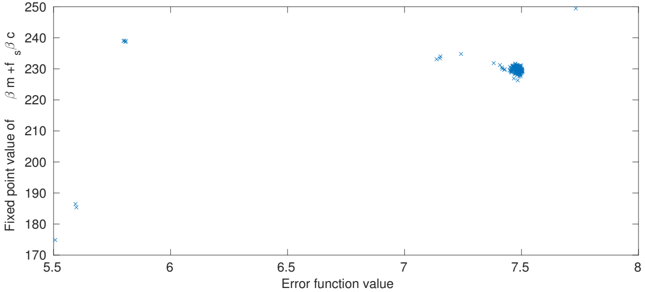
- Many parameters poorly estimated.

Sensitivity Analysis



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

Sensitivity Analysis



- 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

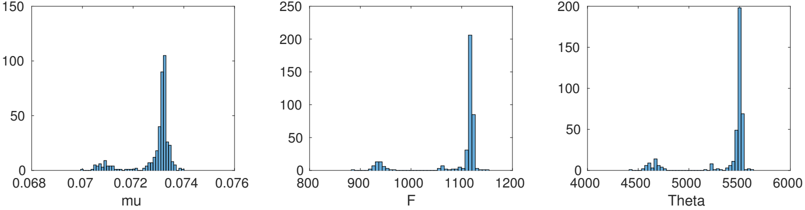
$$\frac{dp}{dt} = Fy(t) - (\gamma + \mu + \delta_g)p - \frac{v_z p}{K_z + p + g}$$

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

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

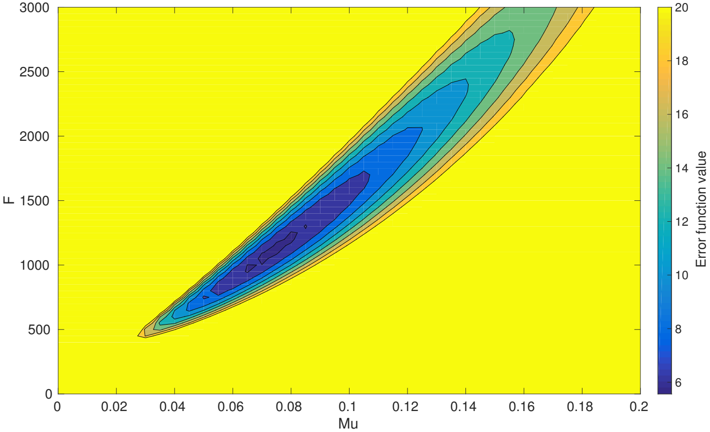
- Model only rate limiting steps - force translation term directly.
- 3 unknown parameters

Simplified Model Results



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

Simplified Model Results



- 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?