Regulation by small RNAs via coupled degradation: mean-field and variational approaches

T. Platini, T. Jia and R. V. Kulkarni

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Presentation of the model

Stochastic model of sRNA-based regulation via coupled degradation

\[ \begin{align*}
\phi & \quad \mu_s \\
\downarrow & \quad \uparrow \\
& \quad k_s \\
& \quad s \text{ RNA} \\
& \quad \gamma \\
& \quad \phi \\
& \quad \downarrow \\
& \quad k_m \\
\phi & \quad \mu_m \\
\end{align*} \]

The kinetic scheme for regulation of mRNA by small RNAs with coupled degradation rate \( \gamma \).
Introducing the Master Equation

We note $P_{m,s}(t)$ the probability distribution of mRNA and sRNA levels per cell.

It’s time derivative: $\partial_t P_{m,s}(t) = \text{Incoming} - \text{Outgoing}$

$$\partial_t P_{m,s} = k_m P_{m-1,s} + k_s P_{m,s-1}$$

$$+ \mu_m (m+1) P_{m+1,s} + \mu_s (s+1) P_{m,s+1}$$

$$+ \gamma (m+1)(s+1) P_{m+1,s+1}$$

$$- (k_m + k_s + \mu_m m + \mu_s s + \gamma m s) P_{m,s},$$

Stationary Properties obtained in the limit $t \rightarrow \infty$. 
The mean field approximation 
neglecting mRNA-sRNA correlations

Writing $P_{m,s} \approx \Pi(m) \times \Pi(s)$

$\Pi(m) = e^{-\lambda} \frac{\lambda^m}{m!}$ is a Poisson distribution

it follows $\langle ms \rangle \rightarrow \langle m \rangle \langle s \rangle$.

it follows $\text{Var}(m) = \langle m^2 \rangle - \langle m \rangle^2 \rightarrow \langle m \rangle$. 
The mean field approximation (neglecting mRNA-sRNA correlations)

It is useful to define

\[
    n_m = \frac{k_m}{\mu_m}, \quad n_s = \frac{k_s}{\mu_s}, \quad \varepsilon_m = \frac{k_s \gamma}{\mu_m \mu_s}, \quad \varepsilon_s = \frac{k_m \gamma}{\mu_m \mu_s},
\]

where \( \{n_m, n_s, \varepsilon_m, \varepsilon_s\} \) forms a set of independent parameters.

Defining

\[
    X = \frac{\langle m \rangle}{n_m}, \quad Y = \frac{\langle s \rangle}{n_s}
\]

The mean field approximation leads to

\[
    \varepsilon_m X Y + X - 1 = 0, \quad \varepsilon_s X Y + Y - 1 = 0.
\]
The mean field approximation predicts that

- $X = \langle m \rangle / n_m = f(\varepsilon_m, \varepsilon_s)$
- $C = \langle ms \rangle / \langle m \rangle \langle s \rangle = 1$
- $D = \langle m \rangle \langle s \rangle / \text{Var}(m) \text{Var}(s) = 1.$

$n_m = k_m / \mu_m, \quad n_s = k_s / \mu_s, \quad \varepsilon_m = \varepsilon_s = 1$
Construction of an Ansatz for $P_{m,s}$

We construct the probability distribution as a superposition of the mean field solution

$$P_{m,s} \simeq \sum_{p,q=1}^{d} \Theta_{p,q} \prod_{\alpha_p}(m) \prod_{\beta_q}(s),$$

with $\prod_x(n) = e^{-x}x^n/n!$ is the Poisson distribution.

We are here left with $d(d+2)$ independent parameter $\{\Theta_{p,q}, \alpha_p, \beta_q\}$.

The simplest case is obtained for $d = 1 : \rightarrow 2$ parameters $\rightarrow$ Mean Field.
The variational approach (Eyink, Phys. Rev E.)

• Master Equation → Quantum Equation
  \[ \partial_t |\Psi(t)\rangle = \mathcal{L} |\Psi(t)\rangle \]
  \( \mathcal{L} \) is expressed as a function of creation and annihilation operators \( a^\dagger, a \) (mRNA), \( b^\dagger \) and \( b \) (sRNA).

• Our Ansatz takes the form
  \[ |\Phi_R\rangle = \sum_{p,q=1}^{d} \Theta_{p,q} e^{\alpha_p(a^\dagger-1)} e^{\beta_q(b^\dagger-1)} |0,0\rangle \]

• Using the variational approach: \( \delta \langle \Phi_L | \mathcal{L} |\Phi_R\rangle = 0 \) leads to
  \[ \sum_{p,q=1}^{d} \Theta_{p,q} \alpha_p^i \beta_q^j \times [\epsilon_s \epsilon_m (ij + i\beta_q + j\alpha_p) \\
  + i \ n_s \epsilon_s (1 - n_m/\alpha_p) + j \ n_m \epsilon_m (1 - n_s/\beta_q)] = 0, \]
  generated for \( i,j = 0,1,2,\ldots,d \) with the pair \( (i = d,j = d) \) excluded.
  For \( d = 2 \) : \( \rightarrow 8 \) parameters (obtained numerically).
Measure the accuracy of our predictions

In the symmetric case $k_m = k_s = k$ and $\mu_s = \mu_m = \mu$
for moderate coupling parameters $\gamma = 1, 5$ to strong coupling $\gamma = 10$.
We keep $\varepsilon_m = \varepsilon_s = 1$

\[ X = \frac{\langle m \rangle}{n_m}, \quad C = \frac{\langle ms \rangle}{\langle m \rangle \langle s \rangle}, \quad D = \frac{\langle m \rangle \langle s \rangle}{\text{Var}(m) \text{Var}(s)} \]
Measure the accuracy of our predictions

\[ X = \frac{\langle m \rangle}{n_m} \quad \text{and} \quad C = \frac{\langle ms \rangle}{\langle m \rangle \langle s \rangle} \]

are plotted as a function of \( \mu_m \).

We keep \( \mu_s = 2 \), \( \gamma = 1 \) and \( \epsilon_s = 1 \).

\[ \epsilon_m = \frac{k_s \gamma}{\mu_m \mu_s} = 4 \]

\[ \epsilon_m = \frac{k_s \gamma}{\mu_m \mu_s} = 1 \]

\[ \epsilon_m = \frac{k_s \gamma}{\mu_m \mu_s} = 1/4 \]
Summary

Phys. Rev. E 84, 021928
✓ Presentation of a simple, yet non-integrable stochastic model of sRNA-based regulation via coupled degradation.
   ✓ - Introduce the Master Equation for $P_{m,s}$.

✓ Presentation of the Mean-Field approximation
   ✓ - Definition of $X$, $C$ and $D$
   ✓ - Identification of phase space regions where MF breaks down.

✓ Construction of the Ansatz as a superposition of Poisson distribution
   ✓ Present the Variational approach:
      systematic way to determine the parameters of $P_{m,s}^*$

✓ - Excellent agreement with simulation data.
Thanks My Collaborators:

T. Jia (VT)       R. Kulkarni (VT)

Thank You For Your Attention