

# Regulation by small RNAs via coupled degradation :

## mean-field and variational approaches

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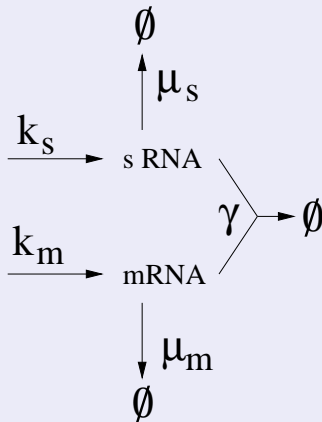
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## Presentation of the model

Stochastic model of sRNA-based regulation via coupled degradation



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 :  $\partial_t P_{m,s}(t) = \text{Incoming} - \text{Outgoing}$

$$\begin{aligned}\partial_t P_{m,s} &= k_m P_{m-1,s} + k_s P_{m,s-1} \\ &+ \mu_m (m+1) P_{m+1,s} + \mu_s (s+1) P_{m,s+1} \\ &+ \gamma (m+1)(s+1) P_{m+1,s+1} \\ &- (k_m + k_s + \mu_m m + \mu_s s + \gamma m s) P_{m,s},\end{aligned}$$

Stationary Properties obtained in the limit  $t \rightarrow \infty$ .

## The mean field approximation neglecting mRNA-sRNA correlations

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

$\Pi(m) = e^{-\lambda} \lambda^m / m!$  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

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

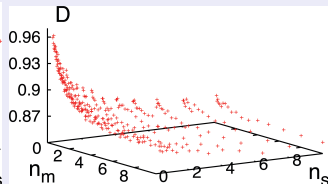
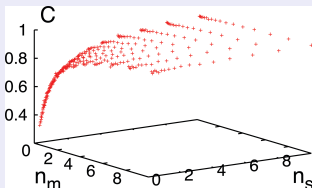
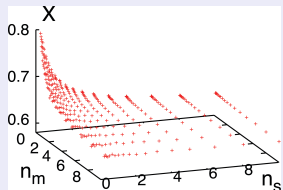
The mean field approximation leads to

$$\varepsilon_m XY + X - 1 = 0, \quad \varepsilon_s XY + Y - 1 = 0.$$

# Measure the accuracy of the mean field approximation

The mean field approximation predicts that

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



$$n_m = \frac{k_m}{\mu_m}, \quad n_s = \frac{k_s}{\mu_s}, \quad \varepsilon_m = \varepsilon_s = 1$$

## Construction of an Ansatz for $P_{m,s}$

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

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

with  $\Pi_x(n) = e^{-x} x^n / n!$  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  $\rightarrow$  Quantum Equation  $\partial_t |\Psi\rangle(t) = \mathcal{L}|\Psi\rangle(t)$   
 $\mathcal{L}$  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

$$\sum_{p,q=1}^d \Theta_{p,q} \alpha_p^i \beta_q^j \times [\epsilon_s \epsilon_m (ij + i\beta_q + j\alpha_p) + i n_s \epsilon_s (1 - n_m/\alpha_p) + j n_m \epsilon_m (1 - n_s/\beta_q)] = 0,$$

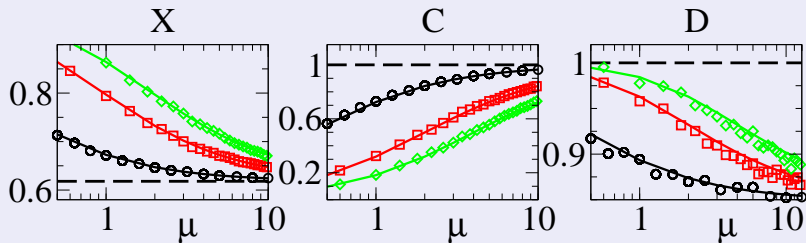
generated for  $i, j = 0, 1, 2, \dots, d$  with the pair  $(i = d, j = d)$  excluded.

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  $\varepsilon_m = \varepsilon_s = 1$



$$X = \frac{\langle m \rangle}{n_m},$$

$$C = \frac{\langle ms \rangle}{\langle m \rangle \langle s \rangle},$$

$$D = \frac{\langle m \rangle \langle s \rangle}{\text{Var}(m) \text{Var}(s)}$$

# Measure the accuracy of our predictions

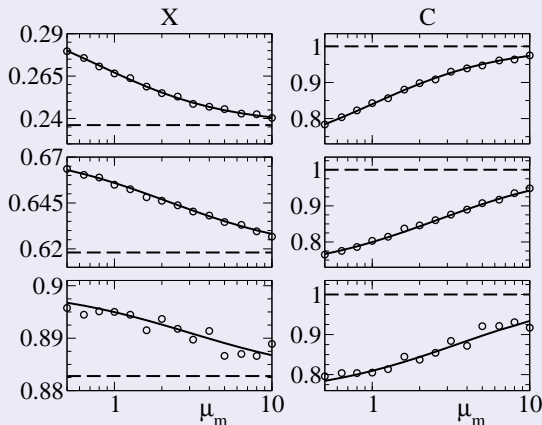
$X = \langle m \rangle / n_m$  and  $C = \langle ms \rangle / \langle m \rangle \langle s \rangle$  are plotted as a function of  $\mu_m$ .

We keep  $\mu_s = 2$ ,  $\gamma = 1$  and  $\varepsilon_s = 1$ .

$$\varepsilon_m = \frac{k_s \gamma}{\mu_m \mu_s} = 4$$

$$\varepsilon_m = \frac{k_s \gamma}{\mu_m \mu_s} = 1$$

$$\varepsilon_m = \frac{k_s \gamma}{\mu_m \mu_s} = 1/4$$



## Summary

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✓ 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