

# LECTURE #11

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MULTISCALE APPROXIMATION

# Stiffness

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- In Markovian reaction networks, the firing rates of reactions may vary widely.
- Most computational effort associated with Monte Carlo methods will be spent on faithfully simulating the firings of fast reactions, even if simulation of such reactions may not be important for determining a particular behavior of interest.
- This leads to stiffness, a serious computational problem that results in inefficiently sampling the ME.

# Stiffness

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- Stiffness will appreciably increase the computational burden of sampling the ME by Monte Carlo, which can make analysis of Markovian reaction networks very difficult to perform in practice.
- We discuss methods available to address this problem.
- The main idea is to eliminate the fast reactions by approximating the ME with one that consists of only slow reactions.

# Multiscale Approximation Methods

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- In many cases of interest, it is not important to know the detailed activities of fast reactions, since the dynamic evolution of the state of a Markovian reaction network may be mostly determined by the slow reactions.
- If that is true, we may be able to approximate the ME by one that consists only of slow reactions.
- If a sufficiently accurate approximation of the ME can be found in terms of slow reactions, then it can be used to appreciably reduce the computational burden associated with Monte Carlo sampling.
- This is because the sampling of slow reactions is much more efficient than the sampling of fast reactions.
- This idea has led to the development of techniques for eliminating fast reactions, known as multiscale approximation methods.

# Multiscale Approximation

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- Let us assume that the first  $M_s$  reactions in a Markovian reaction network are slow.
- The remaining  $M_f = M - M_s$  reactions are assumed to be fast.
- We can decompose the DA process  $\mathbf{Z}(t)$  into two components  $\mathbf{Z}_s(t)$  and  $\mathbf{Z}_f(t)$ :
  - ▣  $\mathbf{Z}_s(t)$  corresponds to slow reactions ( $M_s \times 1$  vector).
  - ▣  $\mathbf{Z}_f(t)$  corresponds to fast reactions ( $M_f \times 1$  vector).

# Multiscale Approximation

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□ From the ME

$$\frac{\partial p_Z(\mathbf{z};t)}{\partial t} = \sum_{m=1}^M \{a_m(\mathbf{z} - \mathbf{e}_m) p_Z(\mathbf{z} - \mathbf{e}_m; t) - a_m(\mathbf{z}) p_Z(\mathbf{z}; t)\}$$

we have that

$$\frac{\partial p_Z(\mathbf{z}_s, \mathbf{z}_f; t)}{\partial t}$$

$$= \sum_{m=1}^M \{a_m(\mathbf{z}_s - \bar{\mathbf{e}}_m, \mathbf{z}_f - \underline{\mathbf{e}}_m) p_Z(\mathbf{z}_s - \bar{\mathbf{e}}_m, \mathbf{z}_f - \underline{\mathbf{e}}_m; t) - a_m(\mathbf{z}_s, \mathbf{z}_f) p_Z(\mathbf{z}_s, \mathbf{z}_f; t)\}$$

$$\mathbf{e}_m = \begin{bmatrix} \bar{\mathbf{e}}_m \\ \underline{\mathbf{e}}_m \end{bmatrix} \quad \begin{matrix} M_s \times 1 \\ M_f \times 1 \end{matrix}$$

□ However

$$p_Z(\mathbf{z}_s, \mathbf{z}_f; t) = p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t) p_{Z_s}(\mathbf{z}_s; t)$$

# Multiscale Approximation

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- In this case, we obtain

$$\frac{\partial p_{Z_s}(\mathbf{z}_s; t)}{\partial t} = \sum_{m \in \mathcal{R}_s} \left\{ a_m(\mathbf{z}_s - \bar{\mathbf{e}}_m; t) p_{Z_s}(\mathbf{z}_s - \bar{\mathbf{e}}_m; t) - a_m(\mathbf{z}_s; t) p_{Z_s}(\mathbf{z}_s; t) \right\}$$

where  $\mathcal{R}_s = \{1, 2, \dots, M_s\}$  and

$$a_m(\mathbf{z}_s; t) = \sum_{\mathbf{z}_f} \alpha_m(\mathbf{z}_s, \mathbf{z}_f) p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t), \quad m \in \mathcal{R}_s$$

see supplement #6 for details

- This result shows that the DAs of the slow reactions follow a ME like the one governing the entire Markovian reaction network, albeit with time varying propensities.

# Multiscale Approximation

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- If we could evaluate the propensity functions

$$a_m(\mathbf{z}_s; t) = \sum_{\mathbf{z}_f} \alpha_m(\mathbf{z}_s, \mathbf{z}_f) p_{\mathbf{Z}_f | \mathbf{Z}_s}(\mathbf{z}_f | \mathbf{z}_s; t), \quad m \in \mathcal{R}_s$$

then we could efficiently simulate the stochastic evolutions of the DAs of the slow reactions by using the exact Gillespie algorithm, or any other appropriate technique, modified to account for the fact that the propensity functions are now time-dependent.



# Multiscale Approximation

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- Given that  $\mathbf{Z}_s(t) = \mathbf{z}_s$ , we can then estimate the population process using the [minimum mean square error](#) (MMSE) estimate, given by

$$\hat{x}_n(t; \mathbf{z}_s) = \mathbb{E}[X_n(t) | \mathbf{Z}_s(t) = \mathbf{z}_s] = x_{0,n} + \sum_{m \in \mathcal{R}_s} s_{nm} z_m(t) + \sum_{m \in \mathcal{R}_f} s_{nm} \mu_Z(m; t, \mathbf{z}_s)$$

where  $\mathcal{R}_f = \{M_s + 1, M_s + 2, \dots, M\}$ , and

$$\mu_Z(m; t, \mathbf{z}_s) = \mathbb{E}[Z_m(t) | \mathbf{Z}_s(t) = \mathbf{z}_s], \quad m \in \mathcal{R}_f$$

is the mean DA of the  $m$ -th fast reaction at time  $t$ , given the state  $\mathbf{z}_s$  of the slow reactions at  $t$ .

[https://en.wikipedia.org/wiki/Minimum\\_mean\\_square\\_error](https://en.wikipedia.org/wiki/Minimum_mean_square_error)

# Multiscale Approximation

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- Calculating the propensity functions  $\alpha_m(\mathbf{z}_s; t)$  for the  $m$ -th slow reaction, and the means  $\mu_Z(m; t, \mathbf{z}_s)$  for  $m$ -th fast reaction, requires knowledge of the conditional probability  $p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t)$ .
- We can show that, within the coarse time scale, the dynamic evolution of this probability is approximately governed by the following ME:

$$\begin{aligned} & \frac{\partial p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t)}{\partial t} \\ &= \sum_{m \in \mathcal{R}_f} \left\{ \alpha_m(\mathbf{z}_s, \mathbf{z}_f - \mathbf{e}_m) p_{Z_f|Z_s}(\mathbf{z}_f - \mathbf{e}_m | \mathbf{z}_s; t) - \alpha_m(\mathbf{z}_s, \mathbf{z}_f) p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t) \right\} \end{aligned}$$

see supplement #6 for details

# Multiscale Approximation

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$$\begin{aligned} & \frac{\partial p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t)}{\partial t} \\ &= \sum_{m \in \mathcal{R}_f} \left\{ \alpha_m(\mathbf{z}_s, \mathbf{z}_f - \mathbf{e}_m) p_{Z_f|Z_s}(\mathbf{z}_f - \mathbf{e}_m | \mathbf{z}_s; t) - \alpha_m(\mathbf{z}_s, \mathbf{z}_f) p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t) \right\} \end{aligned}$$

- Unfortunately, solving this ME of the “fast” reaction subnetwork is as difficult as solving the ME of the entire network.
- Moreover, evaluating the propensity functions of the “slow” subnetwork requires Monte Carlo estimation in general, which adds to computational burden.

# Multiscale Approximation – Summary

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- $\frac{\partial p_{Z_s}(\mathbf{z}_s; t)}{\partial t} = \sum_{m \in \mathcal{R}_s} \left\{ a_m(\mathbf{z}_s - \bar{\mathbf{e}}_m; t) p_{Z_s}(\mathbf{z}_s - \bar{\mathbf{e}}_m; t) - a_m(\mathbf{z}_s; t) p_{Z_s}(\mathbf{z}_s; t) \right\}$
- $a_m(\mathbf{z}_s; t) = \sum_{\mathbf{z}_f} \alpha_m(\mathbf{z}_s, \mathbf{z}_f) p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t), \quad m = 1, 2, \dots, M_s$
- $\frac{\partial p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t)}{\partial t} = \sum_{m \in \mathcal{R}_f} \left\{ \alpha_m(\mathbf{z}_s, \mathbf{z}_f - \mathbf{e}_m) p_{Z_f|Z_s}(\mathbf{z}_f - \mathbf{e}_m | \mathbf{z}_s; t) - \alpha_m(\mathbf{z}_s, \mathbf{z}_f) p_{Z_f|Z_s}(\mathbf{z}_f | \mathbf{z}_s; t) \right\}$
- $\mu_Z(m; t, \mathbf{z}_s) = \mathbb{E}[Z_m(t) | \mathbf{Z}_s(t) = \mathbf{z}_s], \quad m \in \mathcal{R}_f$
- $\hat{x}_n(t; \mathbf{z}_s) = \mathbb{E}[X_n(t) | \mathbf{Z}_s(t) = \mathbf{z}_s] = x_{0,n} + \sum_{m \in \mathcal{R}_s} s_{nm} z_m(t) + \sum_{m \in \mathcal{R}_f} s_{nm} \mu_Z(m; t, \mathbf{z}_s)$

# Multiscale Approximation – Remarks

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- Several approaches have been proposed to address the previous issues.
- For example, it has been assumed that, within successive firings of slow reactions, the fast reactions rapidly reach a stationary state whose probability does not depend on time  $t$ .
- In this case, we can set the right-hand-side of the ME of the “fast” reaction subnetwork equal to zero and use a numerical technique to calculate the desired stationary conditional probability of the “fast” variables given the “slow” variables.
- We can then evaluate the propensity functions of the “slow” reaction subnetwork either by direct summation, if computationally feasible, or by Monte Carlo estimation.

# Multiscale Approximation – Remarks

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- However, numerically solving the ME of the “fast” reaction subnetwork may not be easy, especially for large subnetworks.
- Moreover, evaluating expectations by direct summation or Monte Carlo estimation can be computationally demanding.
- Notably, the main difficulty with the previous approach is to verify that the “fast” reaction subnetwork reaches a stationary state, since there might be only a short induction time between successive firings of slow reactions during which convergence to steady-state may not occur.

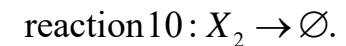
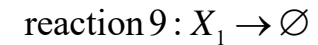
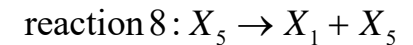
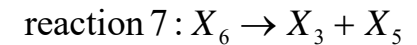
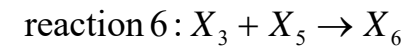
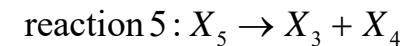
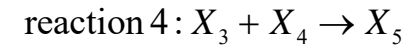
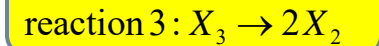
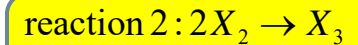
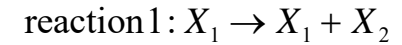
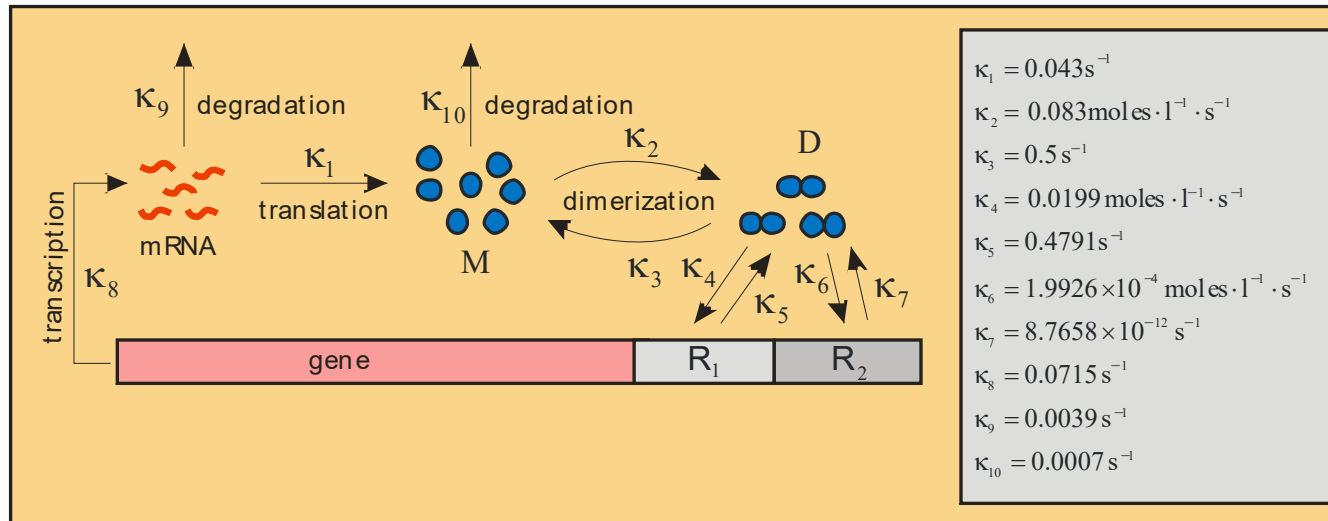
# Multiscale Approximation – Remarks

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- Most multiscale approximation methods developed so far are based on a clear separation between fast and slow reactions.
- This may not be possible.
- For this reason, it may be more appropriate to develop techniques that involve more than two separate time scales.
- A few such techniques have been developed but with limited success.

# Example: Transcription Regulation

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$X_1$  : mRNA

$X_1(0) = 0$

$X_2$  : protein M

$X_2(0) = 2$

$X_3$  : dimer D

$X_3(0) = 4$

$X_4$  : gene

$X_4(0) = 2$

$X_5$  : gene + D at  $R_1$

$X_5(0) = 0$

$X_6$  : gene + D at  $R_1$  + D at  $R_2$

$X_6(0) = 0$



# Example: Transcription Regulation

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- Despite the modest size of the previous network, simulation using exact Monte Carlo sampling of the ME is computationally intensive.
- It took more than 2 hours of CPU time to obtain 2,000 samples of the population dynamics during a period of 35 minutes.
- This serious inefficiency is due to stiffness caused by the reversible reactions associated with protein dimerization being much faster than the remaining reactions.
- Exact Monte Carlo sampling is forced to spend a substantial amount of time simulating the occurrences of these two reactions.

# Example: Transcription Regulation

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- We cannot appreciably reduce computational effort by using Poisson leaping since, for accurately solving the ME, stiffness constrains the leaping parameter to take a very small value thus deeming this approximation method computationally comparable to exact sampling.
- Dimerization however is reversible and occurs on a much faster timescale than the other reactions.
- We expect its effect to largely cancel out.
- Faithful simulation of dimerization may not be necessary.

# Example: Transcription Regulation

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- If we set  $\mathcal{R}_s = \{1,4,5,6,7,8,9,10\}$  and  $\mathcal{R}_f = \{2,3\}$ , then the “slow” subsystem, comprised of the reactions in  $\mathcal{R}_s$ , will be characterized by the ME

$$\frac{\partial p_{\mathbf{z}_s}(\mathbf{z}_s; t)}{\partial t} = \sum_{m \in \mathcal{R}_s} \left\{ a_m(\mathbf{z}_s - \bar{\mathbf{e}}_m; t) p_{\mathbf{z}_s}(\mathbf{z}_s - \bar{\mathbf{e}}_m; t) - a_m(\mathbf{z}_s; t) p_{\mathbf{z}_s}(\mathbf{z}_s; t) \right\}$$

with propensity functions given by

$$\alpha_1(\mathbf{z}_s; t) = \kappa_1(z_8 - z_9)$$

$$\alpha_4(\mathbf{z}_s; t) = \kappa_4[4 - z_4 + z_5 - z_6 + z_7 + \mu_Z(2; t, \mathbf{z}_s) - \mu_Z(3; t, \mathbf{z}_s)](2 - z_4 + z_5)$$

$$\alpha_5(\mathbf{z}_s; t) = \kappa_5(z_4 - z_5 - z_6 + z_7)$$

$$\alpha_6(\mathbf{z}_s; t) = \kappa_6[4 - z_4 + z_5 - z_6 + z_7 + \mu(2; t, \mathbf{z}_s) - \mu(3; t, \mathbf{z}_s)](z_4 - z_5 - z_6 + z_7)$$

$$\alpha_7(\mathbf{z}_s; t) = \kappa_7(z_6 - z_7)$$

$$\alpha_8(\mathbf{z}_s; t) = \kappa_8(z_4 - z_5 - z_6 + z_7)$$

$$\alpha_9(\mathbf{z}_s; t) = \kappa_9(z_8 - z_9)$$

$$\alpha_{10}(\mathbf{z}_s; t) = \kappa_{10}[2 + z_1 - z_{10} - 2\mu(2; t, \mathbf{z}_s) + 2\mu(3; t, \mathbf{z}_s)]$$

where  $\mu_Z(2; t, \mathbf{z}_s)$  and  $\mu_Z(3; t, \mathbf{z}_s)$  are the mean DAs of the two fast reactions 2 & 3, respectively.

# Example: Transcription Regulation

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$$\alpha_1(\mathbf{z}_s; t) = \kappa_1(z_8 - z_9)$$

$$\alpha_4(\mathbf{z}_s; t) = \kappa_4[4 - z_4 + z_5 - z_6 + z_7 + \mu_Z(2; t, \mathbf{z}_s) - \mu_Z(3; t, \mathbf{z}_s)](2 - z_4 + z_5)$$

$$\alpha_5(\mathbf{z}_s; t) = \kappa_5(z_4 - z_5 - z_6 + z_7)$$

$$\alpha_6(\mathbf{z}_s; t) = \kappa_6[4 - z_4 + z_5 - z_6 + z_7 + \mu(2; t, \mathbf{z}_s) - \mu(3; t, \mathbf{z}_s)](z_4 - z_5 - z_6 + z_7)$$

$$\alpha_7(\mathbf{z}_s; t) = \kappa_7(z_6 - z_7)$$

$$\alpha_8(\mathbf{z}_s; t) = \kappa_8(z_4 - z_5 - z_6 + z_7)$$

$$\alpha_9(\mathbf{z}_s; t) = \kappa_9(z_8 - z_9)$$

$$\alpha_{10}(\mathbf{z}_s; t) = \kappa_{10}[2 + z_1 - z_{10} - 2\mu(2; t, \mathbf{z}_s) + 2\mu(3; t, \mathbf{z}_s)]$$

- To calculate these propensities, we need to compute the difference

$$\mu_Z(2; t, \mathbf{z}_s) - \mu_Z(3; t, \mathbf{z}_s)$$

# Example: Transcription Regulation

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- By assuming that the “fast” reaction subsystem of the two dimerization reactions rapidly reaches equilibrium within successive occurrences of slow reactions, we can show that

$$\mu_Z(2;t,\mathbf{z}_s) - \mu_Z(3;t,\mathbf{z}_s) = \frac{1}{2} \left[ A(\mathbf{z}_s) - \sqrt{A^2(\mathbf{z}_s) - 4B(\mathbf{z}_s)} \right]$$

see supplement #7 for details

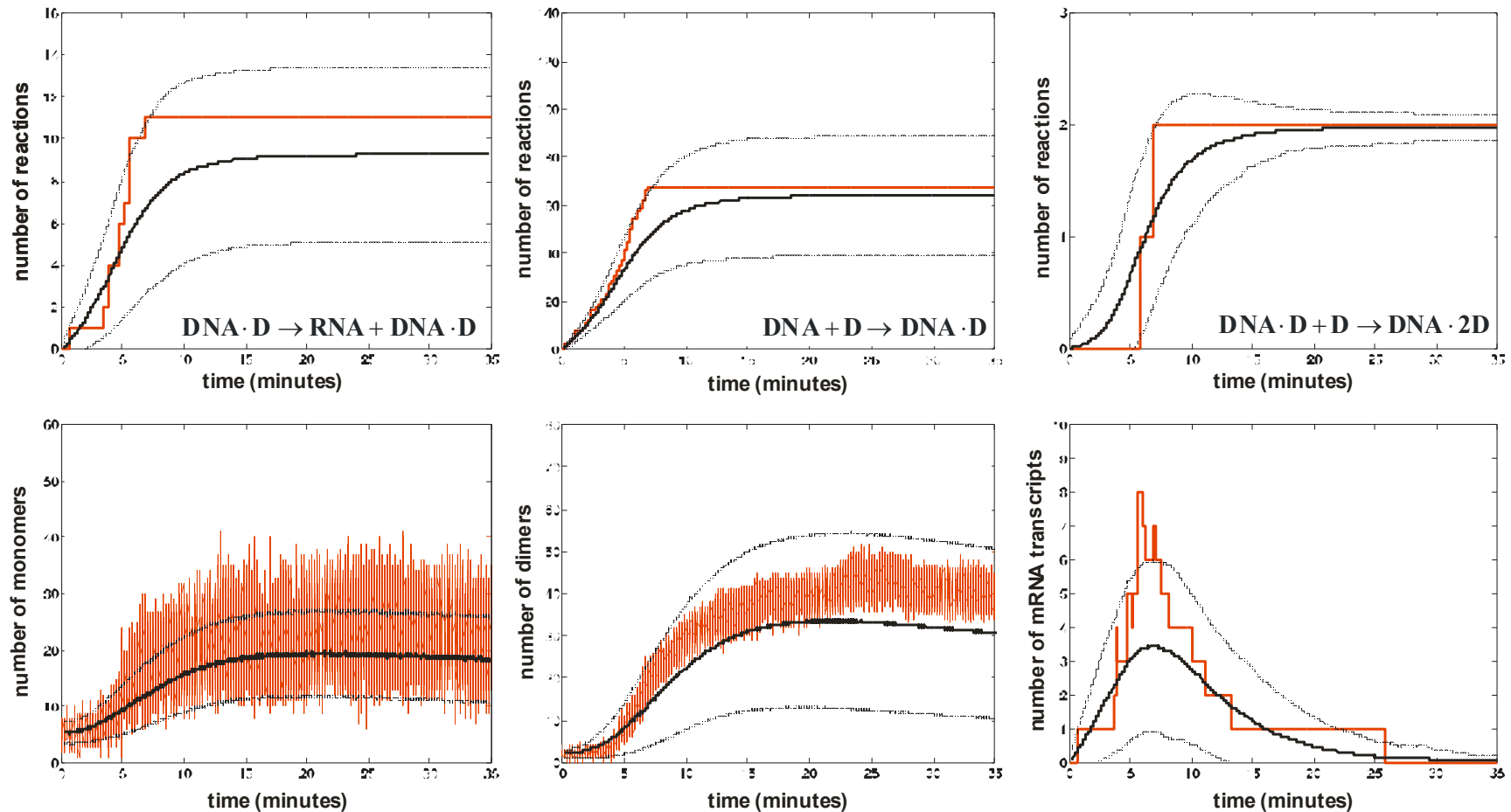
where

$$A(\mathbf{z}_s) = 1.5 + z_1 - z_{10} + (\kappa_3 / 2\kappa_2)$$

$$B(\mathbf{z}_s) = 0.25(1 + z_1 - z_{10})(2 + z_1 - z_{10}) - (\kappa_3 / 2\kappa_2)(4 - z_4 + z_5 - z_6 + z_7)$$

# Example: Transcription Regulation

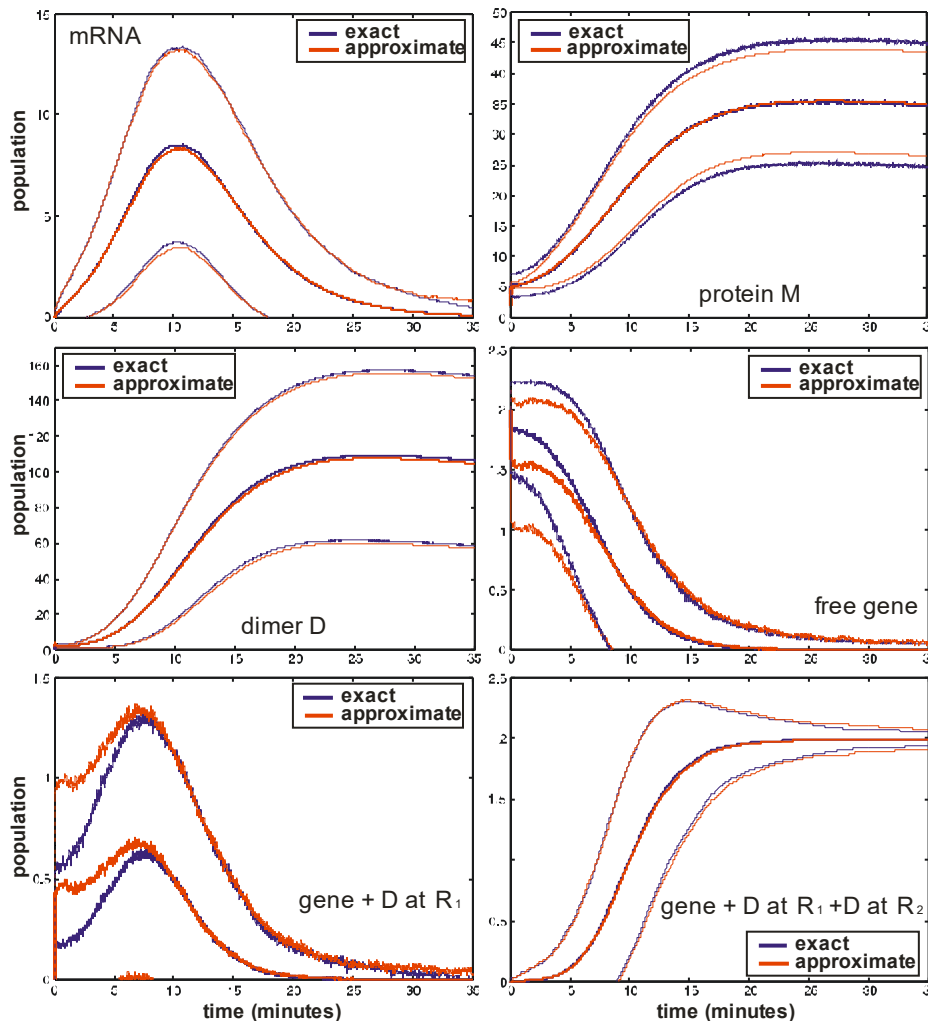
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Typical dynamic evolutions of some DAs and populations (red solid lines), their estimated means (black solid lines), and  $\pm 1$  standard deviations (black dotted lines) obtained by exact Monte Carlo sampling.

# Example: Transcription Regulation

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- ❖ The mean and  $\pm 1$  standard deviation dynamics of the underlying population processes obtained by exact Monte Carlo sampling and multiscale approximation.
- ❖ It took less than a minute of CPU time to draw 2,000 Monte Carlo samples from the ME of the “slow” reaction subsystem (135 minutes required by exact Monte Carlo sampling).
- ❖ The relatively large transient errors in the population dynamics of  $X_4$  and  $X_5$  are due to incorrectly computing the net DA  $z_4(t) - z_5(t)$  of reactions 4 & 5 (binding and unbinding of the dimer on the promoter of the gene).
- ❖ This is a consequence of the imposed approximation of the DAs of the fast reactions 2 & 3 (dimerization) through their mean values.