LECTURE #7

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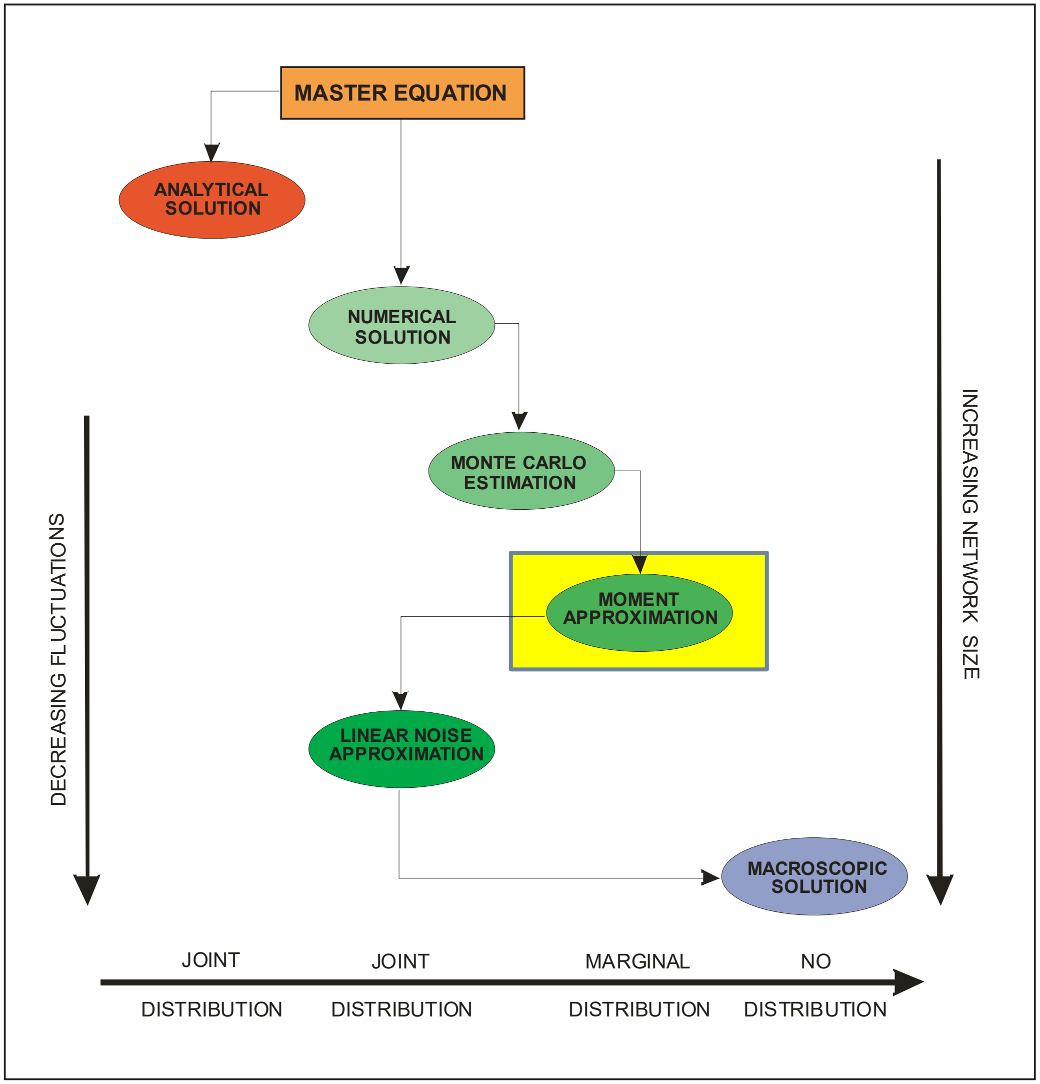
SOLVING THE MASTER EQUATION – PART 4

Available Methods



Moment Approximation

- When a reaction network contains many species and many reactions, it may not be possible to accurately estimate, in <u>reasonable time</u>, the statistical behavior of the DA and population processes by Monte Carlo sampling.
- In this case, we may try an alternative technique known as <u>moment approximation</u> (MA).

Moment Approximation

- Let

$$Z_m(t) = \mu_Z(m;t) + W_m(t), \;\; t > 0, m = 1, 2, \ldots, M$$

where

$$\mu_Z(m;t) \triangleq \mathrm{E}[Z_m(t)]$$

$$W_m(t) \triangleq Z_m(t) - \mu_Z(m;t)$$

- This equation is <u>exact !!</u>

Moment Approximation

- In most cases, we are interested in differential equations that govern the dynamic evolution of the means

$$\mu_Z(m;t) = \mathrm{E}[Z_m(t)]$$

and covariances

$$c_Z(m,m';t) = \mathrm{cov}[Z_m(t), Z_{m'}(t)] = \mathrm{E}[W_m(t) W_{m'}(t)]$$

Moment Approximation

- From the ME, we can show that:

$$\frac{d\mu_Z(m;t)}{dt} = \mathrm{E}\big[\alpha_m(\mathbf{Z}(t))\big], \quad t > 0, m = 1,2,\ldots,M$$

see supplement 5 for details

$$\frac{dc_Z(m,m';t)}{dt} = \mathrm{E}\big[\alpha_m(\mathbf{Z}(t))\big]\delta(m-m')$$

Kronecker delta

$$+\mathrm{E}\big[[Z_{m'}(t) - \mu_Z(m';t)]\alpha_m(\mathbf{Z}(t))\big]$$

$$+\mathrm{E}\big[[Z_m(t) - \mu_Z(m;t)]\alpha_{m'}(\mathbf{Z}(t))\big],$$

$$t > 0, m, m' = 1,2,\ldots,M$$

- Can we solve this system of equations?

Moment Approximation

- This is <u>not possible</u> in general (e.g., we cannot evaluate the expectations).
- Since $\mathbf{Z}(t) = \boldsymbol{\mu}_z(t) + \mathbf{W}(t)$, we can use the following Taylor series expansion:

$$\alpha_m(\mathbf{Z}(t)) = \alpha_m(\boldsymbol{\mu}_z(t)) + \sum_{m_1} h_{m;m_1}(\boldsymbol{\mu}_Z(t))W_{m_1}(t)$$

$$+\frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2}(\boldsymbol{\mu}_Z(t))W_{m_1}(t)W_{m_2}(t)$$

$$+\frac{1}{6}\sum_{m_1}\sum_{m_2}\sum_{m_3} h_{m;m_1,m_2,m_3}(\boldsymbol{\mu}_Z(t))W_{m_1}(t)W_{m_2}(t)W_{m_3}(t)$$

$$+\cdots$$

derivatives of $\alpha_m(\mathbf{z})$

Moment Approximation

- In this case, we obtain:

$$\frac{d\mu_Z(m;t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2}(\boldsymbol{\mu}_Z(t))c_Z(m_1,m_2;t)$$
$$+\frac{1}{6}\sum_{m_1}\sum_{m_2}\sum_{m_3} h_{m;m_1,m_2,m_3}(\boldsymbol{\mu}_Z(t))\boxed{c_Z(m_1,m_2,m_3;t)} + \cdots$$

$$\frac{dc_Z(m,m';t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t))\delta(m-m')$$
$$+\sum_{m_1}\left[h_{m';m_1}(\boldsymbol{\mu}_Z(t))c_Z(m,m_1;t) + h_{m;m_1}(\boldsymbol{\mu}_Z(t))c_Z(m',m_1;t)\right]$$
$$+\frac{1}{2}\left[\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2}(\boldsymbol{\mu}_Z(t))c_Z(m_1,m_2;t)\right]\delta(m-m')$$
$$+\frac{1}{2}\sum_{m_1}\sum_{m_2}\left[h_{m';m_1,m_2}(\boldsymbol{\mu}_Z(t))\boxed{c_Z(m,m_1,m_2;t)} + h_{m;m_1,m_2}(\boldsymbol{\mu}_Z(t))\boxed{c_Z(m',m_1,m_2;t)}\right]$$
$$+\frac{1}{6}\left[\sum_{m_1}\sum_{m_2}\sum_{m_3} h_{m;m_1,m_2,m_3}(\boldsymbol{\mu}_Z(t))\boxed{c_Z(m_1,m_2,m_3;t)}\right]\delta(m-m')$$
$$+\frac{1}{6}\sum_{m_1}\sum_{m_2}\sum_{m_3}\left[h_{m';m_1,m_2,m_3}(\boldsymbol{\mu}_Z(t))\boxed{c_Z(m,m_1,m_2,m_3;t)} + h_{m;m_1,m_2,m_3}(\boldsymbol{\mu}_Z(t))\boxed{c_Z(m',m_1,m_2,m_3;t)}\right]$$
$$+\cdots$$

requires knowledge of third- and fourth-order central moments !!

Moment Approximation

- The previous equations show that the mean and covariance dynamics of the DA process are in general governed by a system of <u>coupled</u> first-order differential equations driven by the third-, fourth-, and higher-order central moments.
- The dependency of these equations on propensity function derivatives tells us how the mean and fluctuation dynamics are affected by the presence of nonlinearities in the propensity functions.

Moment Approximation

- If the propensity functions are linear, then all second- and higher-order derivatives of these functions will be zero, which implies that

$$\frac{d\mu_Z(m;t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t))$$

constants

$$\frac{dc_Z(m,m';t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t))\delta(m-m') + \sum_{m_1}\left[h_{m';m_1} c_Z(m,m_1;t) + h_{m;m_1} c_Z(m',m_1;t)\right]$$

- These equations are exact !!
- In this case, the means can be calculated independently from the covariances.

Moment Approximation

- If the propensity functions are <u>quadratic</u>, then

$$\frac{d\mu_Z(m;t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2} c_Z(m_1,m_2;t)$$

$$\frac{dc_Z(m,m';t)}{dt} = \Big[\alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2} c_Z(m_1,m_2;t)\Big]\delta(m-m')$$
$$+\sum_{m_1}\Big[h_{m';m_1}(\boldsymbol{\mu}_Z)c_Z(m,m_1;t) + h_{m;m_1}(\boldsymbol{\mu}_Z)c_Z(m',m_1;t)\Big]$$
$$+\frac{1}{2}\sum_{m_1}\sum_{m_2}\Big[h_{m';m_1,m_2}\boxed{c_Z(m,m_1,m_2;t)} + h_{m;m_1,m_2}\boxed{c_Z(m',m_1,m_2;t)}\Big]$$

- These equations are <u>exact</u> !!
- In this case, the means <u>cannot</u> be calculated independently from the covariances.
- Calculation requires <u>third-order</u> central moments !!

Moment Approximation

- Note that $\mathbf{X}(t) = \mathbf{x}_0 + \mathbf{S}\mathbf{Z}(t)$ implies

$$\boxed{\begin{aligned} \boldsymbol{\mu}_X(t) &= \mathbf{x}_0 + \mathbf{S}\boldsymbol{\mu}_Z(t) \\ \mathbf{C}_X(t) &= \mathbf{S}\mathbf{C}_Z(t)\mathbf{S}^T \end{aligned}}$$

- Therefore, the means and covariances of the population process can be easily calculated from the means and covariances of the DA process.
- We can also derive differential equations for the <u>central moments</u> of the population process.

Moment Approximation – Moment Closure

- When the propensity functions are nonlinear, the moment equations always form an infinite hierarchy, with lower order moments depending on higher order moments, indicating that exact solutions cannot be obtained in practice.
- To address this problem, we can replace the moments at some stage of the hierarchy with appropriately chosen functions of lower-order moments.
- This approach results in a moment closure scheme that produces a self-contained system of differential equations whose solution provides approximate values for the moments of the DA and populations processes.

Moment Approximation – Moment Closure

- A possible solution to the moment closure problem is to assume the form of the probability distribution of the DA or population processes.
- **Example:** We may assume a probability distribution for the DA process that can be uniquely defined from the means and covariances (the Gaussian is one such distribution).
  - This distribution will impose functional relationships between the higher-order central moments and the means and covariances.
  - This relationship can be used to close the system of moment equations.

Moment Approximation – Moment Closure

- **Example:** We may assume that $p_Z(\mathbf{z};t)$ is approximately <u>Gaussian</u>.
- In this case, the third-order central moments are zero and we have (for at most quadratic propensities):

$$\frac{d\mu_Z(m;t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2} c_Z(m_1,m_2;t)$$

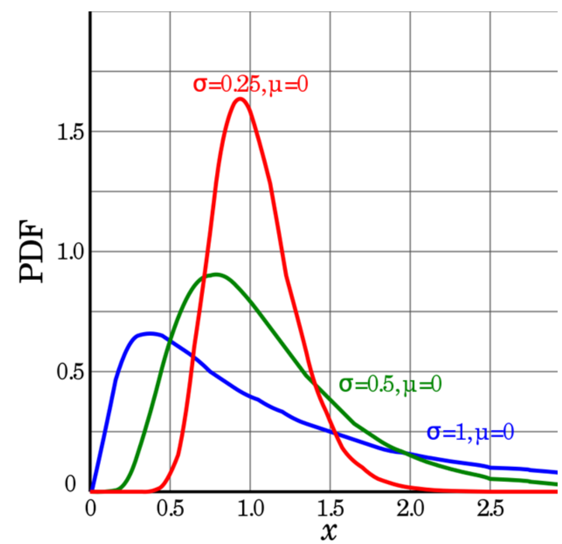
$$\frac{dc_Z(m,m';t)}{dt} = \left[\alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2} c_Z(m_1,m_2;t)\right]\delta(m-m')$$
$$+\sum_{m_1}\left[h_{m';m_1}(\boldsymbol{\mu}_Z)c_Z(m,m_1;t) + h_{m;m_1}(\boldsymbol{\mu}_Z)c_Z(m',m_1;t)\right]$$

- MA techniques based on a Gaussian assumption cannot characterize bimodality or highly skewed probability distributions and may result in undesirable negative DA and population values.

Moment Approximation – Moment Closure

- In addition to the normal distribution, several alternative approximating distributions have been suggested in the literature: log-normal, Poisson, binomial, beta binomial, and mixtures of distributions.

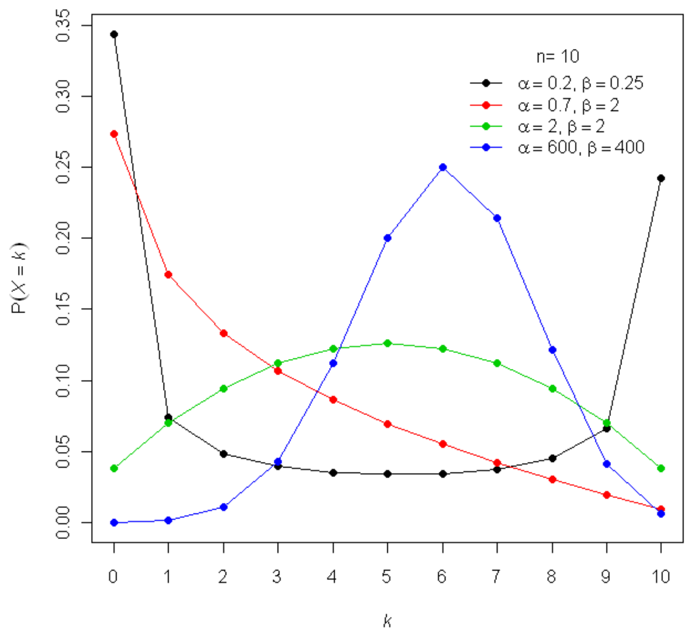
- Using the log-normal distribution has some advantages over using the Gaussian distribution.
  - The log-normal distribution has nonnegative support and exhibits nonzero skewness, two properties that are important in the context of certain nonlinear reaction networks, such as biochemical reaction networks.



https://en.wikipedia.org/wiki/Log-normal_distribution

Moment Approximation – Moment Closure

- On the other hand, the beta binomial distribution is a discrete distribution with a flexible shape that, in some cases, can capture the dynamic evolution of the true probability distribution of the population process better than other distributions.



https://en.wikipedia.org/wiki/Beta-binomial_distribution

Moment Approximation – Moment Closure

- It may be difficult to specify an appropriate probability distribution for the population process, since this distribution must assign zero probabilities to stoichiometrically impossible populations.
- It may be easier to specify a probability distribution for the DA process, since this process is usually confined within a well-defined subset of the positive orthant of the multidimensional DA state-space.
- Approximating the moments of the DA process by employing continuous distributions, such as log-normal, may be difficult to justify due to the discrete nature of this process.

Moment Approximation with MaxEnt

- Although the previous strategy may lead to a sufficiently accurate estimation of the low-order moments of the DA and population processes, it cannot provide an analytical expression for the probability distributions of these processes.
- However, we may be able to address this problem using MaxEnt.

Moment Approximation with MaxEnt

- **Example:** If the propensity functions of the reaction network at hand are <u>at most quadratic</u> and if we use a <u>log-normal-based</u> moment closure scheme, then the MaxEnt approximation of the probability distribution of the DA process associated with the m-th reaction will be given by the following Gibbs distribution:

$$\hat{p}_Z(z_m;t) = \Big(\sum_{u\geq 0} \exp\big\{-\lambda_1(t)u - \lambda_2(t)u^2 - \lambda_3(t)u^3\big\}\Big)^{-1}$$
$$\times \exp\big\{-\lambda_1(t)z_m - \lambda_2(t)z_m^2 - \lambda_3(t)z_m^3\big\}$$

where the coefficients $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ must be determined so that

$$\sum_{z_m \geq 0} z_m \hat{p}_Z(z_m;t) = \mu_Z(m;t)$$
$$\sum_{z_m \geq 0} z_m^2 \hat{p}_Z(z_m;t) = c_Z(m,m;t) + \mu_Z^2(m;t)$$
$$\sum_{z_m \geq 0} z_m^3 \hat{p}(z_m;t) = \left[\frac{c_Z(m,m;t) + \mu_Z^2(m;t)}{\mu_Z(m;t)}\right]^3$$

Moment Approximation with MaxEnt

- In this case the mean and covariance dynamics can be calculated from

$$\frac{d\mu_Z(m;t)}{dt} = \alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2} c_Z(m_1,m_2;t)$$

$$\frac{dc_Z(m,m';t)}{dt} = \left[\alpha_m(\boldsymbol{\mu}_Z(t)) + \frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2} c_Z(m_1,m_2;t)\right]\Delta(m-m')$$
$$+\sum_{m_1}\left[h_{m';m_1}(\boldsymbol{\mu}_Z)c_Z(m,m_1;t) + h_{m;m_1}(\boldsymbol{\mu}_Z)c_Z(m',m_1;t)\right]$$
$$+\frac{1}{2}\sum_{m_1}\sum_{m_2}\left[h_{m';m_1,m_2} c_Z(m,m_1,m_2;t) + h_{m;m_1,m_2} c_Z(m',m_1,m_2;t)\right]$$

where the third-order moments can be related to the first- and second-order moments by

$$\mathrm{E}[Z_1(t)Z_2(t)Z_3(t)] = \frac{\mathrm{E}[Z_1(t)Z_2(t)]\mathrm{E}[Z_1(t)Z_3(t)]\mathrm{E}[Z_2(t)Z_3(t)]}{\mathrm{E}[Z_1(t)]\mathrm{E}[Z_2(t)]\mathrm{E}[Z_3(t)]}$$

property of log-normal distribution

Moment Approximation by Truncation

- Several moment closure schemes have been proposed in the literature based on truncating high-order central moments or cumulants.
- The typical assumption behind these methods is that the solution of the ME has negligible high-order central moments or cumulants, which can be set equal to zero without affecting the mean and covariance dynamics.
- This assumption is not true in general, except for normal random variables whose central moments of odd order and cumulants of order larger than 2 are zero.

https://en.wikipedia.org/wiki/Cumulant

Moment Approximation by Truncation

- For non-normal random variables, there is an infinite number of non-vanishing central moments or cumulants in general.
- **Example:** all cumulants of a Poisson random variable are equal to the mean value.
- Truncation of high-order central moments or cumulants cannot be easily justified and may lead to a distribution that is a non-valid probability distribution.

Moment Approximation – Stabilization

- Recall that

$$\frac{d\mu_Z(m;t)}{dt} = \mathrm{E}[\alpha_m(\mathbf{Z}(t))]$$

$$= \alpha_m(\boldsymbol{\mu}_Z(t)) + \underbrace{\frac{1}{2}\sum_{m_1}\sum_{m_2} h_{m;m_1,m_2}(\boldsymbol{\mu}_Z(t))c_Z(m_1,m_2;t) + \frac{1}{6}\sum_{m_1}\sum_{m_2}\sum_{m_3} h_{m;m_1,m_2,m_3}(\boldsymbol{\mu}_Z(t))c_Z(m_1,m_2,m_3;t) + \cdots}_{T_m(\boldsymbol{\mu}_Z(t))}$$

- The MA method is based on replacing the mean value $\mathrm{E}[\alpha_m(\mathbf{Z}(t))]$ by $\alpha_m(\boldsymbol{\mu}_Z(t)) + T_m(\boldsymbol{\mu}_Z(t))$, where $T_m(\boldsymbol{\mu}_Z(t))$ is a term calculated by solving differential equations for higher-order central moments.

Moment Approximation – Stabilization

- When the propensity function is convex, then Jensen's inequality implies that

$$\mathrm{E}[\alpha_m(\mathbf{Z}(t))] \geq \alpha_m(\mathrm{E}[\mathbf{Z}(t)]) = \alpha_m(\boldsymbol{\mu}_Z(t))$$

which results in

$$\mathrm{E}[\alpha_m(\mathbf{Z}(t))] = \alpha_m(\boldsymbol{\mu}_Z(t)) + T_m(\boldsymbol{\mu}_Z(t)) \geq \alpha_m(\boldsymbol{\mu}_Z(t))$$

- Consequently, we must have

$$\boxed{T_m(\boldsymbol{\mu}_Z(t)) \geq 0}$$

https://en.wikipedia.org/wiki/Jensen_inequality

Moment Approximation – Stabilization

- However, this may not be true, in which case the method may result in additional errors that can lead to instabilities.
- To address this problem, we can replace $\mathrm{E}[\alpha_m(\mathbf{Z}(t))]$ by

$$\alpha_m(\boldsymbol{\mu}_Z(t)) + \max\{0, T_m(\boldsymbol{\mu}_Z(t))\}$$

- In many instances, this simple modification results in a more accurate and more stable implementation of the MA method.

Moment Approximation – Consistency

- A moment closure scheme used in a particular application must produce moments that satisfy several necessary conditions.
- For example, all moments must be <u>nonnegative</u> and <u>invariant</u> under permutations and the resulting covariances must define a <u>symmetric positive semi-definite</u> matrix.
- If a necessary condition is violated by a particular moment closure scheme, then this is indicative of its inappropriateness.

Moment Approximation – Consistency

- The assumptions underlying a given moment closure scheme may be inconsistent with the statistics of a particular reaction network at hand.
- In this case, the moment equations may produce unrealistic solutions or even result in unstable and unbounded solutions.