LECTURE #8

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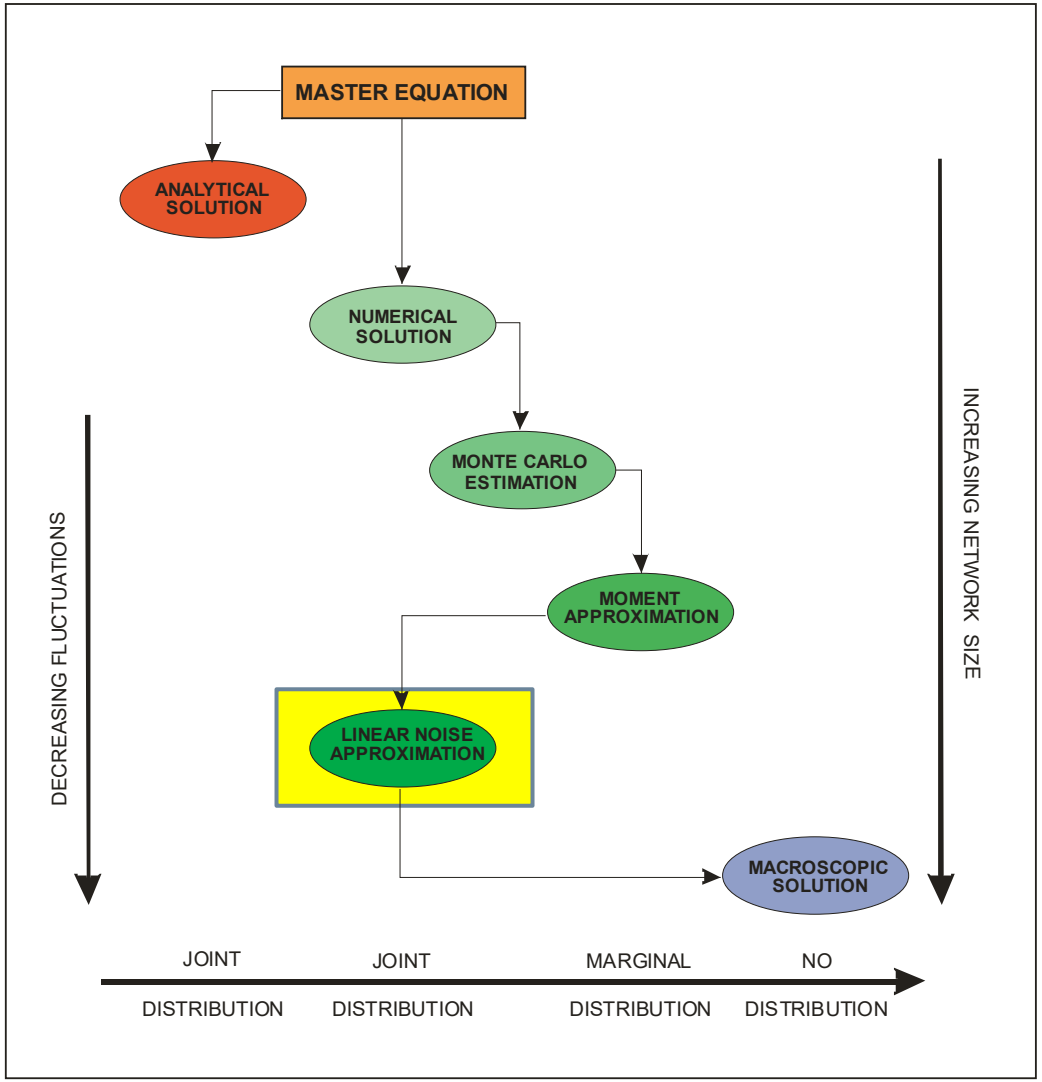
SOLVING THE MASTER EQUATION – PART 5

Available Methods



Linear Noise Approximation

- In certain circumstances, the joint probability distributions of the DA and population processes can be approximated by multivariate Gaussian distributions.
- To see why this is true, let us assume the existence of a system parameter Ω that measures the relative size of stochastic fluctuations in a Markovian reaction network, which we refer to as the system size.
- Fluctuations are small for large Ω .
- This is motivated by the fact that, in chemical reaction systems, stochastic fluctuations gradually diminish as the system approaches the thermodynamic limit
- **Thermodynamic limit:** The limit at which the population of each species and the system volume approach infinity in a way that the densities (concentrations) $\tilde{\mathbf{x}}(t) \triangleq \mathbf{x}(t)/\Omega$ do not change.
- We simply denote the thermodynamic limit as $\Omega \to \infty$.

Linear Noise Approximation

- In many situations, the propensity function of a reaction satisfies the following relationship:

$$\pi_m(\mathbf{x};\Omega) = \Omega\tilde{\pi}_m(\tilde{\mathbf{x}})$$

for some function $\tilde{\pi}_m$ which only depends on the density $\tilde{\mathbf{x}} \triangleq \mathbf{x}/\Omega$.

Linear Noise Approximation

- **Example 1:** The propensity function of the monomolecular reaction

$$X_1 \rightarrow X_2$$

is given by

$$\pi(x_1, x_2) = \kappa x_1 = \Omega(\kappa x_1 / \Omega) = \Omega \tilde{\pi}(\tilde{x}_1, \tilde{x}_2),$$

where Ω is the volume and $\tilde{\pi}(\tilde{x}_1, \tilde{x}_2) = \kappa \tilde{x}_1$.

Linear Noise Approximation

- **Example 2:** The propensity function of the bimolecular reaction with different reactants

$$X_1 + X_2 \rightarrow X_3$$

is given by

$$\pi(x_1, x_2) = \kappa x_1 x_2 = \Omega(\kappa\Omega)(x_1 / \Omega)(x_2 / \Omega) = \Omega\tilde{\pi}(\tilde{x}_1, \tilde{x}_2)$$

where Ω is the volume, $\tilde{\pi}(\tilde{x}_1, \tilde{x}_2) = k\tilde{x}_1\tilde{x}_2$, and $k = \kappa\Omega$ (it has been shown that k does not change with Ω).

Linear Noise Approximation

- **Example 3:** The propensity function of the bimolecular reaction with the same reactants

$$2X_1 \rightarrow X_2$$

is given by (for large enough x_1)

$$\pi(x_1, x_2) = \kappa x_1^2 / 2 = \Omega(\kappa\Omega)(x_1 / \Omega)^2 / 2 = \Omega\tilde{\pi}(\tilde{x}_1, \tilde{x}_2)$$

where Ω is the volume, $\tilde{\pi}(\tilde{x}_1, \tilde{x}_2) = k\tilde{x}_1^2 / 2$, and $k = \kappa\Omega$ (it has been shown that k does not change with Ω).

Linear Noise Approximation

- Since

$$\alpha_m(\mathbf{z}) = \pi_m(\mathbf{x}_0 + \mathbf{S}\mathbf{z})$$

we must also have

$$\alpha_m(\mathbf{z};\Omega) = \Omega\tilde{\alpha}_m(\tilde{\mathbf{z}})$$

where $\tilde{\mathbf{z}} = \mathbf{z}/\Omega$ and

$$\tilde{\alpha}_m(\tilde{\mathbf{z}}) = \tilde{\pi}_m(\tilde{\mathbf{x}}_0 + \mathbf{S}\tilde{\mathbf{z}})$$

Linear Noise Approximation

- To proceed, we assume that

"signal-plus-noise" *ansatz*

$$\tilde{Z}_m(t;\Omega) = \zeta_m(t) + \frac{1}{\sqrt{\Omega}}\Xi_m(t), \quad t > 0, m = 1, 2, \ldots, M$$

- $\tilde{Z}_m(t;\Omega)$ is the density $Z_m(t)/\Omega$ of the DA process.
- $\Xi_m(t)$ is a noise component that quantifies the fluctuations associated with the DA process.
- $\zeta_m(t)$ is a deterministic process that satisfies:

$$\frac{d\zeta_m(t)}{dt} = \tilde{\alpha}_m(\zeta(t)), \quad t > 0, m = 1, 2, \ldots, M$$

macroscopic equations

Linear Noise Approximation

$$\tilde{Z}_m(t;\Omega) = \zeta_m(t) + \frac{1}{\sqrt{\Omega}}\Xi_m(t), \quad t > 0, m = 1, 2, \ldots, M$$

- For each Ω, this equation decomposes the random DA density into a deterministic component and an additive noise component.
- The equation is based on the premise that random fluctuations diminish to zero as fast as $1/\sqrt{\Omega}$.
- In contrast to the exact equation $Z_m(t) = \mu_Z(m;t) + W_m(t)$ (used by the MA method), the previous equation must be justified.
- This can be done by a central limit theorem for the behavior of the probability density function of the DA density process, as $\Omega \to \infty$.

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

Linear Noise Approximation

- It can be shown that, for sufficiently large Ω, the dynamic evolution of the probability density function $p_{\Xi}(\xi;t)$ of the noise vector $\Xi(t)$ is approximately governed by the following linear Fokker-Planck equation:

$$\frac{\partial p_{\Xi}(\xi;t)}{\partial t} = \frac{1}{2}\sum_{m=1}^{M} \tilde{\alpha}_m(\zeta(t)) \frac{\partial^2 p_{\Xi}(\xi;t)}{\partial \xi_m^2} - \sum_{m=1}^{M}\sum_{m'=1}^{M} \frac{\partial \tilde{\alpha}_m(\zeta(t))}{\partial \zeta_{m'}} \frac{\partial [\xi_{m'} p_{\Xi}(\xi;t)]}{\partial \xi_m}$$

initialized with $p_{\Xi}(\xi;0) = \Delta(\xi)$.

Dirac delta function

https://en.wikipedia.org/wiki/Fokker-Planck_equation

Linear Noise Approximation

- In this case, the noise vector process $\boldsymbol{\Xi}(t)$ will be approximately Gaussian at each time t with zero mean and covariance matrix $\mathbf{C}_{\Xi}(t)$ that satisfies the Lyapunov matrix differential equation

$$\frac{d\mathbf{C}_{\Xi}(t)}{dt} = \mathbf{A}(t) + \mathbf{G}(t)\mathbf{C}_{\Xi}(t) + \mathbf{C}_{\Xi}(t)\mathbf{G}^{T}(t)$$

initialized with $C_{\Xi}(0) = \mathbf{0}$.

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

Linear Noise Approximation

$$\frac{d\mathbf{C}_{\Xi}(t)}{dt} = \mathbf{A}(t) + \mathbf{G}(t)\mathbf{C}_{\Xi}(t) + \mathbf{C}_{\Xi}(t)\mathbf{G}^{T}(t)$$

- In this equation, $\mathbf{A}(t)$ and $\mathbf{G}(t)$ are two matrices with elements

$$a_{m,m'}(t) = \tilde{\alpha}_m(\boldsymbol{\zeta}(t))\delta(m - m')$$

$$g_{m,m'}(t) = \frac{\partial \tilde{\alpha}_m(\boldsymbol{\zeta}(t))}{\partial \zeta_{m'}}$$

Kronecker delta

Linear Noise Approximation

$$\tilde{Z}_m(t;\Omega) = \zeta_m(t) + \frac{1}{\sqrt{\Omega}}\Xi_m(t)$$

$$Z_m(t;\Omega) = \Omega\tilde{Z}_m(t;\Omega)$$

Gaussian

- Consequently, the DA process $\mathbf{Z}(t)$ is approximately multivariate Gaussian (for sufficiently large Ω) with

$$\text{mean:} \qquad \boldsymbol{\mu}_Z(t) = \Omega\boldsymbol{\zeta}(t)$$

$$\text{covariance matrix:} \quad \mathbf{C}_Z(t) = \Omega\mathbf{C}_\Xi(t)$$

Linear Noise Approximation

- Because of the "signal-plus-noise" ansatz

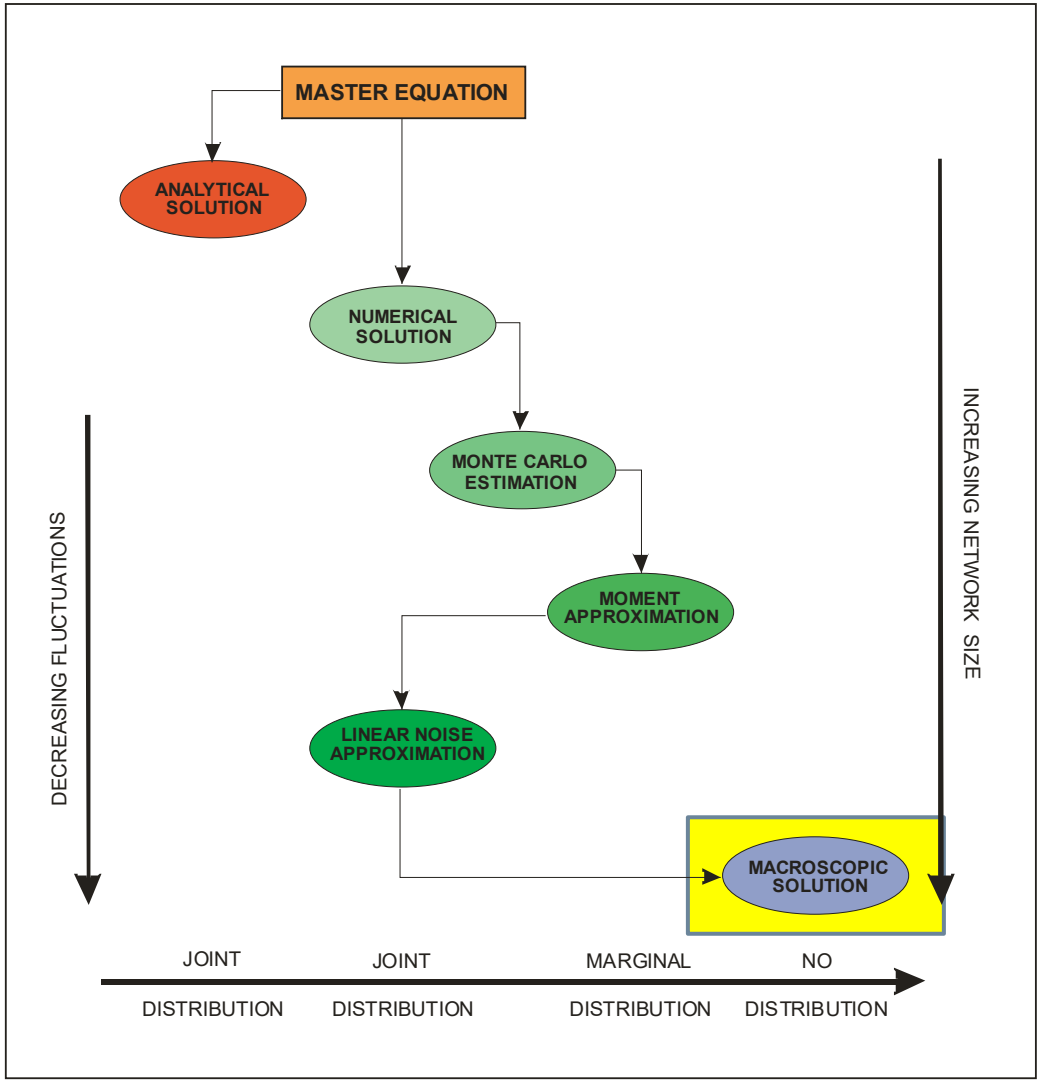
$$\tilde{Z}_m(t;\Omega) = \zeta_m(t) + \frac{1}{\sqrt{\Omega}}\Xi_m(t)$$

  the resulting technique is known as the linear noise approximation (LNA) method.

- In sharp contrast to the MA method, the LNA method decouples the computation of the means from the computation of the covariances.

- It turns out that the LNA method is substantially faster than Monte Carlo estimation and can be used to provide a rapid assessment of the statistical behavior of some Markovian reaction networks.

Available Methods



Macroscopic Solution

- For large nonlinear reaction networks, the MA and LNA methods can become computationally intractable.
- Evaluation of the covariances requires solving a system of $\mathcal{O}(M^2)$ differential equations.
- If that turns out to be the case, then the only option left to characterize the dynamic behavior of the reaction network is in terms of DA or population densities by using, for example, the macroscopic (fluctuation-free) system of M differential equations

$$\frac{d\zeta_m(t)}{dt} = \tilde{\alpha}_m(\zeta(t)), \quad t > 0, m = 1, 2, ..., M$$

macroscopic equations

Macroscopic Solution

- As a matter of fact

$$\tilde{Z}_m(t;\Omega) = \zeta_m(t) + \frac{1}{\sqrt{\Omega}}\Xi_m(t)$$

implies that the DA density process $\tilde{\mathbf{Z}}(t)$ converges in distribution to $\boldsymbol{\zeta}(t)$ as $\Omega \to \infty$.

- On the other hand, the difference between the DA density dynamics predicted by the macroscopic system and the MA method grows as Ω decreases !!

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

Macroscopic Solution

- Indeed, we have

$$\frac{d\mu_Z(m;t)}{dt} = \mathrm{E}\left[\alpha_m(\mathbf{Z}(t))\right] = \alpha_m(\boldsymbol{\mu}_Z(t)) + T_m(\boldsymbol{\mu}_Z(t))$$

$$\frac{d\zeta_m(t)}{dt} = \tilde{\alpha}_m(\boldsymbol{\zeta}(t))$$

$$\alpha_m(\mathbf{z}) = \Omega\tilde{\alpha}_m(\mathbf{z}/\Omega)$$

- This implies [since $\Omega^{-1}\alpha_m(\boldsymbol{\mu}_Z(t)) = \tilde{\alpha}_m(\tilde{\boldsymbol{\mu}}_Z(t))$]

$$\frac{d\tilde{\mu}_Z(m;t)}{dt} = \tilde{\alpha}_m(\tilde{\boldsymbol{\mu}}_Z(t)) + \frac{1}{\Omega}T_m(\boldsymbol{\mu}_Z(t))$$

$$\frac{d\zeta_m(t)}{dt} = \tilde{\alpha}_m(\boldsymbol{\zeta}(t))$$

$$\tilde{\mu}_Z(m;t) = \frac{\mu_Z(m;t)}{\Omega}$$

Macroscopic Solution

- In the limit as $\Omega \to \infty$, we have that

$$\frac{d\tilde{\mu}_Z(m;t)}{dt} = \tilde{\alpha}_m(\tilde{\boldsymbol{\mu}}_Z(t)) + \frac{1}{\Omega} T_m(\boldsymbol{\mu}_Z(t))$$
$$\frac{d\zeta_m(t)}{dt} = \tilde{\alpha}_m(\boldsymbol{\zeta}(t))$$
$$\tilde{\mu}_Z(m;t) = \frac{\mu_Z(m;t)}{\Omega}$$

$$\frac{d\tilde{\mu}_Z(m;t)}{dt} = \tilde{\alpha}_m(\tilde{\boldsymbol{\mu}}_Z(t))$$
$$\frac{d\zeta_m(t)}{dt} = \tilde{\alpha}_m(\boldsymbol{\zeta}(t))$$

in which case $\zeta_m(t) = \tilde{\mu}_Z(m;t)$.

- However, $\zeta_m(t) \neq \tilde{\mu}_Z(m;t)$ for finite values of Ω .

- For small Ω, the difference $\zeta_m(t) - \tilde{\mu}_Z(m;t)$ may be significant, and the macroscopic equation may fail to correctly predict the mean density dynamics of the DA process.

Macroscopic Solution

- Similarly to the DA density process, the population density process $\tilde{\mathbf{X}}(t;\Omega)$ converges in distribution, as $\Omega \to \infty$, to the deterministic process $\boldsymbol{\chi}(t)$ that satisfies the following macroscopic equations:

$$\frac{d\chi_n(t)}{dt} = \sum_{m=1}^{M} s_{nm}\tilde{\pi}_m(\boldsymbol{\chi}(t)), \quad t > 0, n = 1, 2, ..., N$$

where $\tilde{\pi}_m(\tilde{\mathbf{x}}) = \Omega^{-1}\pi_m(\Omega\tilde{\mathbf{x}})$.

Hierarchical ME Approximation

- When the propensity functions of a Markovian reaction network satisfy $\pi_m(\mathbf{x};\Omega) = \Omega\tilde{\pi}_m(\mathbf{x}/\Omega)$, the macroscopic solution, the LNA method, and the MA method provide a hierarchy of approximations to the ME.
- At large values of Ω, close to the thermodynamic limit, the macroscopic equations may provide a sufficiently accurate description of the reaction network.
- For smaller values of Ω, the LNA method will be preferable.
- For even smaller values of Ω, the MA method must be employed.
- Unfortunately, there is currently no effective way to determine the range of Ω values for which each approach is valid.
- Moreover, for very small values of Ω, these approximations may not be accurate and Monte Carlo simulation methods should be employed instead.