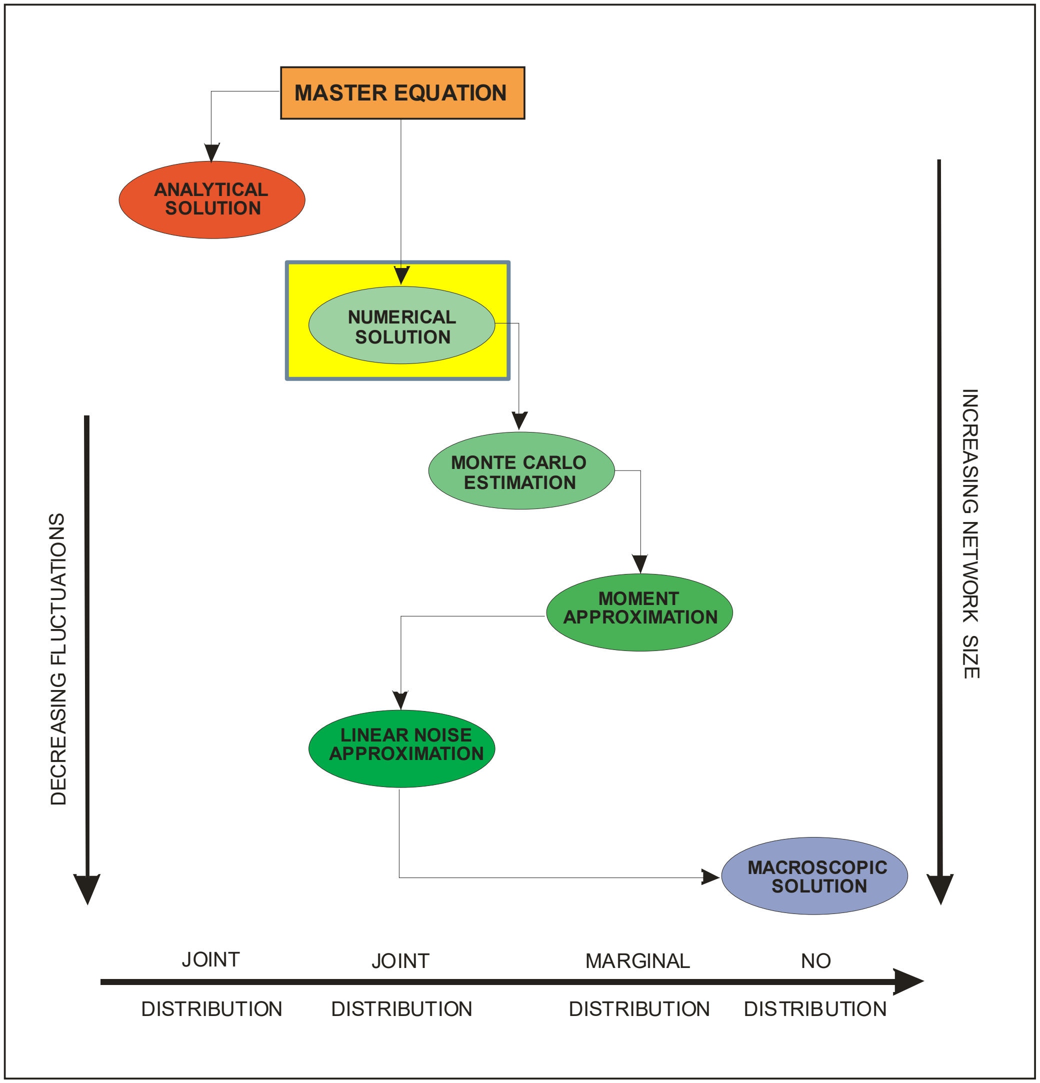
LECTURE #5

JOHN GOUTSIAS
WHITAKER BIOMEDICAL ENGINEERING INSTITUTE
THE JOHNS HOPKINS UNIVERSITY
BALTIMORE, MD 21218

SOLVING THE MASTER EQUATION – PART 2

Available Methods



Numerical Solution

- The ME

$$\frac{\partial p_X(\mathbf{x};t)}{\partial t} = \sum_{m=1}^{M} \{\pi_m(\mathbf{x}-\mathbf{s}_m)p_X(\mathbf{x}-\mathbf{s}_m;t) - \pi_m(\mathbf{x})p_X(\mathbf{x};t)\}, \quad t > 0$$

of the population process can be expressed as a <u>linear</u> system of coupled first-order differential equations:

$$\boxed{\frac{d\mathbf{p}(t)}{dt} = \mathbf{P}\mathbf{p}(t), \quad t > 0}$$

  - $\mathbf{p}(t)$ is a $K \times 1$ vector that contains the nonzero probabilities $p_X(\mathbf{x};t)$.
  - $\mathbf{P}$ is a large $K \times K$ <u>sparse</u> matrix whose structure can be inferred from the ME.

Numerical Solution

- For large networks, matrix $\mathbf{P}$ is highly sparse.
- When the columns of the net stoichiometric matrix $\mathbf{S}$ are all different from each other, the i-th column of $\mathbf{P}$ contains at most $M+1$ nonzero elements.
- The off-diagonal elements are given by

$$\pi_m(\mathbf{x}_i) > 0, \text{ for } m = 1, 2, \ldots, M,$$

where $\mathbf{x}_i$ is the i-th state.
- The diagonal element is given by

$$-\sum_{m=1}^{M} \pi_m(\mathbf{x}_i) < 0$$

- Consequently, the elements of each column of matrix $\mathbf{P}$ sum to zero.

Example

- Consider a Markovian reaction network comprised of <u>five</u> species and the following <u>five</u> reactions $(N = M = 5)$:

$$X_1 + X_2 \xrightarrow{\kappa_1 x_1 x_2} X_3$$
$$X_3 \xrightarrow{\kappa_2 x_3} X_1 + X_2$$
$$X_4 \xrightarrow{\kappa_3 x_4} X_3$$
$$X_4 \xrightarrow{\kappa_4 x_4} X_5$$
$$X_5 \xrightarrow{\kappa_5 x_5} X_4$$

$$\mathbf{S} = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 \\ 1 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & -1 & 1 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\left\{ \mathbf{x}_1 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}, \mathbf{x}_2 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}, \mathbf{x}_3 = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \mathbf{x}_4 = \begin{bmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \right\}$$

state-space

always initialized with $\mathbf{x}(0) = \mathbf{x}_1$

$$\frac{d\mathbf{p}(t)}{dt} = \mathbf{P}\mathbf{p}(t)$$

$$\mathbf{P} = \begin{bmatrix} -\kappa_5 & \kappa_4 & 0 & 0 \\ \kappa_5 & -(\kappa_3 + \kappa_4) & 0 & 0 \\ 0 & \kappa_3 & -\kappa_2 & \kappa_1 \\ 0 & 0 & \kappa_2 & -\kappa_1 \end{bmatrix} \qquad \mathbf{p}(t) = \begin{bmatrix} p(\mathbf{x}_1;t) \\ p(\mathbf{x}_2;t) \\ p(\mathbf{x}_3;t) \\ p(\mathbf{x}_4;t) \end{bmatrix}$$

Example

$$\pi_1(\mathbf{x}) = \kappa_1 x_1 x_2$$
$$\pi_2(\mathbf{x}) = \kappa_2 x_3$$
$$\pi_3(\mathbf{x}) = \kappa_3 x_4$$
$$\pi_4(\mathbf{x}) = \kappa_4 x_4$$
$$\pi_5(\mathbf{x}) = \kappa_5 x_5$$

$$\mathbf{x}_1 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}$$

$$\mathbf{x}_1 - \mathbf{s}_4 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ 0 \\ -1 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} = \mathbf{x}_2$$

impossible states

$$\begin{aligned}
\frac{\partial p_X(\mathbf{x}_1;t)}{\partial t} &= \pi_1(\mathbf{x}_1 - \mathbf{s}_1)\cancel{p_X}(\mathbf{x}_1 - \mathbf{s}_1;t) - \pi_1(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&\quad + \pi_2(\mathbf{x}_1 - \mathbf{s}_2)\cancel{p_X}(\mathbf{x}_1 - \mathbf{s}_2;t) - \pi_2(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&\quad + \pi_3(\mathbf{x}_1 - \mathbf{s}_3)\cancel{p_X}(\mathbf{x}_1 - \mathbf{s}_3;t) - \pi_3(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&\quad + \pi_4(\mathbf{x}_1 - \mathbf{s}_4)p_X(\mathbf{x}_1 - \mathbf{s}_4;t) - \pi_4(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&\quad + \pi_5(\mathbf{x}_1 - \mathbf{s}_5)\cancel{p_X}(\mathbf{x}_1 - \mathbf{s}_5;t) - \pi_5(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&= \pi_4(\mathbf{x}_1 - \mathbf{s}_4)p_X(\mathbf{x}_1 - \mathbf{s}_4;t) - \pi_1(\mathbf{x}_1)\cancel{p_X}(\mathbf{x}_1;t) \\
&\quad - \pi_2(\mathbf{x}_1)\cancel{p_X}(\mathbf{x}_1;t) - \pi_3(\mathbf{x}_1)\cancel{p_X}(\mathbf{x}_1;t) \\
&\quad - \pi_4(\mathbf{x}_1)\cancel{p_X}(\mathbf{x}_1;t) - \pi_5(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&= \pi_4(\mathbf{x}_1 - \mathbf{s}_4)p_X(\mathbf{x}_1 - \mathbf{s}_4;t) - \pi_5(\mathbf{x}_1)p_X(\mathbf{x}_1;t) \\
&= -\kappa_5 p_X(\mathbf{x}_1;t) + \kappa_4 p_X(\mathbf{x}_2;t) \quad \text{(first row of } \mathbf{P}\text{)}
\end{aligned}$$

zero propensities

Numerical Solution & FSP

- Note that (assuming $K < \infty$)

$$\frac{d\mathbf{p}(t)}{dt} = \mathbf{P}\mathbf{p}(t) \quad \Leftrightarrow \quad \mathbf{p}(t) = \exp(t\mathbf{P})\mathbf{p}(0)$$

- Therefore, solving the ME is equivalent to evaluating the <u>matrix exponential</u> $\exp(t\mathbf{P})$.
- Unfortunately, this computation is not possible, since the size of matrix $\mathbf{P}$ is prohibitively large.
- To reduce the size, we could employ a method known as <u>finite-state projection</u> (FSP) method.
- FSP requires appropriate truncation of the state-space to determine the possible (non-zero probability) set of states and development of a computationally feasible algorithm for calculating the matrix exponential.

Numerical Solution – KSA Method

- One of the best methods for computing matrix exponentials is known as the Krylov subspace approximation (KSA) method.
- For a sufficiently small time-step $\tau > 0$, this method approximates the vector $\mathbf{p}(t+\tau) = \exp(\tau \mathbf{P})\mathbf{p}(t)$ when $\mathbf{P}$ is a large and sparse matrix.
- This is done by using a polynomial series expansion of the form:

$$\hat{\mathbf{p}}(t+\tau) = c_0 \mathbf{p}(t) + c_1 \tau \mathbf{P}\mathbf{p}(t) + \cdots + c_{K_0-1}(\tau \mathbf{P})^{K_0-1}\mathbf{p}(t)$$

Numerical Solution – KSA Method

$$\hat{\mathbf{p}}(t+\tau) = c_0\mathbf{p}(t) + c_1\tau\mathbf{P}\mathbf{p}(t) + \cdots + c_{K_0-1}(\tau\mathbf{P})^{K_0-1}\mathbf{p}(t)$$

- The coefficients $c_0, c_1, \ldots, c_{K_0-1}$ are estimated by minimizing the <u>least-squares error</u> (LSE) $\| \mathbf{p}(t+\tau) - \hat{\mathbf{p}}(t+\tau) \|_2^2$.
- The optimal K_0-order polynomial approximation of

  $\mathbf{p}(t+\tau)$ is a point in the K_0-dimensional Krylov subspace:

$$\mathcal{K}(t) = \operatorname{span}\left\{\mathbf{p}(t), \tau\mathbf{P}\mathbf{p}(t), \ldots, (\tau\mathbf{P})^{K_0-1}\mathbf{p}(t)\right\}$$

Numerical Solution – KSA Method

- This element can be approximated by

$$\hat{\mathbf{p}}(t+\tau) = \| \mathbf{p}(t) \|_2 \mathbf{V}(t) \exp\{\tau \mathbf{H}(t)\} \mathbf{e}_1$$

- $\mathbf{e}_1$ is the first column of the $K_0 \times K_0$ identity matrix.
- $\mathbf{V}(t)$ is a $K \times K_0$ matrix whose columns form an orthonormal basis for the Krylov subspace $\mathcal{K}(t)$.
- $\mathbf{H}(t)$ is a $K_0 \times K_0$ Hessenberg matrix (upper triangular with an extra subdiagonal).
- Both matrices are computed by a well-known procedure in linear algebra, known as the Arnoldi procedure.

Numerical Solution – KSA Method

- The KSA method reduces the problem of calculating the exponential of a large and sparse $K \times K$ matrix $\mathbf{P}$ to the problem of calculating the exponential of the much smaller and dense $K_0 \times K_0$ matrix $\mathbf{H}$ ($K_0 = 30 - 50$ is usually sufficient for many applications).
- Computation of the reduced-size problem can be done by standard methods.
- The KSA method can be recursively implemented using:

$$
\begin{aligned}
\hat{\mathbf{p}}((j+1)\tau) &= \exp\{\tau \mathbf{P}\}\, \hat{\mathbf{p}}(j\tau) \\
&= \|\hat{\mathbf{p}}(j\tau)\|_2\, \mathbf{V}(j\tau) \exp\{\tau \mathbf{H}(j\tau)\} \mathbf{e}_1
\end{aligned}
$$

Numerical Solution – FSP/KSA Method

- Practical implementation of the FSP algorithm is difficult.
- The main issue here is the size of the truncated state-space, which is usually very large.
- For this reason, these methods are most often limited to <u>relatively small</u> reaction networks.
- The KSA method is based on several approximations whose cumulative effect may appreciably affect its accuracy, numerical stability and computational efficiency.
- The KSA method <u>does not</u> guarantee that $\hat{\mathbf{p}}(j\tau)$ is a probability vector !!

Numerical Solution – Implicit Euler Method

- The ME

$$\frac{\partial p_Z(\mathbf{z};t)}{\partial t} = \sum_{m=1}^{M} \left\{ a_m(\mathbf{z}-\mathbf{e}_m) p_Z(\mathbf{z}-\mathbf{e}_m;t) - a_m(\mathbf{z}) p_Z(\mathbf{z};t) \right\}, \quad t>0$$

associated with the DA process can be expressed as a linear system of coupled first-order differential equations:

$$\boxed{\frac{d\mathbf{q}(t)}{dt} = \mathbf{Q}\mathbf{q}(t), \quad t>0}$$

  - $\mathbf{q}(t)$ is a $Q \times 1$ vector that contains the nonzero probabilities $p_Z(\mathbf{z};t)$.
  - $\mathbf{Q}$ is a large $Q \times Q$ sparse matrix whose structure can be inferred from the ME.

Numerical Solution – Implicit Euler Method

- Ordering the elements in the Z state-space lexicographically results in a matrix $\mathbf{Q}$ that is lower triangular.
- In this case, and for a given time step $\tau > 0$, we can use the implicit Euler method for solving differential equations to estimate $\mathbf{q}(t)$ at discrete time points $j\tau$.
- Given an estimate $\hat{\mathbf{q}}(j\tau)$ of $\mathbf{q}(j\tau)$, we can obtain an estimate $\hat{\mathbf{q}}((j+1)\tau)$ of $\mathbf{q}((j+1)\tau)$ by solving the following system of linear equations:

$$(\mathbf{I} - \tau\mathbf{Q})\hat{\mathbf{q}}((j+1)\tau) = \hat{\mathbf{q}}(j\tau)$$

$Q \times Q$ identity matrix

https://en.wikipedia.org/wiki/Lexicographic_order
https://en.wikipedia.org/wiki/Backward_Euler_method

Numerical Solution – Implicit Euler Method

- This is because, from the differential equation

$$\frac{d\mathbf{q}(t)}{dt} = \mathbf{Q}\mathbf{q}(t)$$

we have that

$$\frac{d\mathbf{q}((j+1)\tau)}{dt} = \mathbf{Q}\mathbf{q}((j+1)\tau)$$

$$\Rightarrow \frac{\mathbf{q}((j+1)\tau) - \mathbf{q}(j\tau)}{\tau} \simeq \mathbf{Q}\mathbf{q}((j+1)\tau)$$

$$\Rightarrow (\mathbf{I} - \tau\mathbf{Q})\mathbf{q}((j+1)\tau) \simeq \mathbf{q}(j\tau)$$

Numerical Solution – Implicit Euler Method

- The previous step is possible for <u>any</u> value of τ and can be efficiently done by a standard [forward substitution algorithm](https://en.wikipedia.org/wiki/Triangular_matrix#Forward_and_back_substitution).
- The resulting method is <u>always</u> stable, producing a <u>valid</u> probability vector at each iteration.
- Its accuracy can be controlled by a <u>single</u> parameter, the step size τ.
- We can obtain $\hat{p}_X(\mathbf{x};t) = \sum_{\mathbf{z} \in \mathcal{B}(\mathbf{x})} \hat{p}_Z(\mathbf{z};t)$, where $\mathcal{B}(\mathbf{x}) = \{\mathbf{z} : \mathbf{x} = \mathbf{x}_0 + \mathbf{S}\mathbf{z}\}$

https://en.wikipedia.org/wiki/Triangular_matrix#Forward_and_back_substitution

Numerical Solution – Implicit Euler Method

- The implicit Euler (IE) method is computationally superior to KSA when the cardinality of the DA state-space is <u>not much larger</u> than the cardinality of the population state-space.
- This is not always possible: the DA process is <u>non-decreasing</u> as opposed to the population numbers that can either increase or decrease.
- The IE method can only be used when the number of reaction events are sufficiently constrained or remain small during a time interval of interest.

Numerical Solution – Implicit Euler Method

- **<u>Example</u>:** In the case of the simple SIR model of epidemiology, the net stoichiometric matrix is given by

$$\mathbf{S} = \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{bmatrix}$$

and the matrix $\mathbf{S}^T\mathbf{S}$ is invertible.

- Consequently, there is a one to one correspondence between the X and Z state-spaces, since

$$\mathbf{X}(t) = \mathbf{x}_0 + \mathbf{S}\mathbf{Z}(t) \Leftrightarrow \mathbf{Z}(t) = (\mathbf{S}^T\mathbf{S})^{-1}\mathbf{S}^T[\mathbf{X}(t) - \mathbf{x}_0]$$

- In this case, the IE method is preferable to the KSA method.

Numerical Solution – Implicit Euler Method

- **Example**: Modeling a well-documented 1978 influenza epidemic in an English boarding school.
- We can use the IE method to compute the exact solution of the underlying ME.
- There is a total of 763 students in the school.
- Stochastic SIR model:

$$X_1 \leftrightarrow \mathrm{S} \qquad X_2 \leftrightarrow \mathrm{I} \qquad X_3 \leftrightarrow \mathrm{R}$$

$$X_1 + X_2 \to 2X_2 \qquad X_2 \to X_3$$

$$\pi_1(x_1, x_2, x_3) = \kappa_1 x_1 x_2 \qquad \pi_2(x_1, x_2, x_3) = \kappa_2 x_2$$

$$\kappa_1 = 0.00218 / \mathrm{day}$$

$$\kappa_2 = 0.44036 / \mathrm{day}$$

Numerical Solution – Implicit Euler Method

- Initial conditions:

$$X_1(0) = 762$$
$$X_2(0) = 1$$
$$X_3(0) = 0$$

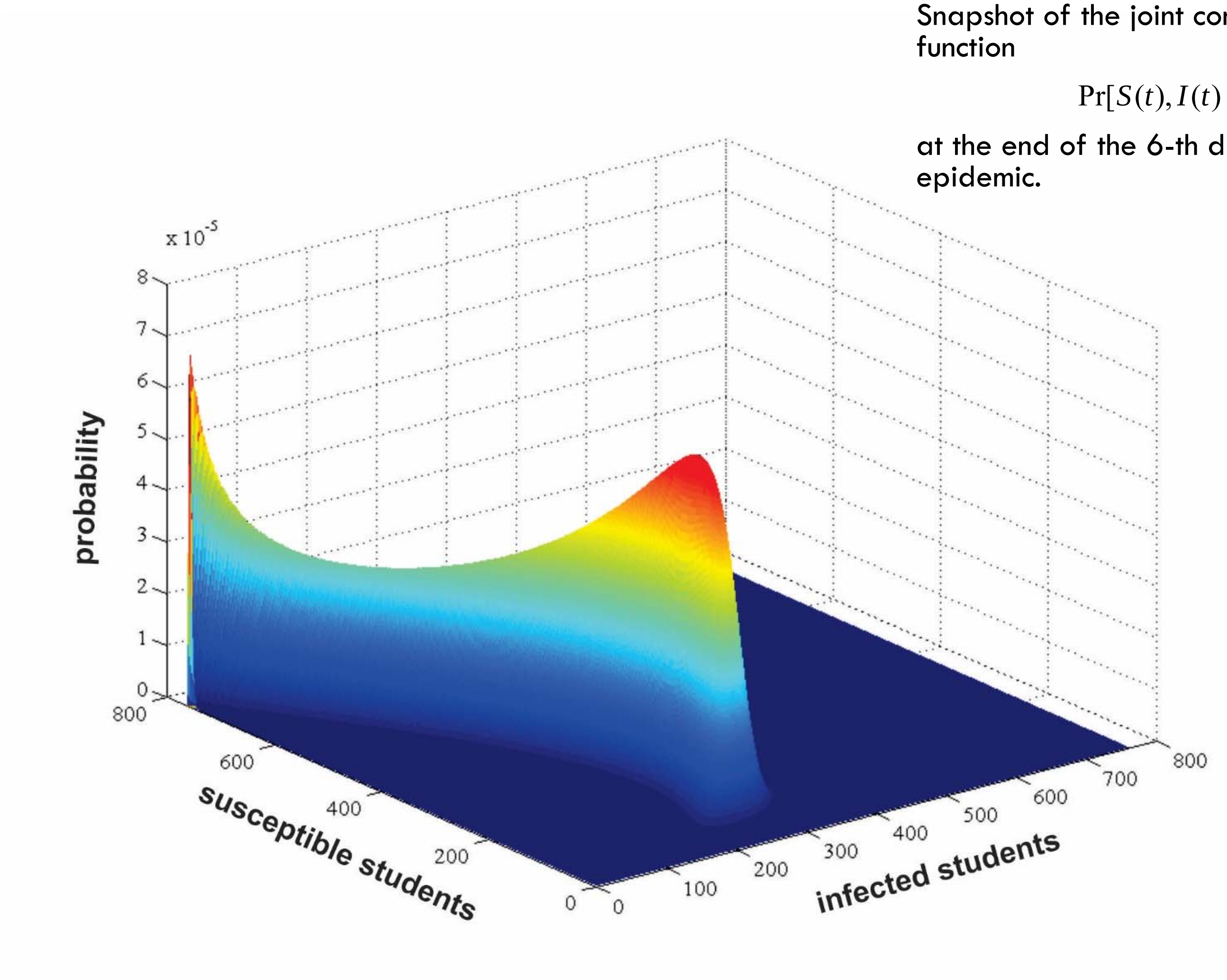
$$X_1 + X_2 \rightarrow 2X_2$$
$$X_2 \rightarrow X_3$$

- The Z state space is a 2-D rectangular grid of points from $(0,0)$ to $(762,763)$.
- It contains a total of $763 \times 764 = 582{,}932$ points.
- KSA method $\Rightarrow$ 4,328 seconds of CPU time.
- IE method $\Rightarrow$ 52 seconds of CPU time.

Numerical Solution – Implicit Euler Method

see video-4-1.mov

Numerical Solution – Implicit Euler Method

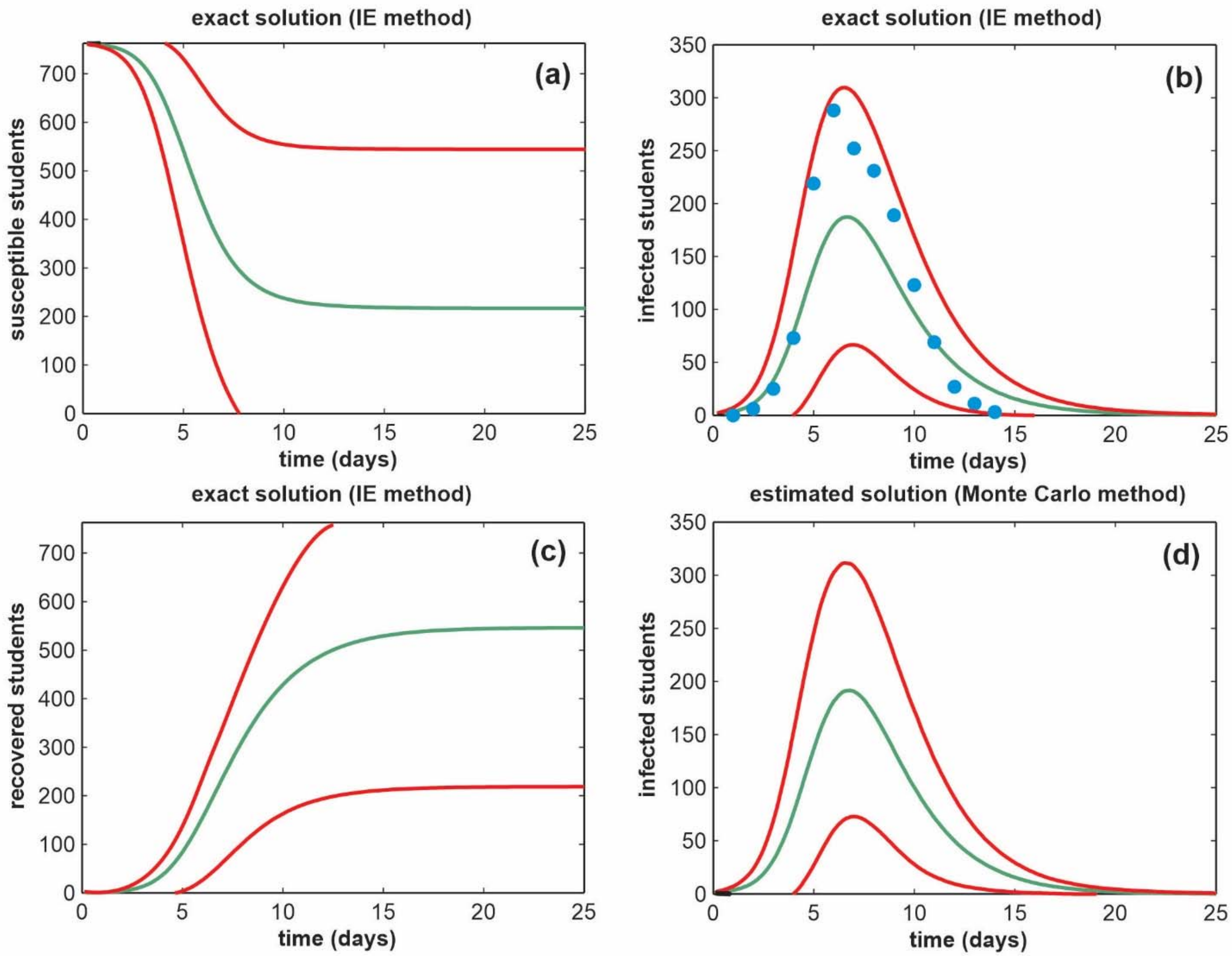


Snapshot of the joint conditional probability mass function

$$\Pr[S(t), I(t) \mid I(t) > 0]$$

at the end of the 6-th day of the influenza epidemic.

Numerical Solution – Implicit Euler Method



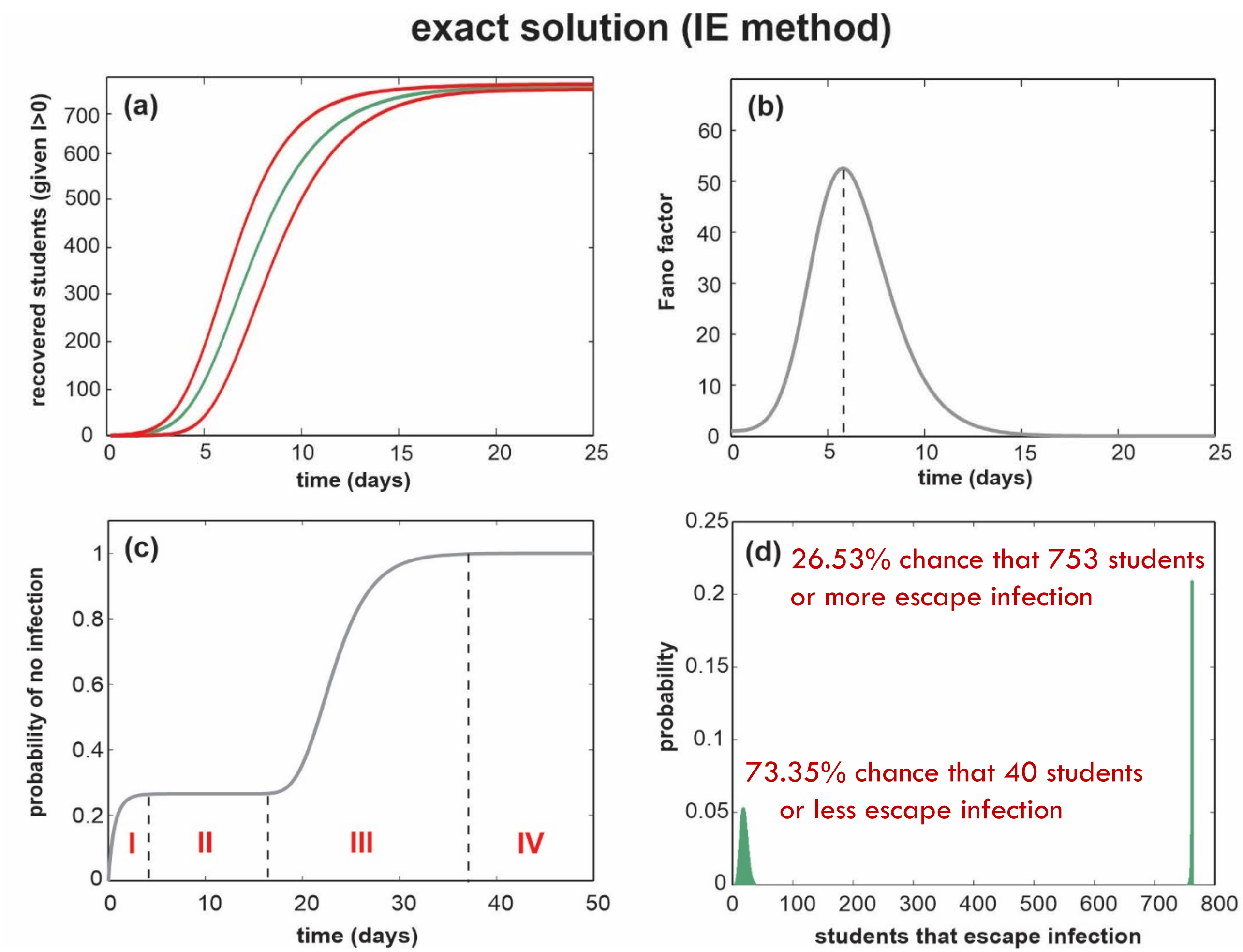
The mean profiles (green lines) and the ± 1 standard deviation profiles (red lines) of

(a) Susceptible students.
(b) Infected students.
(c) Recovered students.

Monte Carlo estimates of the mean and standard deviation profiles of the infected students are depicted in (d).

Blue circles in (b) mark available data.

Numerical Solution – Implicit Euler method



(a) Evolution of the expected number of recovered students (green line) and the ± 1 standard deviations (red lines), given that at least one student is always infected.

(b) The Fano factor (variance/mean) associated with the results in (a) as a function of time.

(c) Dynamic evolution of the probability of no infection $\Pr[I(t)=0]$

(d) The probability mass function $\Pr[S(\infty)=s, I(\infty)=0]$ at steady-state.