THE SLOW-SCALE SSA

Yang Cao, Dan Gillespie, Linda Petzold

With thanks to:

Muruhan Rathinam, Hana El-Samad, John Doyle

and

E. Haseltine & J. Rawlings, *J. Chem. Phys* **117**, 6959 (2002)

Chris Rao & Adam Arkin, *J. Chem. Phys* **118**, 4999 (2003)

Support:

AFOSR/DARPA, MSI/Sandia, DOE, NSF, ICB/ARO

MOTIVATION

- Cellular reactions often take place on *vastly different time scales*.
  - Fast and slow reactions. Fast and slow species.
  - Fast reactions usually "less important" than slow ones.
  - *Example*: $S_1 \underset{c_2}{\overset{c_1}{\rightleftarrows}} S_2$ (fast) and $S_2 \xrightarrow{c_3} S_3$ (slow) .

- SSA will spend most of its time simulating the fast reactions.

  - Is there a way to skip over the fast reactions, and directly simulate only the slow ones?

SOME ISSUES

- Do “fast” and “slow” apply to *reactions* or to *species*?
- How can the fast/slow parts of the system be separated?
- Are there fast/slow *subsystems* that obey *Markovian* master equations?
- What does *theory* say a multi-scale SSA should do?

ASSUMPTIONS

- A well-stirred system at constant volume and temperature.
- N species $\{S_1,\ldots,S_N\}$. System state $X(t)=\big(X_1(t),\ldots,X_N(t)\big)$,

  $X_i(t)$ ≡ number of S_i molecules at time t.
- M reactions $\{R_1,\ldots,R_M\}$. Propensity functions $a_1,\ldots,a_M$,

  $a_j(x)dt$ ≡ probability, given $X(t)=x$, that R_j will fire in next dt.
- When R_j fires, the system's state changes from x to $x+\nu_j$,

  $\nu_j \equiv \big(\nu_{1j},\ldots,\nu_{Nj}\big)$, $\{\nu_{ij}\}$ is the "stoichiometric matrix"

➢ Some reactions/species are *very much faster* than the others.

- OUR PROPOSED APPROACH -

1st Partition the *reactions*: $\{R_1,\ldots,R_M\} = \left(R^{\mathrm{f}}, R^{\mathrm{s}}\right)$

- Fast reactions $R^{\mathrm{f}} \equiv \left\{R_1^{\mathrm{f}},\ldots,R_{M_{\mathrm{f}}}^{\mathrm{f}}\right\}$.
- Slow reactions $R^{\mathrm{s}} \equiv \left\{R_1^{\mathrm{s}},\ldots,R_{M_{\mathrm{s}}}^{\mathrm{s}}\right\}$.
  - *Criterion*: $a_j^{\mathrm{f}}(x) \not\approx a_{j'}^{\mathrm{s}}(x) \quad \forall j, j'$ and for "most" x.

This criterion is loose, subject to later refinements.

2nd Partition the *species*: $\{S_1,\ldots,S_N\} = \left(S^{\mathrm{f}}, S^{\mathrm{s}}\right)$

$$X(t) = \left(X^{\mathrm{f}}(t), X^{\mathrm{s}}(t)\right)$$

- Fast species $S^{\mathrm{f}} \equiv \left\{S_1^{\mathrm{f}},\ldots,S_{N_{\mathrm{f}}}^{\mathrm{f}}\right\} \Rightarrow\ X^{\mathrm{f}}(t) \equiv \left\{X_1^{\mathrm{f}}(t),\ldots,X_{N_{\mathrm{f}}}^{\mathrm{f}}(t)\right\}$.
- Slow species $S^{\mathrm{s}} \equiv \left\{S_1^{\mathrm{s}},\ldots,S_{N_{\mathrm{s}}}^{\mathrm{s}}\right\} \Rightarrow\ X^{\mathrm{s}}(t) \equiv \left\{X_1^{\mathrm{s}}(t),\ldots,X_{N_{\mathrm{s}}}^{\mathrm{s}}(t)\right\}$.
  - *Criterion*: A species is *fast* if its population *gets changed* by at least one fast reaction; otherwise, the species is *slow*.

Some subtle points:

- ✓ A slow species cannot get changed by a fast reaction, but a fast species can get changed by a slow reaction.
- ✓ $a_j^{\mathrm{f}}(x) = a_j^{\mathrm{f}}(x^{\mathrm{f}}, x^{\mathrm{s}})$, $a_j^{\mathrm{s}}(x) = a_j^{\mathrm{s}}(x^{\mathrm{f}}, x^{\mathrm{s}})$.
- ✓ A fast species population need not be “large”.

3rd Define the "virtual fast process" $\hat{X}^{\mathrm{f}}(t)$.

- $\hat{X}^{\mathrm{f}}(t)$ the fast species populations driven by *only* the fast reactions.
- $\hat{X}^{\mathrm{f}}(t)$ is $X^{\mathrm{f}}(t)$ with all the slow reactions "switched off".
- $X^{\mathrm{f}}(t)$ is a *physically real* but *non-Markovian* process.
  It does not satisfy an ordinary master equation.
- $\hat{X}^{\mathrm{f}}(t)$ is a *physically fictitious* but *Markovian* process.
  It *does* satisfy an ordinary master equation: The ME for the fast species, driven by only the fast reactions, with all slow species populations held constant.
- The CME for $\hat{X}^{\mathrm{f}}(t)$ will be simpler than the CME for $X(t)$.
  It determines $\hat{P}(x^{\mathrm{f}}, t \mid x_0^{\mathrm{f}}, x_0^{\mathrm{s}}, t_0) \equiv \Pr\left\{\hat{X}^{\mathrm{f}}(t) = x^{\mathrm{f}} \mid X(t_0) = (x_0^{\mathrm{f}}, x_0^{\mathrm{s}})\right\}$.

4th Now impose *two conditions* on $\hat{X}^{\mathrm{f}}(t)$.

- ***Condition 1.*** $\hat{X}^{\mathrm{f}}(t)$ must be *stable*; i.e.,

$$\lim_{t\to\infty} \hat{P}(x^{\mathrm{f}}, t \,|\, x_0, t_0) \equiv \hat{P}(x^{\mathrm{f}}, \infty \,|\, x_0) \text{ must } \textit{exist}.$$

- ***Condition 2.*** $\hat{X}^{\mathrm{f}}(t) \to \hat{X}^{\mathrm{f}}(\infty)$ in a time that is *very small* compared to the time between *slow* reaction events.

- If changes in the initial choice of fast and slow reactions are required to secure these conditions, so be it.
- These conditions should be satisfiable whenever *stiffness* is present. Then the fast reactions will be "less important" than the slow ones, so skipping over them will make sense.
- If these conditions *cannot* be satisfied, the fast reactions are *not* less important than the slow ones, and skipping over them is not a good idea.

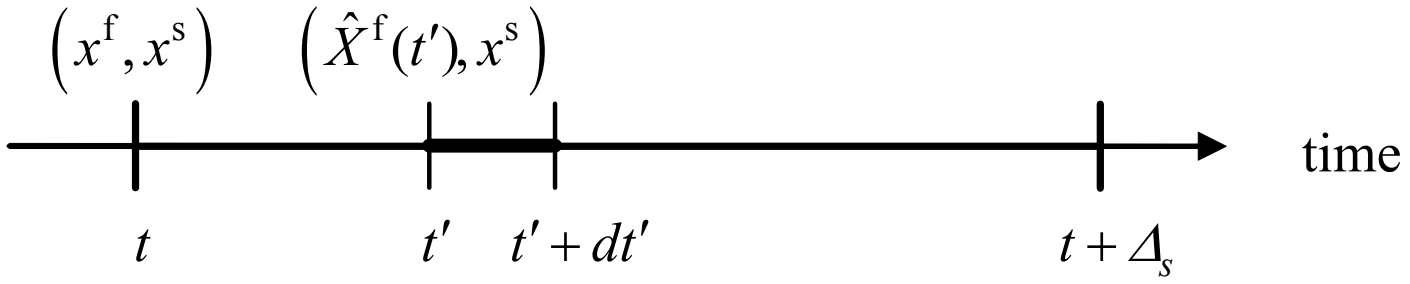
5th A new theorem.

Theorem: With $X(t) = (x^{\mathrm{f}}, x^{\mathrm{s}})$, let Δ_{s} be a time increment that is *large* compared to the time for $\hat{X}^{\mathrm{f}}(t) \to \hat{X}^{\mathrm{f}}(\infty)$, but *small* compared to the time between *slow* reactions. Then the probability that one R_j^{s} will occur in $[t, t+\Delta_{\mathrm{s}})$ is *approximately* $\overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}})\,\Delta_{\mathrm{s}}$, where

$$\overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}}) \approx \sum_{x^{\mathrm{f}\prime}} \hat{P}(x^{\mathrm{f}\prime}, \infty | x^{\mathrm{f}}, x^{\mathrm{s}})\, a_j^{\mathrm{s}}(x^{\mathrm{f}\prime}, x^{\mathrm{s}}) .$$

- $\overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}})$ is called the ***slow-scale propensity function*** for R_j^{s}.
- It's the *average* of $a_j^{\mathrm{s}}(x^{\mathrm{f}}, x^{\mathrm{s}})$ w.r.t. $\hat{X}^{\mathrm{f}}(\infty)$.
- It *replaces* $a_j^{\mathrm{s}}(x^{\mathrm{f}}, x^{\mathrm{s}})$ on the time scale of the *slow* reactions.
- For at least some systems, it can be computed.
- Knowing it and $\hat{X}^{\mathrm{f}}(\infty)$ will allow us to *approximately* simulate the evolution of the system *one slow reaction at a time*.

Proof of the theorem:



$$\mathrm{Prob}\left\{R_j^{\mathrm{s}} \text{ in } [t', t'+dt')\right\} \approx a_j^{\mathrm{s}}\left(\hat{X}^{\mathrm{f}}(t'), x^{\mathrm{s}}\right) dt'.$$

$$\begin{aligned}
\mathrm{Prob}\left\{R_j^{\mathrm{s}} \text{ in } [t, t+\Delta_{\mathrm{s}})\right\} &\approx \int_{t'=t}^{t+\Delta_{\mathrm{s}}} a_j^{\mathrm{s}}\left(\hat{X}^{\mathrm{f}}(t'), x^{\mathrm{s}}\right) dt' \\
&\approx \left\{\frac{1}{\Delta_{\mathrm{s}}} \int_{t}^{t+\Delta_{\mathrm{s}}} a_j^{\mathrm{s}}\left(\hat{X}^{\mathrm{f}}(t'), x^{\mathrm{s}}\right) dt'\right\} \Delta_{\mathrm{s}} \\
&\approx \left\{\textbf{temporal} \text{ average of } a_j^{\mathrm{s}}\left(\hat{X}^{\mathrm{f}}(t'), x^{\mathrm{s}}\right)\right\} \Delta_{\mathrm{s}} \\
&\approx \left\{\textbf{ensemble} \text{ average of } a_j^{\mathrm{s}}\left(\hat{X}^{\mathrm{f}}(\infty), x^{\mathrm{s}}\right)\right\} \Delta_{\mathrm{s}} \\
&= \left\{\sum_{x^{\mathrm{f}\prime}} \hat{P}(x^{\mathrm{f}\prime}, \infty | x^{\mathrm{f}}, x^{\mathrm{s}})\, a_j^{\mathrm{s}}(x^{\mathrm{f}\prime}, x^{\mathrm{s}})\right\} \Delta_{\mathrm{s}}. \quad \textbf{QED}
\end{aligned}$$

Will need to compute $\overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}};x^{\mathrm{f}}) \equiv \left\langle a_j^{\mathrm{s}}(\hat{X}^{\mathrm{f}}(\infty), x^{\mathrm{s}}) \right\rangle$:

- Never requires more than the *first two moments* of $\hat{X}^{\mathrm{f}}(\infty)$.
- Those two moments can often be adequately approximated in terms of the solution of the deterministic RRE.

Will need to generate random samples of $\hat{X}^{\mathrm{f}}(\infty)$:

- This seldom can be done exactly.
- *If* we can estimate $\left\langle \hat{X}^{\mathrm{f}}(\infty) \right\rangle$ and $\mathrm{var}\left\{ \hat{X}^{\mathrm{f}}(\infty) \right\}$, we can often *approximate* $\hat{X}^{\mathrm{f}}(\infty)$ as a *normal* random variable.
- There are ways of estimating $\left\langle \hat{X}^{\mathrm{f}}(\infty) \right\rangle$ and $\mathrm{var}\left\{ \hat{X}^{\mathrm{f}}(\infty) \right\}$ that don't require a full computation of $\hat{P}(x^{\mathrm{f}\prime}, \infty | x^{\mathrm{f}}, x^{\mathrm{s}})$.
- This is an important problem area, requiring further work.

The Slow-Scale SSA

Initialize: Given $X(t_0) = (x_0^{\mathrm{f}}, x_0^{\mathrm{s}})$, set $t \leftarrow t_0$, $x^{\mathrm{f}} \leftarrow x_0^{\mathrm{f}}$, $x^{\mathrm{s}} \leftarrow x_0^{\mathrm{s}}$.

1. In state $(x^{\mathrm{f}}, x^{\mathrm{s}})$ at time t, evaluate $\overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}})$ for $j = 1, \ldots, M_{\mathrm{s}}$.

2. Compute $\overline{a}_0^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}}) = \sum_{j=1}^{M_{\mathrm{s}}} \overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}})$. With $r_1, r_2 = \mathrm{U}(0,1)$, take

$$\tau = \frac{1}{\overline{a}_0^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}})} \ln\left(\frac{1}{r_1}\right),$$

$$j = \text{ smallest integer satisfying } \sum_{j'=1}^{j} \overline{a}_{j'}^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}}) \geq r_2 \, \overline{a}_0^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}}).$$

3. Advance system to the *next slow* reaction (R_j^{s} at time $t + \tau$):

$$t \leftarrow t + \tau,$$

$$\begin{cases} x_i^{\mathrm{s}} \leftarrow x_i^{\mathrm{s}} + \nu_{ij}^{\mathrm{ss}} & (i = 1, \ldots, N_{\mathrm{s}}), \\ x_i^{\mathrm{f}} \leftarrow x_i^{\mathrm{f}} + \nu_{ij}^{\mathrm{fs}} & (i = 1, \ldots, N_{\mathrm{f}}), \end{cases}$$

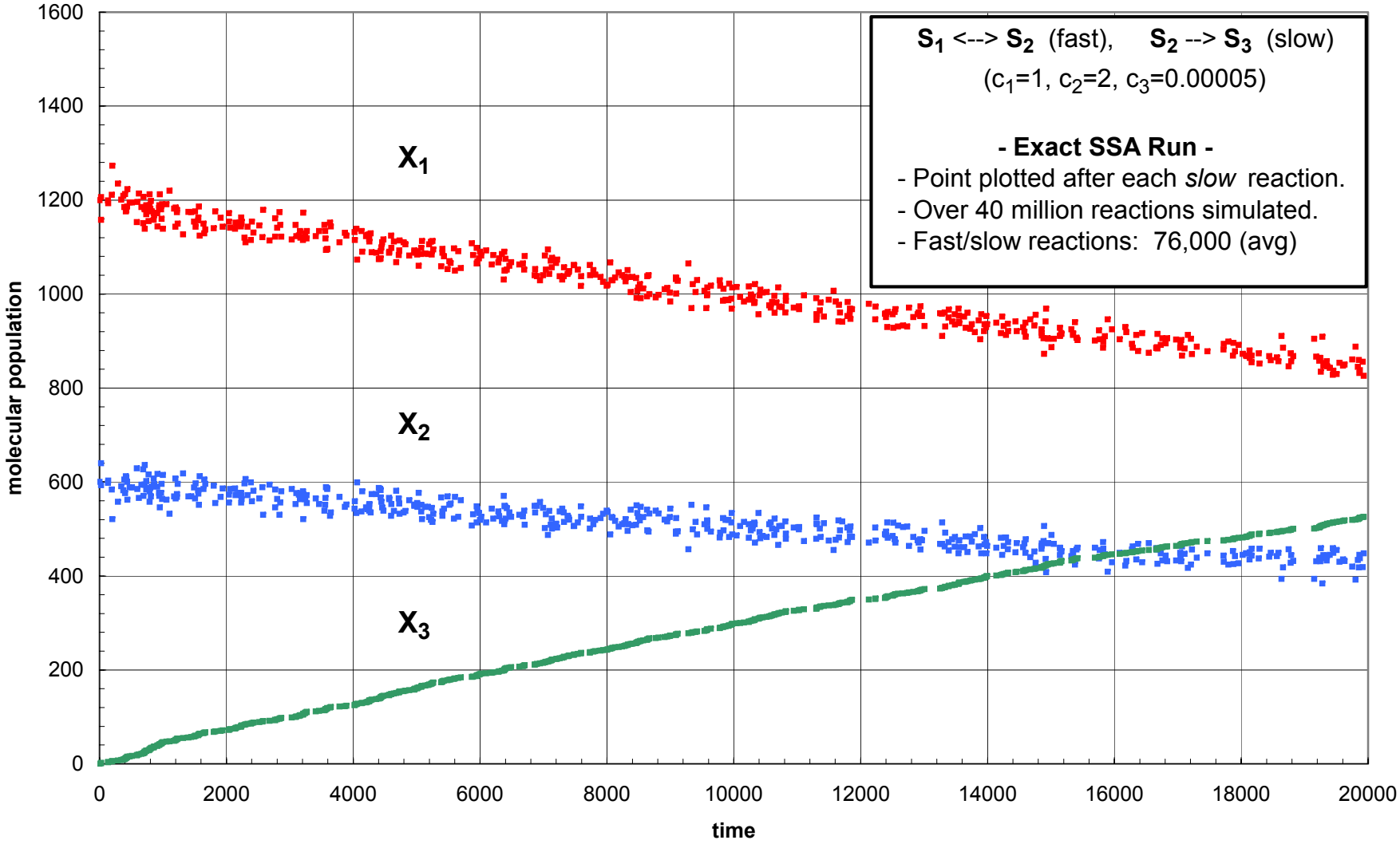
Then "relax" the fast variables: $x^{\mathrm{f}} \leftarrow$ sample of $\hat{X}^{\mathrm{f}}(\infty)$.

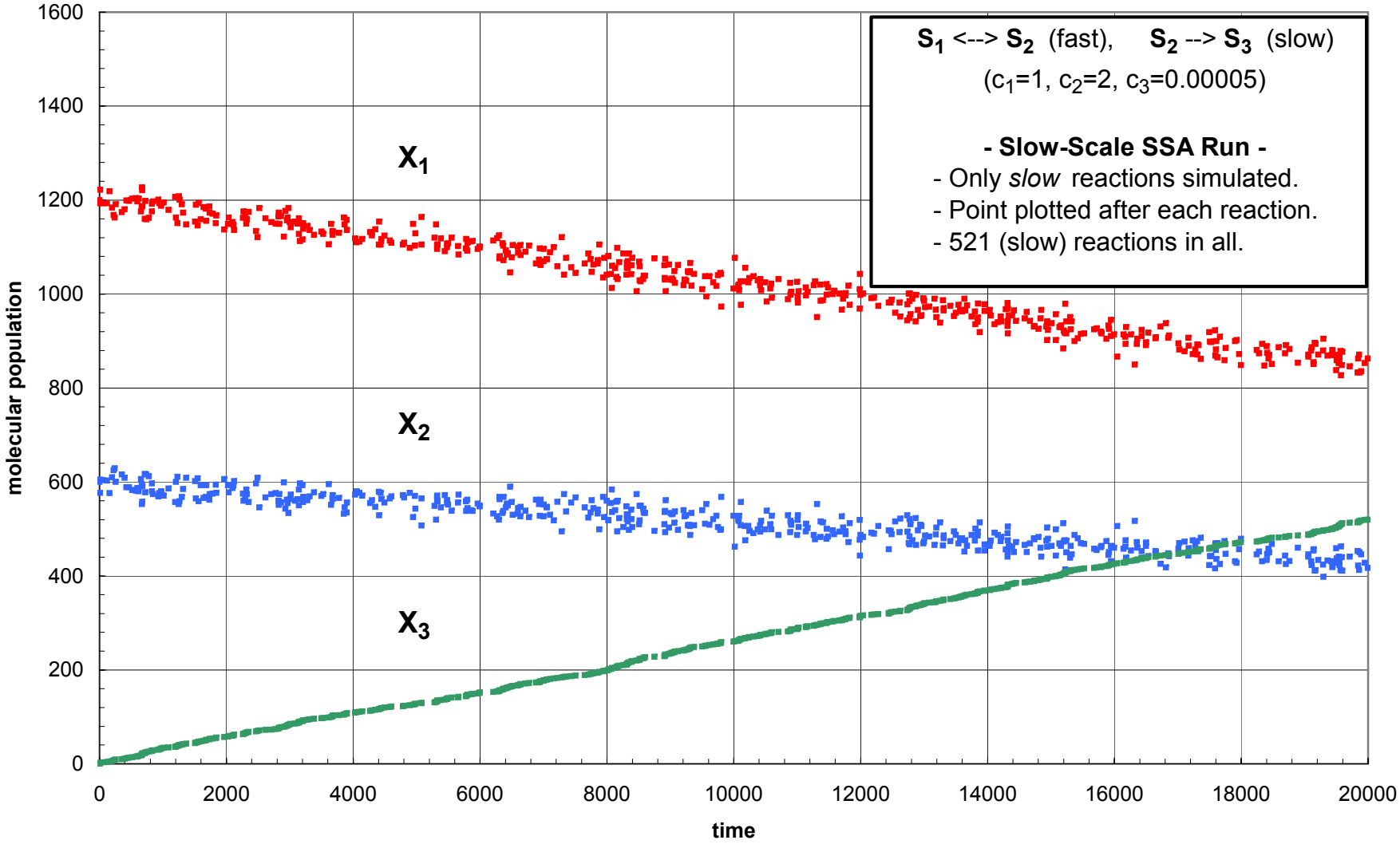
4. Record $X(t) = (x^{\mathrm{f}}, x^{\mathrm{s}})$ if desired. Then return to **1**, or else stop.

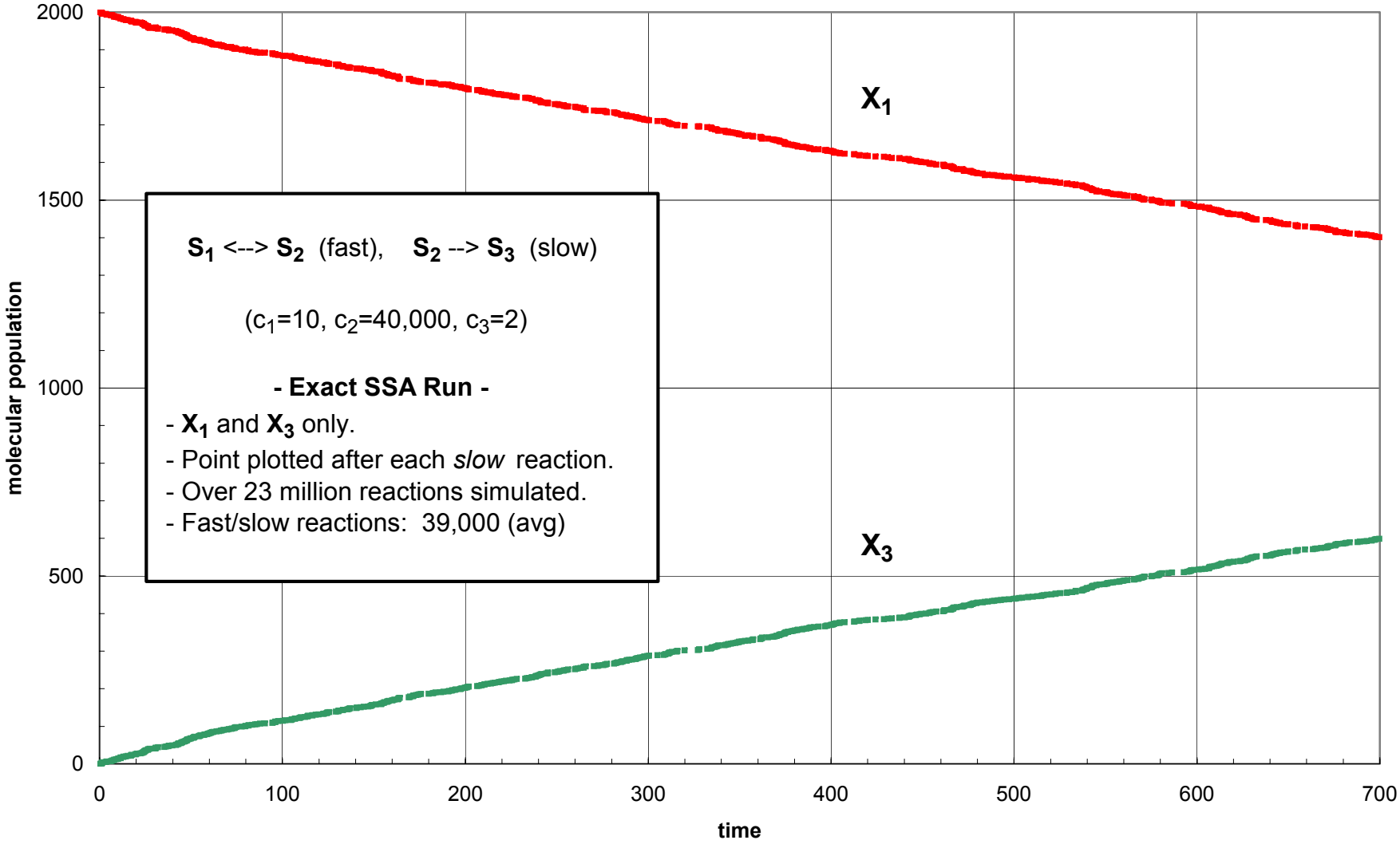
An Example:

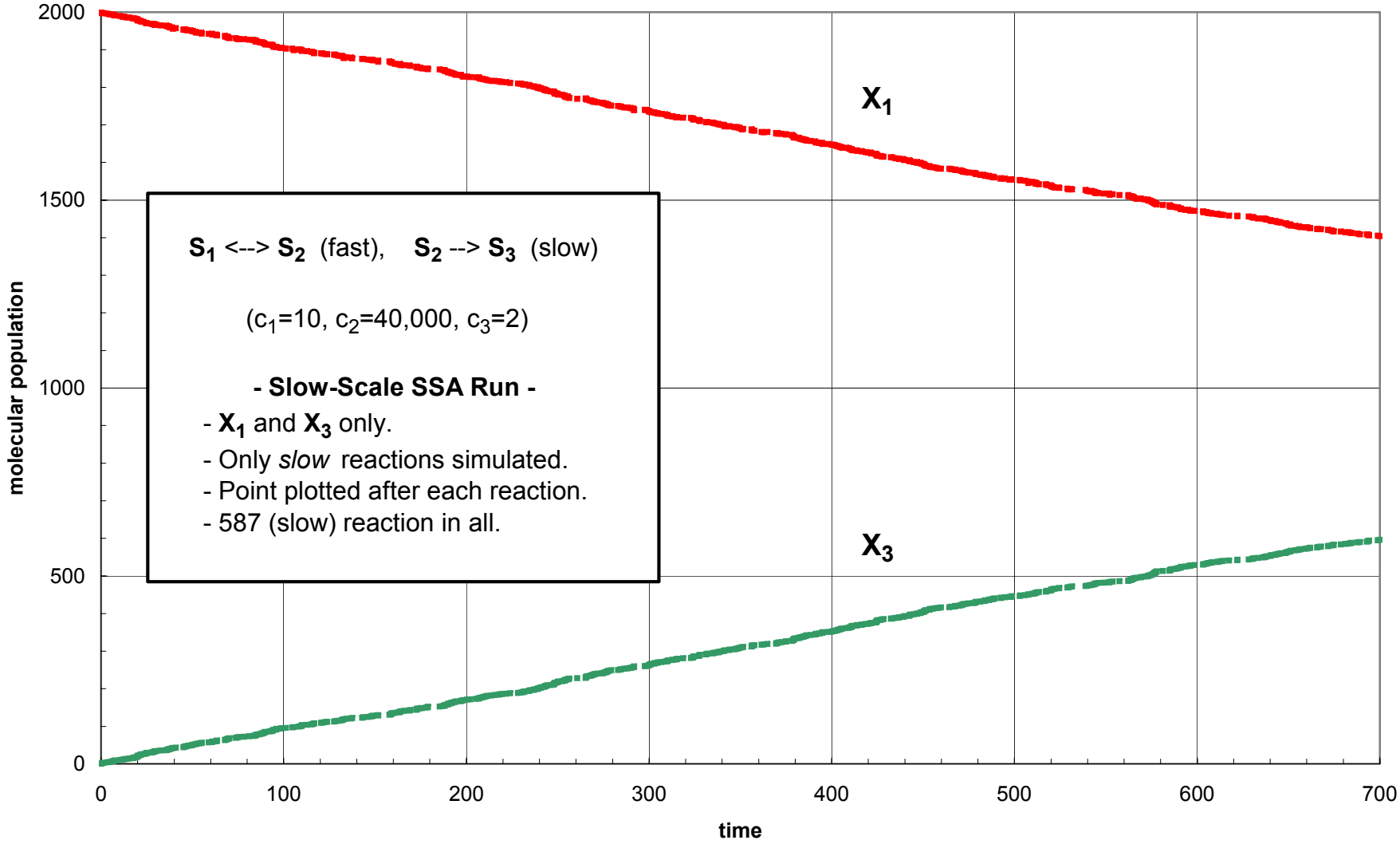
$$\begin{cases} S_1 \underset{c_2}{\overset{c_1}{\rightleftarrows}} S_2 \quad \text{(fast)} \\ S_2 \xrightarrow{c_3} S_3 \quad \text{(slow)} \end{cases}$$

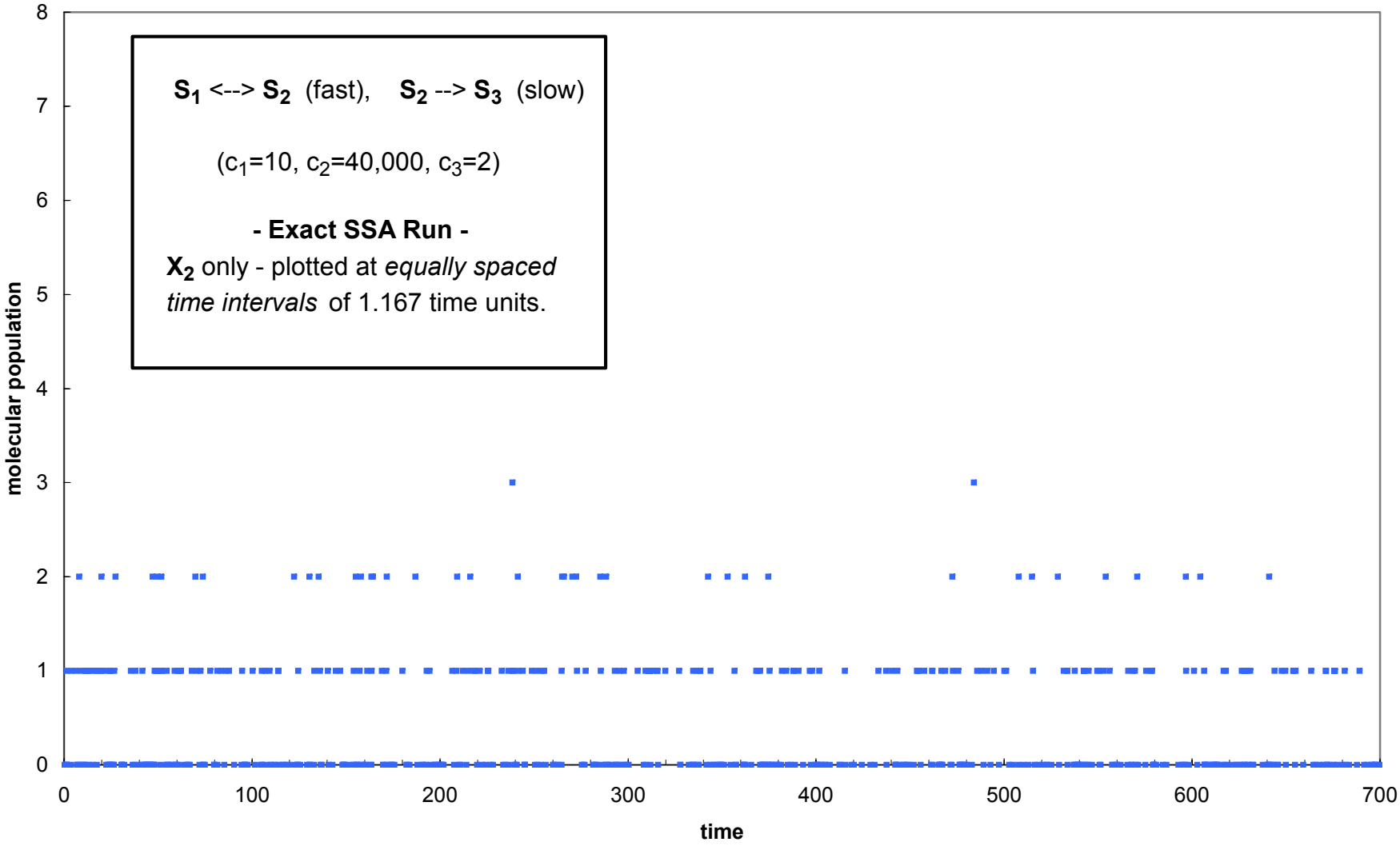
- $\hat{X}_1(t) + \hat{X}_2(t) = \text{const}.$ $\hat{X}^{\text{f}}(\infty)$ can be calculated *exactly*.
  - $\hat{X}_1(\infty)$ is *binomial*: mean $= \dfrac{c_2(x_1+x_2)}{c_1+c_2}$, variance $= \dfrac{c_1c_2(x_1+x_2)}{(c_1+c_2)^2}$.
  - $\hat{X}_2(\infty) = x_1 + x_2 - \hat{X}_1(\infty)$.
- $\overline{a}_3(x_3; x_1, x_2) = c_3 \left\langle \hat{X}_2(\infty) \right\rangle = \dfrac{c_3c_1(x_1+x_2)}{c_1+c_2}$.
- Relaxation time for $\hat{X}^{\text{f}}(t) \to \hat{X}^{\text{f}}(\infty)$ is $\approx 1/(c_1+c_2)$.
- Condition for using the ssSSA: $\dfrac{1}{c_1+c_2} \gg \dfrac{c_1+c_2}{c_3c_1(x_1+x_2)}$.

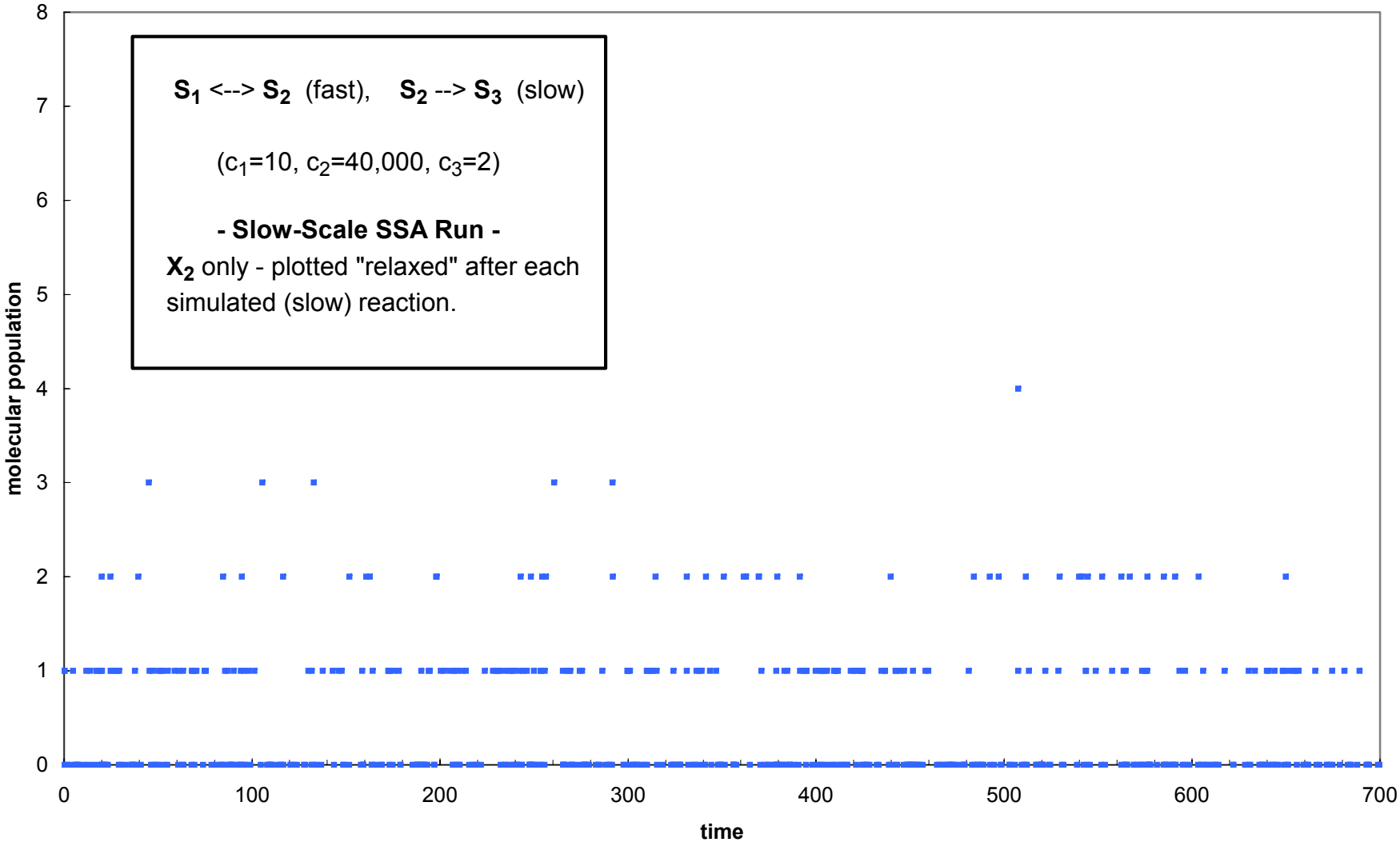

S1 <--> S2 (fast), S2 --> S3 (slow)
(c1=1, c2=2, c3=0.00005)
- Exact SSA Run -
- Point plotted after each slow reaction.
- Over 40 million reactions simulated.
- Fast/slow reactions: 76,000 (avg)
X1
X2
X3
molecular population
time
0
200
400
600
800
1000
1200
1400
1600
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000


S1 <--> S2 (fast), S2 --> S3 (slow)
(c1=1, c2=2, c3=0.00005)
- Slow-Scale SSA Run -
- Only slow reactions simulated.
- Point plotted after each reaction.
- 521 (slow) reactions in all.
X1
X2
X3
molecular population
time
0
200
400
600
800
1000
1200
1400
1600
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000


2000
1500
1000
500
0
molecular population
0
100
200
300
400
500
600
700
time
X1
X3
S1 <--> S2 (fast), S2 --> S3 (slow)
(c1=10, c2=40,000, c3=2)
- Exact SSA Run -
- X1 and X3 only.
- Point plotted after each slow reaction.
- Over 23 million reactions simulated.
- Fast/slow reactions: 39,000 (avg)


2000
1500
1000
500
0
molecular population
0
100
200
300
400
500
600
700
time
X1
X3
S1 <--> S2 (fast), S2 --> S3 (slow)
(c1=10, c2=40,000, c3=2)
- Slow-Scale SSA Run -
- X1 and X3 only.
- Only slow reactions simulated.
- Point plotted after each reaction.
- 587 (slow) reaction in all.


S1 <--> S2 (fast), S2 --> S3 (slow)
(c1=10, c2=40,000, c3=2)
- Exact SSA Run -
X2 only - plotted at equally spaced time intervals of 1.167 time units.
molecular population
time
0
1
2
3
4
5
6
7
8
0
100
200
300
400
500
600
700


S1 <--> S2 (fast), S2 --> S3 (slow)
(c1=10, c2=40,000, c3=2)
- Slow-Scale SSA Run -
X2 only - plotted "relaxed" after each simulated (slow) reaction.
molecular population
time
0
1
2
3
4
5
6
7
8
0
100
200
300
400
500
600
700

Another Example:

$$\begin{cases} S_1 + S_1 \underset{c_2}{\overset{c_1}{\rightleftharpoons}} S_2 \quad \text{(fast)} \\ S_1 \xrightarrow{c_3} \varnothing, \;\; S_2 \xrightarrow{c_4} S_3 \quad \text{(slow)} \end{cases}$$

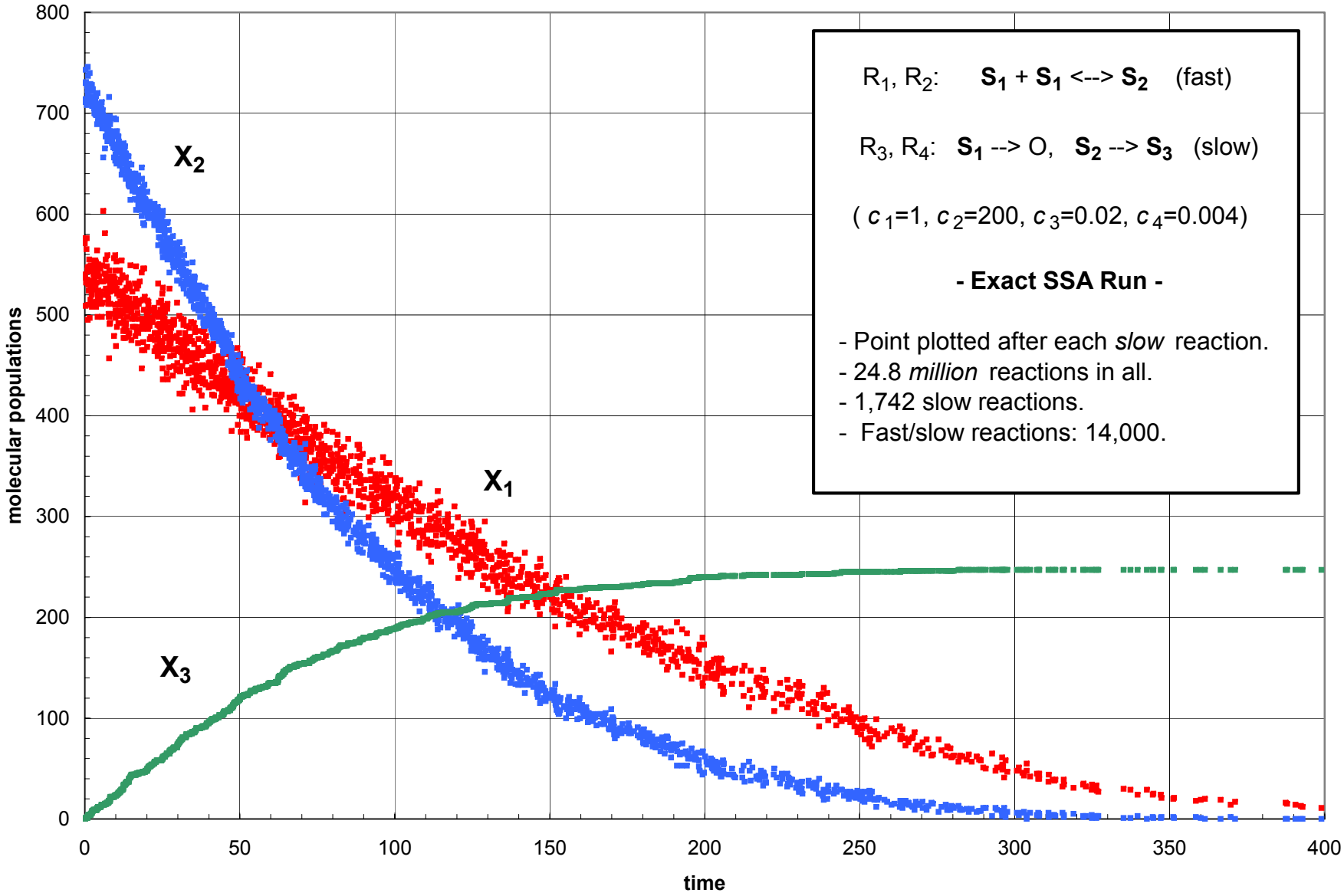
- The "decay-dimerizing" reactions, but in a *very stiff* regime.
- $\hat{X}_1(t) + 2\hat{X}_2(t) = \text{const}$. But no simple formula for $\hat{X}^{\text{f}}(\infty)$.
- Can approximate the mean and variance of $\hat{X}^{\text{f}}(\infty)$ as

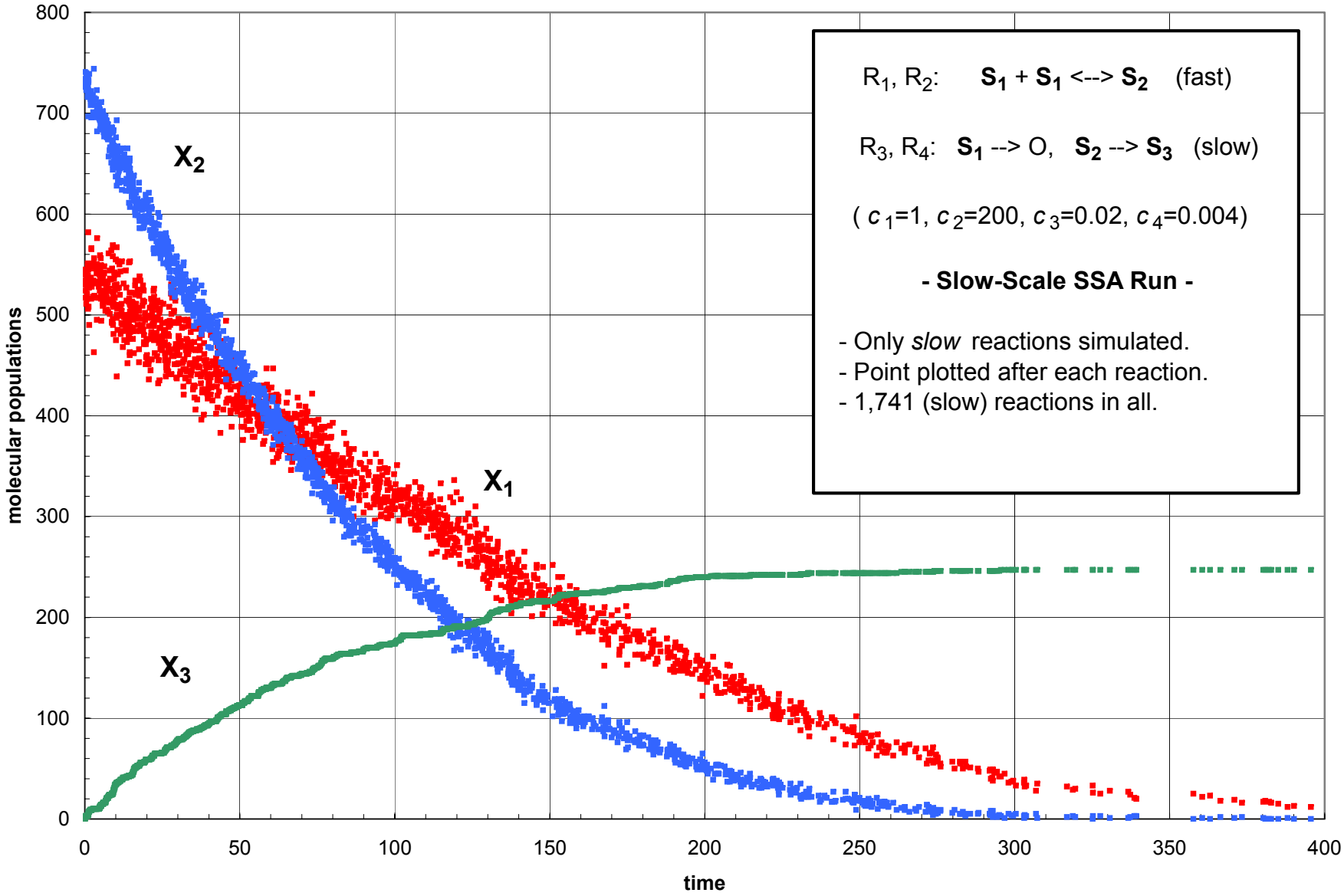
$$\left\langle \hat{X}_2(\infty) \right\rangle \approx \frac{1}{4}\left\{ \left(2(x_1 + 2x_2) + \frac{c_2}{c_1} \right) - \sqrt{\left(2(x_1 + 2x_2) + \frac{c_2}{c_1} \right)^2 - 4(x_1 + 2x_2)^2} \right\},$$

$$\text{var}\left\{ \hat{X}_2(\infty) \right\} \approx \frac{c_2 \left\langle \hat{X}_2(\infty) \right\rangle}{-4c_1 \left\langle \hat{X}_2(\infty) \right\rangle + c_1 \left(2(x_1 + 2x_2) + 3 \right) + c_2},$$

$$\hat{X}_1(\infty) = (x_1 + 2x_2) - 2\hat{X}_2(\infty).$$

- Slow-scale propensities: $\overline{a}_3(x) = c_3 \left\langle \hat{X}_1(\infty) \right\rangle, \quad \overline{a}_4(x) = c_4 \left\langle \hat{X}_2(\infty) \right\rangle.$
- Sample $\hat{X}_2(\infty)$ *approximately* as $\text{N}\left(\left\langle \hat{X}_2(\infty) \right\rangle, \text{var}\left\{ \hat{X}_2(\infty) \right\} \right)$.


800
700
600
500
400
300
200
100
0
molecular populations
0
50
100
150
200
250
300
350
400
time
X2
X1
X3
R1, R2: S1 + S1 <--> S2 (fast)
R3, R4: S1 --> O, S2 --> S3 (slow)
(c 1=1, c 2=200, c 3=0.02, c 4=0.004)
- Exact SSA Run -
- Point plotted after each slow reaction.
- 24.8 million reactions in all.
- 1,742 slow reactions.
- Fast/slow reactions: 14,000.


800
700
600
500
400
300
200
100
0
molecular populations
0
50
100
150
200
250
300
350
400
time
X2
X1
X3
R1, R2: S1 + S1 <--> S2 (fast)
R3, R4: S1 --> O, S2 --> S3 (slow)
(c 1=1, c 2=200, c 3=0.02, c 4=0.004)
- Slow-Scale SSA Run -
- Only slow reactions simulated.
- Point plotted after each reaction.
- 1,741 (slow) reactions in all.

SUMMARY

- Have produced a clear operational procedure for defining
  - fast and slow reactions,
  - fast and slow species,
  - a *virtual fast process* $\hat{X}^{\mathrm{f}}(t)$ (which is Markovian).
- Have elucidated the critical role of the two *stiffness conditions*:
  - $\hat{X}^{\mathrm{f}}(t)$ must be stable;
  - $\hat{X}^{\mathrm{f}}(t) \to \hat{X}^{\mathrm{f}}(\infty)$ very rapidly on the time scale of the slow reactions.
- Have established ***The Slow-Scale Propensity Function Theorem***:

  If the time scales of the fast and slow reactions are well separated, then on the time scale of the slow reactions $a_j^{\mathrm{s}}(x^{\mathrm{f}}, x^{\mathrm{s}})$ can be approximately replaced with $\overline{a}_j^{\mathrm{s}}(x^{\mathrm{s}}; x^{\mathrm{f}}) \approx \left\langle a_j^{\mathrm{s}}(\hat{X}^{\mathrm{f}}(\infty), x^{\mathrm{s}}) \right\rangle$.
- Leads to the ***Slow-Scale SSA***, which skips over all the fast reactions.

RESULTS SO FAR

- Showed for two simple systems that the ssSSA works well.

  - It greatly outperforms *explicit* tau-leaping on very stiff systems.

- Demonstrated that neither the *size* nor the *importance* of fluctuations can be inferred from molecular population levels alone.

- Clarified the source of the "high-frequency filtering" effect observed in the *E. coli* heat shock response mechanism.

FUTURE EFFORTS

- Apply the ssSSA to the enzyme-substrate reaction, and explore the connection with Michaelis-Menten kinetics.
- Investigate the relation between the ssSSA and *implicit* tau-leaping.
- Develop general methods for computing the asymptotic properties of common virtual fast processes.
- See about further accelerating the ssSSA by using regular tau-leaping as a follow-on procedure.