Structure and Approximation for Markov Chains in (Bio)chemical Kinetics

Bioinformatics
Informal Seminar
Hillary Term, 2006
Lecture 1 - Markov Processes
Topics

- Transition functions
- Infinitesimal generator
- Stoichiometry
- Gillespie’s algorithm
- Random time change
- Law of Mass Action
Markov Process

A random process \( \{X_t; t \geq 0\} \) having state space \( S \) is called a **time homogeneous Markov process** provided that there exists a function \( p \) so that

\[
P_x\{X_{t+s} \in A | X_u; u \leq t\} = P_x\{X_{t+s} \in A | X_t\} = p(s, X_t, A),
\]

\( p(s, x, A) \) is the probability that the process \( X \) lands in the set \( A \) at time \( s \) given that the process began at position \( x \) at time 0. We will stick to state spaces that are complete, separable metric spaces. Let \( \mathcal{B}(S) \) denote the Borel sets.

In practice, the function \( p \) is rarely known explicitly.
Transition functions

The function $p : [0, \infty) \times S \times B(S) \to [0, 1]$ called a \textit{time homogeneous transition function} satisfies,

1. for every $(t, x) \in [0, \infty) \times S$, $p(t, x, \cdot)$ is a probability measure,

2. for every $x \in S$, $p(0, x, \cdot) = \delta_x$,

3. for every $B \in B(S)$, $p(\cdot, \cdot, B)$ is measurable, and

4. (Chapman-Kolmogorov equation) for every $s, t \geq 0$, $x \in S$, and $B \in B(S)$,

$$p(t + s, x, B) = \int_S p(s, y, B)p(t, x, dy).$$
First order differential equations as trivial Markov processes.

Let $\{\vec{x}_t; t \geq 0\}$ satisfy

$$\frac{d}{dt} \vec{x} = F(\vec{x})$$

Choose $p(s, \vec{x}_0, A) = 1$ if the solution $\vec{x}_s$ to the ODE starting at $\vec{x}_0$ at time 0 is an element of $A$ and 0 if it is not to see that the solution is a Markov process.
Infinitesimal Transitions and the Generator

The stochastic nature of chemical kinetics is captured by the transitions rates

\[ P_x\{X_{\Delta t} = y\} = g(x, y)\Delta t + o(\Delta t), \ x \neq y. \]

The generator \( G \) is the rate of change of averages for a function \( f : S \to \mathbb{R} \) of the process.

\[ Gf(x) = \lim_{\Delta t \to 0} \frac{E_x f(X_{\Delta t}) - f(x)}{\Delta t} \]

where \( E_x \) and \( P_x \) denote the expectation and probability conditioned that the process begins at \( x \) at time 0.
To relate these two concepts, write

\[
Ex f(X_{\Delta t}) = \sum_{y \neq x} f(y)g(x, y)\Delta t + f(x)(1 - \sum_{y \neq x} g(x, y)\Delta t) + o(\Delta t)
\]

\[
Ex f(X_{\Delta t}) - f(x) = \sum_{y \neq x} g(x, y)(f(y) - f(x))\Delta t + o(\Delta t)
\]

\[
G f(x) = \sum_{y \in S} g(x, y)(f(y) - f(x))
\]

Thus, \( G \) can be written as an \textit{infinitesimal transition matrix}. The \( xy \)-entry \( x \neq y \) is \( g(x, y) \). The diagonal entry

\[
g(x, x) = -\sum_{y \neq x} g(x, y).
\]
Poisson Process

A *Poisson process* $\{N_t; \geq 0\}$ with parameter $\lambda$ is a jump Markov Process with state space $n \in \mathbb{N}$ and generator

$$Gf(n) = \lambda(f(n + 1) - f(n)).$$

**Exercise.** Show that for $m > 0$,

$$p(t, n, \{n + m\}) = \frac{(\lambda t)^m}{m!}e^{-\lambda t}$$

is the transition function for the Poisson process, parameter $\lambda$. 
Stoichiometry, the Accounting behind Chemistry

Consider the chemical process. $2A + B \rightarrow C$.

Thus 2 molecules of $A$ and one of $B$, the reagents, form one molecule of $C$ the product.

The state space for this process is $\vec{x} \in \mathbb{N}^3$ and the generator

$$Gf(x^A, x^B, x^C) = k(x^A, x^B, x^C)(f(x^A - 2, x^B - 1, x^C + 1) - f(x^A, x^B, x^C))$$

or

$$Gf(\vec{x}) = k(\vec{x})(f(\vec{x} + \vec{v}) - f(\vec{x}))$$

with stoichiometry $\vec{v} = (-2, -1, 1)$. 
If the mixture is *well stirred* (spatially homogeneous), then

$$k(x^A, x^B, x^C) \propto \left(\frac{x^A}{2}\right) x^B,$$

the number of choices under *sampling with replacement*.

If we have a collection of chemical processes, then we can record them in a table

<table>
<thead>
<tr>
<th>stoichiometry</th>
<th>rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\vec{v}_1$</td>
<td>$k_1(\vec{x})$</td>
</tr>
<tr>
<td>$\vec{v}_2$</td>
<td>$k_2(\vec{x})$</td>
</tr>
<tr>
<td>$\vdots$</td>
<td>$\vdots$</td>
</tr>
<tr>
<td>$\vec{v}_m$</td>
<td>$k_m(\vec{x})$</td>
</tr>
</tbody>
</table>

or write it as the generator of a jump Markov process

$$Gf(\vec{x}) = \sum_i k_i(\vec{x})(f(\vec{x} + \vec{v}_i) - f(\vec{x}))$$
For Markov processes that move from one state to another by jumping the *exponential distribution* plays an important role.

Let $\tau = \inf \{ t \geq 0; X_t \neq X_0 \}$, then

$$e_x(t + s) = P_x \{ \tau > t + s \} = P_x \{ \tau > t + s, \tau > t \}$$

$$= P_x \{ \tau > t + s | \tau > t \} P_x \{ \tau > t \}$$

and

$$P_x \{ \tau > t + s | \tau > t \} = P_x \{ \tau > t + s | X_t = x, \tau > t \}$$

$$= P_x \{ \tau > t + s | X_t = x \} = P_x \{ \tau > s \} = e_x(s)$$

Thus,

$$e_x(t + s) = e_x(s)e_x(t)$$

or for some $\lambda \in [0, \infty]$, $e_x(t) = \exp(-\lambda(x)t)$. 

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Gillespie’s Algorithm

Let \( t + \tau_1 \) be the first jump after time \( t \). Then

\[
P_x\{X_\tau = y, \tau > t\} = P_x\{X_\tau = y, \tau > t, X_t = x\}
\]

\[
= P_x\{X_{t+\tau_1} = y | \tau > t, X_t = x\}P_x\{\tau > t, X_t = x\}
\]

For the first term

\[
P_x\{X_{t+\tau_1} = y | \tau > t, X_t = x\} = P_x\{X_{t+\tau_1} = y | X_t = x\}
\]

\[
= P_x\{X_\tau = y\} = t(x, y)
\]

For the second term \( P_x\{\tau > t, X_t = x\} = P_x\{\tau > t\} \).

Thus, the time of the first jump and the place of the first jump are independent.
Write \( p(x, y) = P_x\{X_\tau = y\} \), then \( E_x f(X_{\Delta t}) \)

\[
= E_x [f(X_{\Delta t})|\tau < \Delta t] P_x\{\tau < \Delta t\} + E_x [f(X_{\Delta t})|\tau \geq \Delta t] P_x\{\tau \geq \Delta t\}
= \sum_{y \neq x} f(y)p(x, y)(1 - e^{-\lambda(x)\Delta t}) + f(x)e^{-\lambda(x)\Delta t} + o(\Delta t)
\]

Thus,

\[
E_x f(X_{\Delta t}) - f(x) = (1 - e^{-\lambda(x)\Delta t}) \left( \sum_{y \neq x} f(y)p(x, y) - f(x) \right) + o(\Delta t)
\]

\[
G f(x) = \lambda(x) \sum_{y \in S} t(x, y)(f(y) - f(x))
\]
Equating the two expressions for the generator, we find that

\[ g(x, x) = -\lambda(x) \]

and for \( y \neq x \)

\[ g(x, y) = \lambda(x)t(x, y) \quad \text{or} \quad \frac{g(x, y)}{\lambda(x)} \]

For example,

\[
G = \begin{pmatrix}
-5 & 2 & 3 & 0 \\
4 & -10 & 3 & 3 \\
2 & 2 & -5 & 1 \\
5 & 0 & 0 & -5
\end{pmatrix}, \quad
T = \begin{pmatrix}
0 & .4 & .6 & 0 \\
.4 & 0 & .3 & .3 \\
.4 & .4 & 0 & .2 \\
1 & 0 & 0 & 0
\end{pmatrix}, \quad
\lambda = \begin{pmatrix}
5 \\
10 \\
5 \\
5
\end{pmatrix}
\]
Random Time Change

Let $Y$ be a Markov process with generator $G_Y$ and let $c$ be a positive function bounded and bounded away from zero. Our goal is to describe solutions to

$$X_t = X_0 + Y\left(\int_0^t c(X_s) \, ds\right).$$

Think of $c$ at the rate of a *clock* for the process $X$. Then

$$G_X f(x) = \lim_{\Delta t \to 0} \frac{E_x f(X_{\Delta t}) - f(x)}{\Delta t}$$

$$= c(x) \lim_{\Delta t \to 0} \frac{E_x f(x + Y\int_0^{\Delta t} c(X_s) \, ds) - f(x)}{c(x) \Delta t}$$

$$= c(x) \lim_{\Delta t \to 0} \frac{E_x f(x + Yc(x)\Delta t) - f(x)}{c(x) \Delta t}$$

$$= c(x) G_Y f(x)$$
Multiple Random Time Change

More generally, for independent processes \( \{Y^i; 1 \leq i \leq m\} \) with generators \( \{G_i; 1 \leq i \leq m\} \)

\[
X_t = X_0 + \sum_i Y^i \left( \int_0^t c_i(X_s) \, ds \right)
\]

is a Markov process with generator

\[
G_X f(x) = \sum_i c_i(x) G_i f(x).
\]
Representing Equation for Chemical Kinetics

Let \( \{Y^i; 1 \leq i \leq m\} \) be independent Poisson processes with parameter 1. If \( X \) has generator

\[
Gf(\bar{x}) = \sum_i k_i(\bar{x})(f(\bar{x} + \bar{v}_i) - f(\bar{x})),
\]

then it has representation

\[
X_t = X_0 + \sum_i \bar{v}_i Y^i \left( \int_0^t k_i(X_s) \, ds \right).
\]
The Kolmogorov Forward Equation

For $f : S \to \mathbb{R}$, \[ \frac{d}{dt} \mathbb{E}[f(X_t)] = \mathbb{E}[(Gf)(X_t)]. \]

By induction, we see that the generator determines the finite dimensional distributions and hence the distribution of the process.

Example. Consider the simple chemical process 

\[ C \to D \]

with generator 

\[ Gf(c) = \kappa c(f(c - 1) - f(c)) \]

and choose $f(c) = c$, then $Gf(c) = -\kappa c$. Write $m(t) = \mathbb{E}C_t$. Here the forward equation becomes 

\[ \frac{d}{dt} m(t) = -\kappa m(t), \quad m(t) = c_0 e^{-\kappa t}. \]
Now choose $f(c) = c(c-1)$ then

$$Gf(c) = \kappa c((c-1)(c-2) - c(c-1)) = -2\kappa c(c-1).$$

Write $m_2(t) = EC_t(C_t - 1)$. The forward equation is now

$$\frac{d}{dt}m_2(t) = -2\kappa m_2(t), \quad m_2(t) = c_0(c_0 - 1)e^{-2\kappa t}$$

Therefore,

$$\text{Var}(C_t) = EC_t^2 - (EC_t)^2$$

$$= EC_t(C_t - 1) + EC_t - (EC_t)^2$$

$$= c_0(c_0 - 1)e^{-2\kappa t} + c_0e^{-\kappa t} - c_0^2e^{-2\kappa t}$$

$$= c_0e^{-\kappa t} - c_0e^{-2\kappa t} = c_0e^{-\kappa t}(1 - e^{-\kappa t})$$

$$= m(t)(c_0 - m(t))/c_0$$
Now take $f(c) = z^c$, then

$$Gf(c) = \kappa c(z^c - z^{c-1}) = \kappa cz^{c-1}(1 - z).$$

Setting $G_{c_0}(z, t) = E_{c_0}z^{C_t}$, the forward equation gives

$$\frac{\partial}{\partial t}G_{c_0}(z, t) = \kappa(1 - z)\frac{\partial}{\partial z}G_{c_0}(z, t).$$

Check that the solution is $G_{c_0}(z, t) = (e^{-\kappa t}(z - 1) + 1)^{c_0}$ and thus $C_t$ is a $Bin(c_0, e^{-\kappa t})$ random variable.
Law of Mass Action

Now, let $n$ be a measure of volume and let

$$\bar{C}_t^n = \frac{C_t^n}{n}$$

be the concentration. Then, for initial concentration $\bar{c}_0$,

$$E\bar{C}_t^n = \bar{c}_0 e^{-kt} = m_1(t) \quad \text{and} \quad \text{Var}(\bar{C}_t^n) = \frac{1}{\bar{c}_0 n} m(t)(\bar{c}_0 - m(t))$$

and

$$\lim_{n \to \infty} \bar{C}_t^n = m(t).$$

For large values of $n$, the concentration decreases exponentially nearly deterministically.
Strong Law of Large Numbers

let \( Y \) be a Poisson process, parameter 1. Then

\[
\lim_{n \to \infty} \frac{1}{n} Y_{nt} = t
\]

almost surely uniformly on bounded intervals. Write the representation above for the concentration \( \bar{X}^n_t \) to obtain

\[
\bar{X}^n_t = \bar{X}^n_0 + \sum_i v_i \frac{1}{n} Y^i \left( \int_0^t k_i(n \bar{X}^n_s) \, ds \right)
\]

\[
\approx \bar{X}^n_0 + \sum_i \bar{v}_i \int_0^t \tilde{k}_i(\bar{X}^n_s) \, ds
\]
Where $\bar{k}_i$ gives the rates under *sampling without replacement*

Thus, $\bar{X}^n$ nearly solves

$$\frac{d\bar{x}}{dt} = F(\bar{x})$$

with

$$F(\bar{x}) = \sum_i \bar{v}^i \bar{k}_i(\bar{x})$$

Formally, we have the theorem:

$$\sup_{0 \leq s \leq t} ||\bar{X}_t^n - \bar{x}(t)|| \to 0 \text{ with probability } 1$$
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Lecture 2 - Martingales and Brownian Motion
Topics

• Filtration and stopping times

• Connection to Markov processes

• Optional sampling theorem

• Strong Markov property

• Brownian motion

• Quadratic variation
Filtration and Stopping Times

A collection of $\sigma$-algebras $\{\mathcal{F}_t; t \geq 0\}$ is a filtration if $s < t$ implies $\mathcal{F}_s \subset \mathcal{F}_t$. $\mathcal{F}_t$ is meant to capture the information available to an observer at time $t$.

The natural filtration for a process $X$ is $\mathcal{F}_t^X = \sigma\{X_s, s \leq t\}$

$X$ is called adapted to $\{\mathcal{F}_t; t \geq 0\}$ if $X_t$ is $\mathcal{F}_t$-measurable.

A nonnegative random variable $\tau$ is called a stopping time if $\{\tau \leq t\} \in \mathcal{F}_t$. 

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Conditional Expectation

Let $Y$ be any integrable random variable and $\mathcal{G}$ any sub-$\sigma$-algebra of $\mathcal{F}$. Then $Z = E[Y|\mathcal{G}]$ is characterized by

$$Z \text{ is } \mathcal{G}\text{-measurable and } E[Z; A] = E[Y; A] \text{ for all } A \in \mathcal{G}.$$ 

Properties

- If $Y \in L^2(\mathcal{F})$, then $Z$ is projection onto $L^2(\mathcal{G})$.

- If $Y_1$ is $\mathcal{G}$-measurable, then $E[Y_1 Y_2|\mathcal{G}] = Y_1 E[Y_2|\mathcal{G}]$.

- If $Y_1$ is independent of $\mathcal{G}$ then $E[Y_1|\mathcal{G}] = EY_1$. 

Martingale

A martingale is meant to capture the sense of a fair game.

**Definition.** A real valued process $M$ with $E|M_t| < \infty$ for all $t \geq 0$ and adapted to a filtration $\{\mathcal{F}_t : t \geq 0\}$ is an $\mathcal{F}_t$-martingale if

$$E[M_t|\mathcal{F}_s] = M_s \quad \text{for all } t > s,$$

i.e., for and event $A \in \mathcal{F}_s$,

$$E[M_t; A] = E[M_s; A]$$

$M_t$ and $M_s$ have the same averages over sets in $\mathcal{F}_s$.

In particular, $EM_t = EM_0$. 
Connection to Markov Process $X$ with generator $G$.

$$M_t = f(X_t) - \int_0^t Gf(X_s) \, ds$$

is a martingale.

For the Poisson process, $N$, take

$f(n) = n$ to see that $N_t - \lambda t$ is a martingale.

$f(n) = e^{i\theta n}$ to see that

$$E e^{i\theta N_0} = E e^{i\theta N_t} - \int_0^t E[\lambda(e^{i\theta(N_s+1)} - e^{i\theta N_s})] \, ds$$

$$= E e^{i\theta N_t} - \int_0^t \lambda(e^{i\theta} - 1)E[e^{i\theta N_s}] \, ds$$

or $E e^{i\theta N_t} = E e^{i\theta N_0} \exp \lambda t(e^{i\theta} - 1)$.
Optional Sampling Theorem

Let $\tau$ be a stopping time. Define the $\sigma$-algebra

$$\mathcal{F}_\tau = \{A; A \cap \{\tau \leq t\} \in \mathcal{F}_t \text{ for all } t \geq 0\}.$$ 

The optional sampling theorem states that for bounded stopping times $\sigma \leq \tau$, and martingale $M$,

$$E[M_\tau | \mathcal{F}_\sigma] = M_\sigma.$$ 

In particular, $EM_\tau = EM_\sigma$. This yields Dynkin’s formula, for a Markov process $X$, generator $G$:

$$Ef(X_\tau) = Ef(X_0) + E[\int_0^\tau Gf(X_s) \, ds].$$ 

Define $M_{t}^{\tau} = M_{\min\{\tau,t\}}$, then $M^{\tau}$ is a martingale.
Example. Let $N$ be a Poisson process, parameter $\lambda$. Define the stopping time $\tau_n = \inf\{t \geq 0 : N_t = n\}$. Assume $N_0 = 0$.

1. $\tau_n < \infty$ almost surely, so by the optional sampling theorem,

$$0 = E N_{\tau_n} - \lambda E \tau_n$$

and, therefore $E \tau_n = \frac{n}{\lambda}$.

2. By considering the Markov process $(t, X_t)$, we find the martingales

$$f(t, X_t) - \int_0^t \left( \frac{\partial}{\partial s} + G \right) f(s, X_s) \, ds.$$

Thus $\exp(i\theta N_t - \lambda t(e^{i\theta} - 1))$, is a martingale. Then

$$1 = E[\exp(i\theta N_{\tau_n} - \lambda \tau_n(e^{i\theta} - 1)]$$
and thus

\[ e^{-i\theta n} = E[\exp(-\lambda \tau_n (e^{i\theta} - 1))]. \]

Set

\[ \alpha = \lambda (e^{i\theta} - 1) \text{ or } \theta = -i \ln\left(\frac{\alpha + \lambda}{\lambda}\right) \]

yielding

\[ E e^{-\alpha \tau} = \left(\frac{\lambda}{\lambda + \alpha}\right)^n \]

This is the \( n \)-th power of the Laplace transform of an exponential random variable and, hence, the Laplace transform of a \( \Gamma(n, \lambda) \) random variable.
Strong Markov Property

As with the structure theorem for jump Markov processes, we would like to use the Markov property based from a random time. The **strong Markov property** states that for a finite stopping time $\tau$

$$P_x\{X_{\tau+s} \in A | \mathcal{F}_\tau^X\} = P_x\{X_{\tau+s} \in A | X_\tau\} = p(A, X_\tau, s),$$

This property holds for any Markov having a version that has realizations that are right continuous having limits from the left.
Brownian Motion \( \{B_t; t \geq 0\} \) is defined by

1. The realizations are continuous.

2. The displacement over disjoint intervals of time are independent

3. For \( s, t > 0 \), \( B_{t+s} - B_t \) is a \( N(\mu s, \sigma^2 s) \) random variable.

The case \( \mu = 0, \sigma = 1 \) is called *standard Brownian motion*. 
The Generator for Standard Brownian Motion

\[ E_x f(B_t) = \frac{1}{\sqrt{2\pi t}} \int f(y) \exp\left(-\frac{(x-y)^2}{2t}\right) \, dy \]

\[ = \frac{1}{\sqrt{2\pi}} \int f(x + y\sqrt{t}) \exp\left(-\frac{y^2}{2}\right) \, dy. \]

Then, \( \frac{1}{t}(E_x f(B_t) - f(x)) \)

\[ = \frac{1}{\sqrt{2\pi}} \int \frac{1}{t}((f(x + y\sqrt{t}) - f(x)) \exp\left(-\frac{y^2}{2}\right) \, dy \]

\[ = \frac{1}{\sqrt{2\pi}} \int \frac{1}{t}(y\sqrt{t} f'(x) + \frac{1}{2} y^2 tf''(x + \gamma y\sqrt{t}) \exp\left(-\frac{y^2}{2}\right) \, dy \]

\[ = \frac{1}{\sqrt{2\pi}} \int \frac{1}{2} y^2 f''(x + \gamma y\sqrt{t}) \exp\left(-\frac{y^2}{2}\right) \, dy \]

for some \( \gamma \in (0, 1) \). Thus, the generator \( Gf(x) = \frac{1}{2} f''(x) \).
Standard Brownian Motion Martingales

Note that if \((\frac{\partial}{\partial t} + G)f = 0\), then \(f(t, B_t)\) is a martingale.

1. \(B_t\), Brownian motion itself.

2. \(B_t^2 - t\)

3. \(\exp(i\theta B_t + \frac{1}{2}\theta^2 t)\)
Examples.

• Assume $B_0 = 0$. Choose $a, b > 0$ and define the stopping time $\tau = \inf\{t : B_t \notin (-a, b)\}$. By the optional sampling theorem applied to the martingale $B$,

$$0 = bP\{B_\tau = b\} - aP\{B_\tau = a\}, \quad P\{B_\tau = b\} = \frac{a}{b + a}.$$

• Use the martingale $B_t^2 - t$ to obtain

$$0 = EB_{\min\{\tau, n\}}^2 - E \min\{\tau, n\}.$$ 

For the first term use the bounded convergence theorem. For the second term use the monotone convergence theorem.

$$E\tau = EB_{\tau}^2 = b^2 \frac{a}{b + a} + a^2 \frac{b}{b + a} = ab.$$
Set $X_t = B_t - \mu t$. For $x > 0$, define $\tau_x = \inf\{t \geq 0 : X_t = x\}$

Now

$$\exp(\theta X_t - \alpha t) = \exp(\theta B_t - (\alpha + \theta \mu) t)$$

is a martingale provided that

$$\alpha + \theta \mu = \frac{1}{2} \theta^2,$$

that is,

$$\theta_{\pm} = \mu \pm \sqrt{\mu^2 + 2 \alpha}.$$

Note that if $\alpha > 0$, $\theta_- < 0 < \theta_+$. Thus the martingale

$$\exp(\theta_+ X_t - \alpha t)$$

is bounded on $[0, \tau_x]$. The optional sampling theorem applies and

$$1 = E[\exp(\theta_+ X_{\tau_x} - \alpha \tau_x)] = e^{\theta x} E[e^{-\alpha \tau_x}].$$
Consequently,

\[ E[e^{-\alpha \tau_x}] = \exp(-x(\sqrt{\mu^2 + 2\alpha + \mu})). \]

Take \( \alpha \to 0 \), then \( \exp(-\alpha \tau_x) \to I_{\{\tau_x<\infty\}} \). Therefore,

\[ P\{\tau_x < \infty\} = \begin{cases} 
1 & \mu \leq 0, \\
\frac{1}{\sqrt{2\pi t^3}}e^{-2\mu x} & \mu > 0.
\end{cases} \]

In addition, the Laplace transform can be inverted to see that \( \tau_x \) has density

\[ f_{\tau_x}(t) = \frac{x}{\sqrt{2\pi t^3}} \exp(-\frac{(x + \mu t)^2}{2t}). \]
Continuous Martingales

**Exercise.** Let $M$ be a martingale with $EM_t^2 < \infty$ for all $t > 0$. Then, for $s, t > 0$,

$$\text{Var}(M_{s+t}|\mathcal{F}_t) = E[M_{s+t}^2|\mathcal{F}_t] - M_t^2 = E[(M_{s+t} - M_t)^2|\mathcal{F}_t].$$

Thus,

$$E[M_{s+t}^2 - M_t^2] = E[(M_{s+t} - M_t)^2].$$

**Important facts:** Uniformly integrable martingales have a limit as $t \to \infty$. $\lim_{n \to \infty} \sup_t E[|X_t|; \{|X_t| > n\}] = 0$

A continuous martingale having finite variation on compact intervals is constant.
By considering the martingale $\tilde{M}_t = M_t - M_0$, we can assume that $M_0 = 0$.

Let $\sigma_n$ be the time that the variation of $M$ reaches $n$. Then by considering the martingale $M^{\sigma_n}$, we can assume that $M$ has variation bounded above by $n$.

Now, let $0 = t_0 < t_1 < \cdots < t_{k-1} < t_k = t$, then $EM_t^2 = \sum_{j=1}^{k} E[M_{t_{j+1}}^2 - M_j^2] = E[\sum_{j=1}^{k} (M_{t_{j+1}} - M_t)^2] \leq nE[\max_{1 \leq j \leq k} |M_{t_{j+1}} - M_{t_j}|]$. The random variable above is bounded above by $n$ and converges to 0 almost surely as the mesh of the partition tends to 0. Thus, $EM_t^2 = 0$ and $M_t = 0$ a.s.
Quadratic Variation

Write the partition $\Pi$ for $0 = t_0 < t_1 < \cdots < t_k \cdots$, $\lim_{k \to \infty} t_k = \infty$. The \textit{quadratic variation process} of $X$ along $\Pi$ is

$$Q^\Pi_t(X) = \sum_{j=1}^{\infty} (X_{\min\{t,t_{j+1}\}} - X_{\min\{t,t_j\}})^2.$$  

We say that $X$ has \textit{finite quadratic variation} if there exists a process $\langle X, X \rangle$ such that

$$Q^\Pi_t(X) \rightarrow^P \langle X, X \rangle_t \text{ as mesh}(\Pi) \rightarrow 0.$$

Every continuous bounded martingale $M$ has finite quadratic variation that is the unique continuous increasing adapted process vanishing at zero such that

$$M_t^2 - \langle M, M \rangle_t \text{ is a martingale.}$$
For standard Brownian motion, $B$, $\langle B, B \rangle_t = t$. To see this from the definition, write
\[
Q^\Pi_t(B) - t = \sum_{j=1}^{\infty} ((B_{\min\{t,t_{j+1}\}} - B_{\min\{t,t_j\}})^2 - (\min\{t, t_{j+1}\} - \min\{t, t_j\})).
\]
and $E[(Q^\Pi_t(B) - t)^2]$
\[
= \sum_{j=1}^{\infty} E[((B_{\min\{t,t_{j+1}\}} - B_{\min\{t,t_j\}})^2 - (\min\{t, t_{j+1}\} - \min\{t, t_j\})))^2] \\
= \sum_{j=1}^{\infty} E[(B_{\min\{t,t_{j+1}\}} - B_{\min\{t,t_j\}})^2]
\]
\[
= \sum_{j=1}^{\infty} E[(B_{\min\{t,t_{j+1}\}} - B_{\min\{t,t_j\}})^2] \cdot (\min\{t, t_{j+1}\} - \min\{t, t_j\})^2 \\
= E[(Z^2 - 1)^2] \sum_{j=1}^{\infty} (\min\{t, t_{j+1}\} - \min\{t, t_j\})^2 \to 0
\]
as $\text{mesh}(\Pi) \to 0$. (Note that convergence in $L^2$ implies convergence in probability.) Here $Z$ is $N(0, 1)$. 
**Quadratic Covariation**

From a quadratic form, use polarization to create a bilinear form.

Let $M$ and $N$ be two continuous local martingales, then there is a unique continuous adapted process $\langle M, N \rangle$, called the *brackets process*, of bounded variation vanishing at zero so that

$$M_t N_t - \langle M, N \rangle_t$$

is a local martingale

The brackets process is positive definite, symmetric and bilinear.

If $M$ and $N$ are independent processes, then $\langle M, N \rangle$ is zero.

With obvious changes in notation,

$$C_t^\Pi(M, N) \to^P \langle M, N \rangle_t \text{ as mesh}(\Pi) \to 0.$$
Structure and Approximation for Markov Chains in (Bio)chemical Kinetics

Bioinformatics
Informal Seminar
Hillary Term, 2006
Lecture 3 - Stochastic Integrals
Topics

• Semimartingales as stochastic integrators

• The basic isometry

• The definition of the stochastic integral

• The Itô formula

• Stochastic differential equations

• Itô diffusions
Semimartingales

The elements of the class of processes that will become the stochastic integraters are called continuous $\mathcal{F}_t$ semimartingales. These are processes which can be written

$$X = M + V$$

where $M$ is a continuous local martingale and $V$ is a continuous adapted process having finite variation on a sequence of stopping times $\{\tau_n; n \geq 1\}, \lim_{n \to \infty} \tau_n = \infty$ bounded time intervals.

1. $V$ has zero quadratic variation.

2. $\langle M, V \rangle = \lim_{\text{mesh}(\Pi_n) \to 0} C_{\Pi_n}(M, V) = 0$. 
Relevant Hilbert Spaces

$\mathcal{H}^2$ to be the space of $L^2$-bounded martingales. These are martingales $M$, such that

$$\sup_{t \geq 0} EM_t^2 < \infty.$$  

Use $\mathcal{H}_0^2$ for those elements $M \in \mathcal{H}^2$ with $M_0 = 0$.

$M$ is a uniformly integrable martingale. Its limit exists as $t \to \infty$ and is in $L^2(P)$. Thus we can place the following norm

$$||M||_{\mathcal{H}^2}^2 = EM_{\infty}^2.$$  

A continuous local martingale $M$ is in $\mathcal{H}_0^2$ if and only if $E\langle M, M \rangle_{\infty} < \infty$. In this case, $M^2 - \langle M, M \rangle$ is a uniformly integrable martingale.
For the variety of integrals we shall develop, we write alternatively

\[ X \cdot Y = \int X \, dY. \]

For the process \( V \) described above, this is the usual Riemann-Stieljes integral.

For \( M \in \mathcal{H}^2 \) define \( \mathcal{L}^2(M) \) to be the space of adapted processes \( K \) such that

\[
\|K\|_M^2 = E[(K^2 \cdot \langle M, M \rangle)_\infty] = E[\int_0^\infty K_s^2 \, d\langle M, M \rangle_s] < \infty.
\]
Simple Processes

A *simple process* has the form,

\[ K = K_0 I_{\{0\}} + \sum_{j=1}^{n} K_j I_{(t_{j-1}, t_j]} . \]

To be adapted, we must have that \( K_j \) is \( F_{t_{j-1}} \)-measurable. The Itô stochastic integral

\[ (K \cdot M)_\infty = \int_0^{\infty} K_s^- \ dM_s = \sum_{j=1}^{n} K_j (M_{t_{j-1}} - M_{t_j}) \]

takes the sample point to the left.
The Basic Isometry

\[ E(K \cdot M)^2_\infty = E\left[ \sum_{j=1}^{n} \sum_{k=1}^{n} K_j(M_{tj} - M_{tj-1})K_k(M_{tk} - M_{tk-1}) \right]. \]

For the off diagonal terms, \( j < k \),

\[ E[K_j(M_{tj} - M_{tj-1})K_k(M_{tk} - M_{tk-1})], \]

\[ = E[K_j(M_{tj} - M_{tj-1})K_kE[M_{tk} - M_{tk-1}|\mathcal{F}_{tk-1}]] = 0. \]
Thus, \( E(K \cdot M)^2 \infty \)

\[
= E\left[ \sum_{j=1}^{n} K_j^2 (M_{t_j} - M_{t_{j-1}})^2 \right] = E\left[ \sum_{j=1}^{n} K_j^2 E\left[ (M_{t_j} - M_{t_{j-1}})^2 | \mathcal{F}_{t_{j-1}} \right] \right] \\
= E\left[ \sum_{j=1}^{n} K_j^2 E\left[ \langle M, M \rangle_{t_j} - \langle M, M \rangle_{t_{j-1}} | \mathcal{F}_{t_{j-1}} \right] \right] \\
= E\left[ \sum_{j=1}^{n} K_j^2 (\langle M, M \rangle_{t_j} - \langle M, M \rangle_{t_{j-1}}) \right] \\
= E\left[ \int_{0}^{\infty} K_s^2 d\langle M, M \rangle_s \right] = \|K\|_{M}^2
\]

Thus, the mapping

\[ K \rightarrow K \cdot M \]

is a Hilbert space isometry from \( L^2 \) to \( \mathcal{L}^2(M) \).
The Definition of the Stochastic Integral is made by completing the isometry $K \rightarrow K \cdot M$ for adapted processes $K \in \mathcal{L}^2(M)$.

Define the process $(K \cdot M)_t = \int_0^t K_s \, dM_s = (KI_{[0,t]} \cdot M)_\infty$

Note that this process is a martingale whenever $M$ is a martingale.

Some Useful Identities. Provided the integrals exist:

- $(a_1K_1 + a_2K_2) \cdot M = a_1K_1 \cdot M + a_2K_2 \cdot M$.

- $(HK) \cdot M = H \cdot (K \cdot M)$.

- $\langle H \cdot M, K \cdot N \rangle = (HK) \cdot \langle M, N \rangle$. 
Integration by Parts

Let $X$ be a continuous semimartingale, and let $\{\Pi^n; n \geq 1\}$ be a sequence of partitions of $[0, \infty)$, $\Pi^n = \{0 = t^n_0 < t^n_1 < \cdots\}$, $\text{mesh}(\Pi^n) \to 0$. Expand to obtain,

$$\sum_{j=1}^{\infty} (X_{\min\{t,t_j\}} - X_{\min\{t,t_{j-1}\}})^2
= X_t^2 - X_0^2 - 2 \sum_{j=1}^{\infty} X_{\min\{t,t_{j-1}\}} (X_{\min\{t,t_j\}} - X_{\min\{t,t_{j-1}\}}).$$

Then, $\sum_{j=1}^{\infty} (X_{\min\{t,t_j\}} - X_{\min\{t,t_{j-1}\}})^2 \to^P \langle X, X \rangle_t$.

and $\sum_{j=1}^{\infty} X_{\min\{t,t_{j-1}\}} (X_{\min\{t,t_j\}} - X_{\min\{t,t_{j-1}\}}) \to^P \int_0^t X_s \, dX_s$

uniformly on compact intervals. Thus

$$X_t^2 = X_0^2 + 2 \int_0^t X_s \, dX_s + \langle X, X \rangle_t.$$
Now, use polarization to obtain. for continuous semimartingales $X$ and $Y$, that

\[ X_t Y_t = X_0 Y_0 + \int_0^t X_s \, dY_s + \int_0^t Y_s \, dX_s + \langle X, Y \rangle_t. \]

**Example.** Let $B$ be standard Brownian motion, then

\[ \langle B, B \rangle_t = t, \quad \text{thus} \quad B_t^2 - t = 2 \int_0^t B_s \, dB_s \]

and

\[ \langle t, B \rangle_t = 0, \quad \text{thus} \quad tB_t = \int_0^t s \, dB_s + \int_0^t B_s \, ds. \]
The Itô Formula

Let $f \in C^2(\mathbb{R}^d, \mathbb{R})$ and $X = (X^1, \ldots, X^d)$ be a vector continuous
semimartingale, then $f \circ X$ is a continuous semimartingale and

$$
\begin{align*}
\text{df}(X_t) &= \sum_{i=1}^{d} \frac{\partial f}{\partial x_i}(X_s) \ dX_i^s \\
&\quad + \frac{1}{2} \sum_{i=1}^{d} \sum_{j=1}^{d} \frac{\partial^2 f}{\partial x_i \partial x_j}(X_s) \ d\langle X^i, X^j \rangle_s.
\end{align*}
$$

Use a stopping time to localize to a compact set, use induction
on the degree of the polynomial, and use the Stone-Weierstrass
theorem to take a limit.
Moments of the Normal

By Itô’s formula

\[ B_t^{2n} = 2n \int_0^t B_s^{2n-1} \, dB_s + \frac{2n(2n-1)}{2} \int_0^t B_s^{2n-2} \, ds. \]

Thus,

\[ EB_t^{2n} = \frac{2n(2n-1)}{2} \int_0^t EB_s^{2n-2} \, ds. \]

For example,

\[ EB_t^4 = 6 \int_0^t s \, ds = 3t^2. \]
Examples.

- Let \( f : \mathbb{R}^+ \times \mathbb{R} \to \mathbb{C} \) satisfy

\[
\frac{\partial f}{\partial t} + \frac{1}{2} \frac{\partial^2 f}{\partial x^2} = 0
\]

If \( M \) is a local martingale, then so is \( \{f(\langle M, M \rangle_t, M_t); t \geq 0\} \). In particular,

\[
\mathcal{E}(\theta M)_t = \exp(\theta M_t - \frac{\theta^2}{2} \langle M, M \rangle_t), \quad \lambda \in \mathbb{C}
\]

is a local martingale.

This local martingale satisfies the stochastic differential equation

\[
dY_t = \theta Y_t \, dM_t.
\]
• Note that for standard Brownian motion,

\[ \exp(\theta B_t - \frac{\theta^2}{2} t) \] is a martingale.

• For \( B = (B^1, \ldots, B^d) \), a \( d \)-dimensional Brownian motion then

\[ \langle B^i, B^j \rangle = \delta_{ij} t. \]

• If \( f \in C^2(\mathbb{R}^+ \times \mathbb{R}^d) \), and if \( B \) is a \( d \)-dimensional Brownian motion then

\[
f(t, B_t) - \int_0^t \left( \frac{\partial f}{\partial s} + \frac{1}{2} \Delta f \right)(s, B_s) \, ds
\]

is a martingale. Thus, if \( f \) is harmonic in \( \mathbb{R}^d \), then \( f \circ B \) is a local martingale. In addition, \( \frac{1}{2} \Delta \) is the restriction of the generator of \( B \) to \( C^2(\mathbb{R}^d) \).
Recurrence of Brownian Motion

Let $f$ be a function of the radius, then the Laplacian can be replaced by its radial component $A$, the Bessel operator. If $R_t = |B_t|$, we have the martingale

$$f(t, R_t) - \int_0^t (Af + \frac{\partial f}{\partial t})(s, R_s) \, ds$$

Check that $s(r) = \ln r$ solves $As = 0$ in $\mathbb{R}^2$ and that $s(r) = -r^{2-d}$ solves $As = 0$ in $\mathbb{R}^d, d \geq 3$. So if $r_i < r < r_o$, then

$$P_r\{\tau_{r_o} > \tau_{r_i}\} = \frac{s(r_o) - s(r)}{s(r_o) - s(r_i)}.$$

Now let $r_o \to \infty$, then for $d = 2$, $P_r\{\tau_{r_i} < \infty\} = 1$.

For $d \geq 3$, $P_r\{\tau_{r_i} < \infty\} = \left(\frac{r_i}{r}\right)^{d-2}$. 

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Lévy’s characterization theorem

Assume that $X$ is a $\mathbb{R}^d$, $X_0 = 0$. The following are equivalent.

1. $X$ is $d$-dimensional standard Brownian motion.

2. $X$ is a continuous local martingale and $\langle X^i, X^j \rangle = \delta_{ij}t$.

$(2 \rightarrow 1)$ Take $\theta = i$ and $M = \xi \cdot X$ in the exponential martingale, then $\langle M, M \rangle_t = |\xi|^2 t$ and we have the martingale

$$\exp(i\xi \cdot X_t + \frac{1}{2}|\xi|^2 t).$$

Thus, for $s < t$, $E[\exp(i\xi \cdot X_t + \frac{1}{2}|\xi|^2 t)|\mathcal{F}_s] = \exp(i\xi \cdot X_s + \frac{1}{2}|\xi|^2 s)$ or

$$E[\exp(i\xi \cdot (X_t - X_s)|\mathcal{F}_s] = \exp(-\frac{1}{2}|\xi|^2(t - s)).$$
Stochastic Differential Equations

Let $f$ and $g$ be adapted functions taking values in $\mathbb{R}^{d \times r}$ and $\mathbb{R}^d$ respectively and let $B$ be a standard $r$-dimensional Brownian motion. Consider the stochastic differential equation

$$dX_t = f(s, X) \, dB_s + g_i(s, X) \, ds.$$ 

A solution is a pair $(X, B)$ of $\mathcal{F}_t$-adapted processes that satisfy this equation.
Notions of Uniqueness

1. For \((X, B), (\tilde{X}, \tilde{B})\) solutions on the probability same space with the same filtration and the same initial conditions. Then the stochastic differential equation is said to satisfy \textit{pathwise uniqueness} if \(P\{X_t = \tilde{X}_t \text{ for all } t\} = 1\)

2. For \((X, B), (\tilde{X}, \tilde{B})\) be solutions so that the distributions of \(X_0\) and \(\tilde{X}_0\) are equal. Then the stochastic differential equation above is said to satisfy \textit{uniqueness in law} if \(X\) and \(\tilde{X}\) have the same distribution.
Itô Diffusions

A continuous stochastic process $X$ is called a time homogeneous Itô diffusion if there exists measurable mappings

$$\sigma : \mathbb{R}^d \to \mathbb{R}^{d \times r}, \text{ (the diffusion matrix)}$$

and

$$b : \mathbb{R}^d \to \mathbb{R}^d, \text{ (the drift)}$$

and an $r$-dimensional Brownian motion $B$ so that

$$dX_t^j = \sum_{k=1}^{r} \sigma_{jk}(X_t) \ dB_t^k + b_j(X_t) \ dt$$

has a solution that is unique in law.

If $\sigma$ and $b$ satisfy an appropriate Lipschitz hypothesis, then we have pathwise uniqueness. If $\sigma$ and $b$ are locally bounded and Borel measurable, then pathwise uniqueness to the Itô stochastic differential equation above implies uniqueness in law.
If \( X \) is an Itô diffusion and if \( f \in C^2(\mathbb{R}^d, \mathbb{R}) \), then

\[
\begin{align*}
df(X_t) &= \sum_{j=1}^{d} \frac{\partial f}{\partial x^j}(X_s) \, dX_s^j + \frac{1}{2} \sum_{j=1}^{d} \sum_{k=1}^{d} \frac{\partial^2 f}{\partial x^j \partial x^k}(X_s) \, d\langle X^j, X^k \rangle_s \\
&= \sum_{j=1}^{d} \left( b_i(X_s) \frac{\partial f}{\partial x^j}(X_s) + \frac{1}{2} (\sigma \sigma^T)_{jk}(X_s) \frac{\partial^2 f}{\partial x^j \partial x^k}(X_s) \right) \, ds \\
&+ \sum_{k=1}^{d} \sum_{k=1}^{r} \sigma_{jk}(X_s) \frac{\partial f}{\partial x^j}(X_s) \, dB_s^k.
\end{align*}
\]
Consequently, we have the martingales

\[ M_t^f = f(X_0) + \int_0^t Gf(X_s) \, ds \]

with \( Gf(x) = \sum_{j=1}^d b_j(x) \frac{\partial f}{\partial x^j}(x) + \frac{1}{2} \sum_{j=1}^d \sum_{k=1}^d a_{jk}(x) \frac{\partial^2 f}{\partial x^j \partial x^k}(x) \) and \( a = \sigma \sigma^T \).

Therefore, an Itô diffusion is a Markov process with continuous realizations. \( G \) is the restriction of its generator to \( f \in C^2(\mathbb{R}^d, \mathbb{R}) \).
Structure and Approximation for Markov Chains in (Bio)chemical Kinetics

Bioinformatics
Informal Seminar
Hillary Term, 2006
Lecture 4 - Multiscale Approximations
Topics

- Van Kampen diffusion approximation
- Multiscale approximation
- Michaelis-Menten kinetics
- Simple crystalization
- Enzyme kinetics
- Reversible isomerization
Central limit theorem for the Poisson Process

Let $Y$ be a Poisson process with parameter 1 and define the sequences of processes

$$\tilde{B}^n_t = \sqrt{n} \left( \frac{Y_{nt}}{n} - t \right).$$

Note that $\tilde{B}^n$ has stationary and independent increments. $\tilde{B}^n_t$ has mean zero, and variance $t$.

Then, $\tilde{B}^n$ converges in distribution to $\tilde{B}$, a standard Brownian motion. Thus, we can write

$$\frac{1}{n} Y_{nt} - t \approx \frac{1}{\sqrt{n}} \tilde{B}_t.$$
Recall the law of mass action for the concentration

\[ \bar{X}_t^n = \bar{X}_0^n + \sum_i \vec{v}_i \frac{1}{n} Y^i \left( \int_0^t k_i(n \bar{X}_s^n) \, ds \right) \]

\[ \approx \bar{X}_0^n + \sum_i \vec{v}_i \frac{1}{n} Y^i \left( n \int_0^t k_i(\bar{X}_s^n) \, ds \right) \]

\[ \approx \bar{X}_0^n + \sum_i \vec{v}_i \left( \int_0^t k_i(\bar{X}_s^n) \, ds \right) \]

\[ \approx \bar{X}_0^n + \int_0^t F(\bar{X}_s^n) \, ds, \quad F(\bar{x}) = \sum_i \vec{v}_i k_i(\bar{x}) \]
Let $Y^i$ be independent Poisson processes with parameter 1.

\[
\tilde{X}_t^n \approx \tilde{X}_0^n + \sum_i \tilde{v}_i \left( \frac{1}{n} Y^i (n \int_0^t k_i(\tilde{X}_s^n) \, ds) - \int_0^t k_i(\tilde{X}_s^n) \right) + \int_0^t F(\tilde{X}_s^n)
\]

\[
\approx \tilde{X}_0^n + \frac{1}{\sqrt{n}} \sum_i \tilde{v}_i \tilde{B}^i (\int_0^t k_i(\tilde{X}_s^n) \, ds) + \int_0^t F(\tilde{X}_s^n)
\]

where $\tilde{B}^i$ are independent standard Brownian motions.

The process that satisfies equality in this equation is a Markov process with generator

\[
G^n = \frac{1}{2n} \sum_i k(x)(\tilde{v}_i \cdot \nabla)^2 + F \cdot \nabla.
\]
Van Kampen Diffusion Approximation

Note that

\[ G^n = \frac{1}{2n} \sum_j \sum_k (\sum_i k_i(\vec{x}) v_i^j v_i^k) \frac{\partial}{\partial x_j} \frac{\partial}{\partial x_k} \]

is the generator of an Itô diffusion, namely,

\[ dX^j_t = \frac{1}{\sqrt{n}} \sum_{k=1}^r \sigma_{jk}(X_t) \ dB^k_t + F_j(X_t) \ dt. \]

where \( \sigma_{ji}(\vec{x}) = \sqrt{k_i(\vec{x})} \ v_i^j \) and \( B^1, \ldots, B^r \) are independent standard Brownian motions.
**Multiscale Approximation**

Let $n$, a scaling parameter, denote the order of magnitude of the most abundant chemical.

For each chemical, define $\alpha_j \in [0, 1]$ that gives the relative abundance of chemical $i$.

For each reaction, define $\beta_i$ to give relative rates for reactions.

Writing $z^{n,j} = n^{-\alpha_j} x^j$, $k(x) = n^{\beta_i} \bar{k}_i(z)$, the model takes the form

\[
Z_t^{n,j} = Z_0^{n,j} + n^{-\alpha_j} \sum_i v_i^j Y_i \left( \int_0^t n^{\beta_i} \bar{k}_i(Z_s) \, ds \right).
\]

So, choose $\beta_i$ so that $\bar{k}_i(z)$ is $O(1)$ for relevant values of $z$. 

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Michaelis-Menten Kinetics \( A + E \leftrightarrow AE \quad AE \rightarrow B + E \).

<table>
<thead>
<tr>
<th>stoichiometry</th>
<th>rate</th>
</tr>
</thead>
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<tr>
<td>((-1, -1, 1, 0))</td>
<td>(\kappa_1 x^A x^E)</td>
</tr>
<tr>
<td>((-1, -1, 1, 0))</td>
<td>(\kappa_{-1} x^{AE})</td>
</tr>
<tr>
<td>((0, 1, -1, 1))</td>
<td>(\kappa_2 x^{AE})</td>
</tr>
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</table>

\[
X_t^A = X_0^A + Y^{-1}(\int_0^t \kappa_{-1} X_s^{AE} \, ds) - Y^1(\int_0^t \kappa_1 X_s^A X_s^E \, ds)
\]

\[
X_t^{AE} = X_0^{AE} - Y^{-1}(\int_0^t \kappa_{-1} X_s^{AE} \, ds) + Y^1(\int_0^t \kappa_1 X_s^A X_s^E \, ds)
- Y^2(\int_0^t \kappa_2 X_s^{AE} \, ds)
\]

\[
X_t^E = X_0^E + Y^{-1}(\int_0^t \kappa_{-1} X_s^{AE} \, ds) - Y^1(\int_0^t \kappa_1 X_s^A X_s^E \, ds)
+ Y^2(\int_0^t \kappa_2 X_s^{AE} \, ds)
\]
Set \( X_t^E + X_t^{AE} = X_0^E + X_0^{AE} = n^\alpha, \) \( \alpha < 1, \)

\( \alpha_A = 1, \) \( \alpha_E = \alpha_{AE} = \alpha, \) \( \beta_1 = -\alpha, \) \( \beta_{-1} = \beta_2 = 1 - \alpha. \)

Thus,

\[
Z_t^{n,A} = Z_0^{n,A} + \frac{1}{n} Y^{-1} \left( \int_0^t n\tilde{\kappa}_{-1}(1 - Z_s^{n,E}) \, ds \right) \\
- \frac{1}{n} Y^1 \left( \int_0^t n\tilde{\kappa}_1 Z_s^{n,A} Z_s^{n,E} \, ds \right)
\]

\[
Z_t^{n,E} = Z_0^{n,E} - \frac{1}{n^\alpha} Y^{-1} \left( \int_0^t n\tilde{\kappa}_{-1}(1 - Z_s^{n,E}) \, ds \right) \\
+ \frac{1}{n^\alpha} Y^1 \left( \int_0^t n\tilde{\kappa}_1 Z_s^{n,A} Z_s^{n,E} \, ds \right) + \frac{1}{n^\alpha} Y^2 \left( \int_0^t n\tilde{\kappa}_2(1 - Z_s^{n,E}) \, ds \right)
\]
Divide by $n^{1-\alpha}$ to see that as $n \to \infty$ to see that

$$
\int_0^t (\tilde{\kappa}_1 + \tilde{\kappa}_2)(1 - Z_{s,E}^n) \, ds + \int_0^t \tilde{\kappa}_1 Z_{s,A}^n Z_{s,E}^n \, ds \to 0.
$$

Also,

$$
Z_{t}^{n,A} - Z_{0}^{n,A} - \int_0^t \tilde{\kappa}_1 (1 - Z_{s,E}^n) \, ds + \int_0^t \tilde{\kappa}_1 Z_{s,A}^n Z_{s,E}^n \, ds \to 0.
$$

If $Z_{n,A}^n \to z^A$ and $Z_{n,E}^n \to z^E$, then

$$
(\tilde{\kappa}_1 + \tilde{\kappa}_2)(1 - z_t^E) + \tilde{\kappa}_1 z_t^A z_t^E = 0,
$$

$$
\frac{d}{dt} z_t^A = \tilde{\kappa}_1 (1 - z_t^E) + \tilde{\kappa}_1 z_t^A z_t^E = \frac{\tilde{\kappa}_1 \tilde{\kappa}_2 z_t^A}{\tilde{\kappa}_1 + \tilde{\kappa}_2 - \kappa z_t^A}.
$$
Simple Crystalization

\[ 2A \rightarrow B \quad A + C \rightarrow D. \]

<table>
<thead>
<tr>
<th>Stoichiometry</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>((-2, 1, 0, 0))</td>
<td>( \kappa_1 \left( \frac{x^A}{2} \right) )</td>
</tr>
<tr>
<td>((-1, 0, -1, 1))</td>
<td>( \kappa_2 x^A x^C )</td>
</tr>
</tbody>
</table>

\[
X^A_t = X^A_0 - 2Y^1 \left( \int_0^t \frac{1}{2} \kappa_1 X^A_s (X^A_s - 1) \, ds \right) - Y^2 \left( \int_0^t \kappa_2 X^A_s X^C_s \, ds \right)
\]

\[
X^B_t = X^B_0 + Y^1 \left( \int_0^t \frac{1}{2} \kappa_1 X^A_s (X^A_s - 1) \, ds \right)
\]

\[
X^C_t = X^C_0 - Y^2 \left( \int_0^t \kappa_2 X^A_s X^C_s \, ds \right)
\]
Set

\[ X_0^A = 10^6 = n, \quad X_0^B = 0, \quad X_0^C = 10, \quad \kappa_1 = \kappa_2 = 10^{-7} = \frac{1}{10} n^{-1}. \]

Thus, \( \alpha_A = \alpha_B = 1, \quad \alpha_C = 0, \quad \beta_1 = \beta_2 = -1 \)

and

\[
Z^n_t^A = 1 - \frac{2}{n} Y^1(n \int_0^t \frac{1}{20} Z^n_s^A (Z^n_s^A - \frac{1}{n}) \, ds) - \frac{1}{n} Y^2(\int_0^t \frac{1}{10} Z^n_s^A Z^n_s^C \, ds)
\]

\[
Z^n_t^B = \frac{1}{n} Y^1(n \int_0^t \frac{1}{20} Z^n_s^A (Z^n_s^A - \frac{1}{n}) \, ds)
\]

\[
Z^n_t^C = 10 - Y^2(\int_0^t \frac{1}{10} Z^n_s^A Z^n_s^C \, ds)
\]
let \( n \to \infty \) to obtain the simplified equations

\[
Z_t^A = 1 - \int_0^t \frac{1}{10} (Z_s^A)^2 \, ds
\]

\[
Z_t^B = \int_0^t \frac{1}{20} (Z_s^A)^2 \, ds
\]

\[
Z_t^C = 10 - Y^2 \left( \int_0^t \frac{1}{10} Z_s^A Z_s^C \, ds \right)
\]

Thus, \( Z_t^A = \frac{1}{1+t/10} \), \( Z_t^B = \frac{1}{200} \left( 1 - \frac{1}{1+t/10} \right) \)

and \( Z_t^C = 10 - Y^2 \left( \int_0^t \frac{1}{10+s} Z_s^C \, ds \right) \)
Consequently, $Z^C_t$ is a *time inhomogeneous* Markov process with generator

$$G_t f(z) = \frac{z}{10 + t}(f(z - 1) - f(z)).$$

We can find the generating function for this process and with it conclude that

$$Z^C_t \text{ is } Bin(10, \exp(-\int_0^t \frac{1}{10+s}) = Bin(10, \frac{10}{10+s}).$$
**Enzyme Kinetics**  \( E + S \leftrightarrow ES \quad ES \rightarrow P + E \).

<table>
<thead>
<tr>
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<tr>
<td>((-1, -1, 1, 0))</td>
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\[
X_t^S = X_0^S + Y^{-1}(\int_0^t \kappa_{-1} X_s^{ES} \, ds) - Y^1(\int_0^t \kappa_1 X_s^E X_s^S \, ds)
\]

\[
X_t^{ES} = X_0^{ES} - Y^{-1}(\int_0^t \kappa_{-1} X_s^{ES} \, ds) + Y^1(\int_0^t \kappa_1 X_s^E X_s^S \, ds) - Y^2(\int_0^t \kappa_2 X_s^{ES} \, ds)
\]

\[
X_t^E = X_0^E + Y^{-1}(\int_0^t \kappa_{-1} X_s^{ES} \, ds) - Y^1(\int_0^t \kappa_1 X_s^E X_s^S \, ds) + Y^2(\int_0^t \kappa_2 X_s^{ES} \, ds)
\]
Take $X^E_0 = 1000 = n$, $X^S_0 = 100 = n^{2/3}$, 
$\kappa_1 = \kappa_{-1} = 1$, $\kappa_2 = 0.1 = n^{-1/3}$.

Thus, $\alpha_E = 1$, $\alpha_S = \alpha_{ES} = 2/3$, $\beta_1 = \beta_{-1} = 0$, $\beta_2 = -1/3$.

\[
Z_{t}^{n,S} = 1 + \frac{1}{n^{2/3}} Y^{-1}(\int_{0}^{t} n^{2/3} Z_{s}^{n,ES} ds) - \frac{1}{n^{2/3}} Y^{1}(\int_{0}^{t} n^{5/3} Z_{s}^{n,E} Z_{s}^{n,S} ds)
\]
\[
Z_{t}^{n,ES} = \frac{-1}{n^{2/3}} Y^{-1}(\int_{0}^{t} n^{2/3} Z_{s}^{n,ES} ds) + \frac{1}{n^{2/3}} Y^{1}(\int_{0}^{t} n^{5/3} Z_{s}^{n,E} Z_{s}^{n,S} ds)
- \frac{1}{n^{2/3}} Y^{2}(\int_{0}^{t} n^{1/3} Z_{s}^{n,ES} ds)
\]
\[
Z_{t}^{n,E} = 1 + \frac{1}{n} Y^{-1}(\int_{0}^{t} n^{2/3} Z_{s}^{n,ES} ds) - \frac{1}{n} Y^{1}(\int_{0}^{t} n^{5/3} Z_{s}^{n,E} Z_{s}^{n,S} ds)
+ \frac{1}{n} Y^{2}(\int_{0}^{t} n^{1/3} Z_{s}^{n,ES} ds)
\]
Rescale time $t \to n^{1/3}t$ to obtain

\[
\tilde{Z}^{n,S}_t = 1 + \frac{1}{n^{2/3}} Y^{-1}(\int_0^t n\tilde{Z}^{n,ES}_s ds) - \frac{1}{n^{2/3}} Y^1(\int_0^t n^2 \tilde{Z}^{n,E}\tilde{Z}^{n,S}_s ds)
\]

\[
\tilde{Z}^{n,ES}_t = -\frac{1}{n^{2/3}} Y^{-1}(\int_0^t n\tilde{Z}^{n,ES}_s ds) + \frac{1}{n^{2/3}} Y^1(\int_0^t n^2 \tilde{Z}^{n,E}\tilde{Z}^{n,S}_s ds)
\]

\[-\frac{1}{n^{2/3}} Y^2(\int_0^t n^{2/3} \tilde{Z}^{n,ES}_s ds)\]

\[
\tilde{Z}^{n,E}_t = 1 + \frac{1}{n} Y^{-1}(\int_0^t n\tilde{Z}^{n,ES}_s ds) - \frac{1}{n} Y^1(\int_0^t n^2 \tilde{Z}^{n,E}\tilde{Z}^{n,S}_s ds)
\]

\[-\frac{1}{n} Y^2(\int_0^t n^{2/3} \tilde{Z}^{n,ES}_s ds)\]

\[
\tilde{Z}^{n,E}(0) = 0
\]
Check that for any $s \in (\delta, t)$, $\tilde{Z}_{s}^{n,S} \to 0$ uniformly as $n \to \infty$ and that

$$\tilde{Z}_{t}^{n,S} + \tilde{Z}_{s}^{n,ES} = 1 - \frac{1}{n^{2/3}} Y^{2}(\int_{0}^{t} n^{2/3} \tilde{Z}_{s}^{n,ES} ds)$$

Thus, $\tilde{Z}_{n,S}^{n} + \tilde{Z}_{n,ES}^{n}$ converges to

$$\tilde{Z}_{t}^{ES} = 1 - \int_{0}^{t} \tilde{Z}_{s}^{ES} ds, \quad Z_{t}^{ES} = \exp(-t).$$

$$\tilde{Z}_{t}^{E} = \int_{0}^{t} \tilde{Z}_{s}^{ES} ds = 1 - \exp(-t).$$
Reversible Isomerization \( S_1 \leftrightarrow S_2 \quad S_2 \rightarrow S_3 \).

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\[
X_t^1 = X_0^1 - Y^1(\int_0^t \kappa_1 X_s^1 \, ds) + Y^2(\int_0^t \kappa_2 X_s^2 \, ds)
\]

\[
X_t^2 = X_0^2 + Y^1(\int_0^t \kappa_1 X_s^1 \, ds) - Y^2(\int_0^t \kappa_2 X_s^2 \, ds) - Y^3(\int_0^t \kappa_3 X_s^2 \, ds)
\]

\[
X_t^3 = X_0^3 + Y^3(\int_0^t \kappa_3 X_s^2 \, ds)
\]
\[ X_0^1 = 1200 = 1.2n, \quad X_0^2 = 600 = 0.6n, \quad X_0^3 = 0, \]
\[ \kappa_1 = 1, \quad \kappa_2 = 2, \quad \kappa_3 = 5 \times 10^{-5} = 5n^{-5/3}. \]

Then, \( \alpha_1 = \alpha_2 = 1, \alpha_3 = 0, \quad \beta_1 = \beta_2 = 0, \beta_3 = -5/3. \) and

\[
Z_t^{n,1} = Z_0^{n,1} - \frac{1}{n}Y^1\left( \int_0^t nZ_s^{n,1} \, ds \right) + \frac{1}{n}Y^2\left( \int_0^t 2nZ_s^{n,2} \, ds \right)
\]
\[
Z_t^{n,2} = Z_0^{n,2} + \frac{1}{n}Y^1\left( \int_0^t nZ_s^{n,1} \, ds \right) - \frac{1}{n}Y^2\left( \int_0^t 2nZ_s^{n,2} \, ds \right)
\]
\[
\quad - \frac{1}{n}Y^3\left( \int_0^t 5n^{-2/3}Z_s^{n,2} \, ds \right)
\]
\[
Z_t^{n,3} = \frac{1}{n}Y^3\left( \int_0^t 5n^{-2/3}Z_s^{n,2} \, ds \right)
\]
Let $n \to \infty$, the limiting system is

$$
\begin{align*}
Z^1_t &= Z_0^1 - \int_0^t Z^1_s \, ds + \int_0^t 2Z^2_s \, ds \\
Z^2_t &= Z_0^2 + \int_0^t Z^1_s \, ds - \int_0^t 2Z^2_s \, ds \\
Z^3_t &= 0.
\end{align*}
$$

Consequently, $Z^1_t + Z^2_t = Z_0^1 + Z_0^2$, and

$$
D_t = Z^1_t - 2Z^2_t = D_0 - 3 \int_0^t D_s \, ds, \text{ or } D_t = D_0 \exp(-3t).
$$

To achieve some dynamics on $Z^{n,3}$, we move to a faster time scale.
Set \( \tilde{Z}_{t}^{n,j} = Z_{n^{2/3}t}^{n,j} \), \( j = 1, 2, 3 \), to obtain the system:

\[
\begin{align*}
\tilde{Z}_{t}^{n,1} &= \tilde{Z}_{0}^{n,1} - \frac{1}{n} Y^{1}(\int_{0}^{t} n^{5/3} \tilde{Z}_{s}^{n,1} \, ds) + \frac{1}{n} Y^{2}(\int_{0}^{t} 2n^{5/3} \tilde{Z}_{s}^{n,2} \, ds) \\
\tilde{Z}_{t}^{n,2} &= \tilde{Z}_{0}^{n,2} + \frac{1}{n} Y^{1}(\int_{0}^{t} n^{5/3} \tilde{Z}_{s}^{n,1} \, ds) - \frac{1}{n} Y^{2}(\int_{0}^{t} 2n^{5/3} \tilde{Z}_{s}^{n,2} \, ds) - \frac{1}{n} Y^{3}(\int_{0}^{t} 5\tilde{Z}_{s}^{n,2} \, ds) \\
\tilde{Z}_{t}^{n,3} &= \frac{1}{n} Y^{3}(\int_{0}^{t} 5\tilde{Z}_{s}^{n,2} \, ds)
\end{align*}
\]
Divide the first equation by $n^{2/3}$ to see that as $n \to \infty$,

$$\int_0^t \bar{Z}_{s,1}^n \, ds + \int_0^t 2\bar{Z}_{s,2}^n \, ds \to 0.$$ 

Assume that $\bar{Z}_{0,1}^n + \bar{Z}_{0,2}^n = C$, we have that

$$\int_0^t 2\bar{Z}_{s,2}^n \, ds \to \frac{1}{3}Ct$$

and $\bar{Z}^{n,3}$ converges to

$$Z_t^3 = Y^3(\frac{5}{3}Ct),$$

a Poisson process with parameter $5C/3$. 