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2022

Randomness
Formulation
Chapman-
Kolmogorov
Master equation

A!
Aalto University

Stochastic formulation of reaction networks
Stochastic analysis and simulation of reactive and diffusive systems

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Basics on randomness
Stochastic formulation

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Measurements

Consider the reversible transformation of some protein between two forms

$$\mathcal{U} \xrightarrow{\kappa_m} \mathcal{M}$$
$$\mathcal{M} \xrightarrow{\kappa_u} \mathcal{U}$$
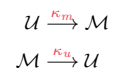
Consider the time s between successive modifications (reaction events)
- ⤳ Each s is single instance of reaction time measurement
- ⤳ Each s takes the form of a positive real number

Our interest is not in individual time-between-reaction measurements
- We are interested in their class of measurements

Because the time between modification varies depending on a number of un-modelled conditions, this time is represented as a random variables which we denoted with S
- ⤳ The single values s are replaced by the range of values of S
- ⤳ From single/unique/deterministic times to random ones

S is a rule (mapping) that assigns a unique number $s \geq 0$ to each time measurement
- (S is a continuous random variable)

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Measurements (cont.)

The number $n_u(t)$ of un-modified molecules, at time t, is an integer in a measurement

If we monitor this abundance for a system, we get a unique time-function $(n_u(t))_{t \geq 0}$
- A certain value $n(t) = n_u(t)$ of unmodified molecules, at each time point t

Again, we are interested in the abundance for an arbitrary (a class of) system(s)
- ⤳ Copy-numbers $n_u(t)$ are no longer single/unique/deterministic quantities
- ⤳ They are modelled/replaced as time-dependent random quantities $N_u(t)$
- (To account for the fact that they will vary between systems)

$N(t)$ is a rule that assigns a unique integer $n_u(t) \in \{0, 1, 2, \dots\}$ to each measurement
- ($N_u(t)$ is a discrete random variable)

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Probability

Consider again the reversible transformation of some protein between two forms

$$\mathcal{U} \xrightarrow{\kappa_m} \mathcal{M}$$
$$\mathcal{M} \xrightarrow{\kappa_u} \mathcal{U}$$
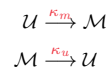
Suppose that every molecule can be labelled, irrespective of its form ($\mathcal{U}$ or $\mathcal{M}$)

$$\Omega = \{\omega_1, \omega_2, \ldots, \omega_n, \ldots, \omega_{\overline{n}}\}$$

Imagine picking one molecule, no consideration about its form and/or position
- ⤳ The outcome of this experiment cannot be determined uniquely
- ⤳ We only know that it will be an element $\omega_n \in \Omega$

Intuitively, each molecule can be assumed to be equally likely to be selected
- We assign to each molecule ω_n the same likelihood

$$\mathbb{P}_{\omega_n} = \frac{1}{\overline{n}} \qquad (\text{for all } \omega_n \in \Omega)$$

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Probability (cont.)

$$\mathbb{P}_{\omega_n} = \frac{1}{\overline{n}} \qquad (\text{for all } \omega_n \in \Omega)$$

We are interested in being able to assign these numbers not only to single molecules
- (For example, what are the chances of picking molecules labelled $\omega_n < 0.1\overline{n}$?)

In reality, we are interested in subsets A of Ω, or events, and their likelihood

$$\mathbb{P}\left[\{\omega_n, , \omega_n \in \Omega\}\right] = \frac{1}{\overline{n}}$$
$$\mathbb{P}\left[\{\omega_n : \omega_n < 1/\overline{n}, \omega_n \in \Omega\}\right] = \cdots$$
$$\mathbb{P}\left[A = \{\omega_n : \text{ something else }, \omega_n \in \Omega\}\right] = \cdots$$
$$\cdots = \cdots$$

Not all subsets of Ω are events and we are not interested in all of its possible subsets

The space of the events of interest, a collection of subsets of Ω, is the event space $\mathcal{A}$
- $\mathbb{P}\left[\cdot\right]$ is a set function, a rule for assigning probabilities (likelihoods) to sets

$$\mathbb{P} : \mathcal{A} \to [0, 1]$$

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Probability (cont.)

Given a collection of elementary events, we can combine events to form new events

Consider, for example, the event $A = \{\{1\}, \{3\}\}$ as union $\{1\} \cup \{3\}$
- Given a function $\mathbb{P}\left[\cdot\right]$, we can write

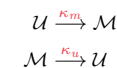$$\mathbb{P}\left[A\right] = \mathbb{P}\left[\{1\}\right] + \mathbb{P}\left[\{3\}\right]$$

Now consider event $B = \{\{1\}, \{2\}\}$ and then the event $\{A\} \cup \{B\}$

$$\mathbb{P}\left[A \cup B\right] = \mathbb{P}\left[\{\{1\}, \{3\}\} \cup \{\{1\}, \{2\}\}\right]$$
$$\neq \mathbb{P}\left[A\right] + \mathbb{P}\left[B\right]$$

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Random variables

Consider again the reversible transformation of a protein between two forms $\mathcal{U}$ and $\mathcal{M}$

$$\mathcal{U} \xrightarrow{\kappa_m} \mathcal{M}$$
$$\mathcal{M} \xrightarrow{\kappa_u} \mathcal{U}$$

Suppose that now molecules are labelled in terms of their form (say, $\mathcal{U} = 1$ and $\mathcal{M} = 0$)

Suppose also that before picking a molecule we know that n_u molecules are unmodified
- Thus, we also know that $(\overline{n} - n_u) = n_m$ molecules are in modified form

Consider the event A 'a molecule is of form 1', or $Y = 1$

$$\mathbb{P}\left[Y = 1 | n_u\right] = \frac{n_u}{\overline{n}}$$
$$\neq \underbrace{\mathbb{P}\left[Y = 1\right]}_{\text{unknown}}$$

Conditional on knowing n_u, the probability $\mathbb{P}\left[Y = 1 | n_u\right]$ is given by the ratio between the number of elements in the event space A and the number in the sample space Ω

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Random variables | Discrete

Given $\mathbb{P}\left[Y=1\right]=p_u$ (with p_u to be determined), we have a description of variable Y

$$\begin{cases} \mathbb{P}\left[Y=1\right] & = p_u \\ \mathbb{P}\left[Y=0\right] & = \underbrace{1-p_u}_{p_m} \end{cases}$$

Such a description is referred to as probability (mass) distribution (function)

- Function $\mathbb{P}\left[\cdot\right]$ assigns a likelihood to all possible values y of Y
- (In this problem, probabilities can be assigned to $y \in \{0,1\}$)

Random variable Y is a Bernoulli variable and function $\mathbb{P}\left[\cdot\right]$ is a Bernoulli distribution

- The distribution function has one parameter, p_u

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Random variables | Average

The average is a measure of the expected value from a distribution of probabilities

The average is often associated with a list of values of some measured quantity

1. It is computed by summing all the values collected in the list
2. Then, by dividing it by the number of values in the list

Consider the random variable Y that assign value $y=1$ to un-modified molecules

If n_u out of $\overline{n}$ molecules are known to be un-modified, after summing the labels

$$\underbrace{(1)+(1)+\cdots+(1)}_{n_u \text{ times}}+\underbrace{(0)+(0)+\cdots+(0)}_{(\overline{n}-n_u)\text{ times}}=n_u$$

Conditional on having n_u un-modified molecules, we have the conditional average

$$\begin{aligned}\langle\, Y|n_u\,\rangle &= \frac{(1)\times n_u+(0)\times(\overline{n}-n_u)}{\overline{n}} \\ &= \underbrace{\frac{(1)\times n_u}{\overline{n}}}_{n/\overline{n}}+\underbrace{\frac{(0)\times(\overline{n}-n_u)}{\overline{n}}}_{}\end{aligned}$$

$$\underbrace{}_{n_u/\overline{n}}$$

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Random variables | Average (cont.)

$$\langle\, Y|n_u\,\rangle = \underbrace{(1)\times\frac{n_u}{\overline{n}}+(0)\times\frac{(\overline{n}-n_u)}{\overline{n}}}_{n_u/\overline{n}}$$

The conditional average is a ratio between the size of event $\mathcal{A}$ and the sample space Ω

- It is also equal to the (conditional) probability of $Y=1$

This procedure can be extended to find the unconditional average value of variable Y

$$\begin{aligned}\langle\, Y\,\rangle &= \underbrace{(1)}_{y=1}\times\underbrace{p_u}_{\mathbb{P}\left[Y=1\right]}+\underbrace{(0)}_{y=0}\times\underbrace{(1-p_u)}_{\mathbb{P}\left[Y=0\right]} \\ &= p_u\end{aligned}$$

We can also further generalise the procedure to any discrete random variable Y

$$\langle\, Y\,\rangle = \sum_{y\in A} y\,\mathbb{P}\left[Y=y\right]$$

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Random variables | Variance

The variance is a measure of the spread of the distribution around the average

The variance is the average of the squared deviations $\langle\,(Y-\langle\, Y\,\rangle)^2\,\rangle$

$$\langle\,(Y-\langle\, Y\,\rangle)^2\,\rangle = \sum_{y\in A}(y-\langle\, Y\,\rangle)^2\mathbb{P}\left[Y=y\right]$$

For the problem of the $\mathcal{M}$ and $\mathcal{U}$ molecules, we have

$$\begin{aligned}\langle\,(Y-\langle\, Y\,\rangle)^2\,\rangle &= \left[(1)-p_u\right]^2 p_u+\left[(0)-p_u\right]^2(1-p_u) \\ &= (1-p_u)p_u\end{aligned}$$

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Random variables | Continuous

Consider a protein that can change its length l between two fixed real values a and b

Now imagine an experiment where we can measure the length L of the protein

↝ L can be modelled as a random variable with values in $[a, b]$

We use length $b - a$ of the interval as measure of size and assign probabilities to events

$$l \leq L \leq l + \Delta l$$

If all subintervals of the same length are equally probable, then for any l

$$\mathbb{P}\left[l \leq L \leq l + \Delta l\right] = \frac{\Delta l}{b - a}$$

(We used again the relative-size interpretation of probability)

Now consider a vanishingly small interval $\Delta l \to 0$, we get a probability per unit length

$$\frac{\mathbb{P}\left[l \leq L \leq l + \mathrm{d}l\right]}{\mathrm{d}l} = \frac{1}{(b - a)} \qquad (l \in [a, b])$$

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Random variables | Continuous (cont.)

$$\frac{\mathbb{P}\left[l \leq L \leq l + \mathrm{d}l\right]}{\mathrm{d}l} = \frac{1}{(b - a)} \qquad (l \in [a, b])$$

The probability per unit length is a probability density $p(l)$ of a continuous variable L

The probability that L falls in the interval (a, b)

$$\mathbb{P}\left[a < L < b\right] = \int_a^b \underbrace{p(l)\mathrm{d}l}_{\mathbb{P}[l \in [t, l + \mathrm{d}l]]}$$

$$= 1$$

The expected value of L,

$$\langle L \rangle = \int_l l p(l)\mathrm{d}l$$

$$= (a + b)/2$$

The variance of L,

$$\langle (l - \langle L \rangle)^2 \rangle = \int_l (l - \langle L \rangle)^2 p(l)\mathrm{d}l$$

$$(b - a)^2/12$$

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Random variables | Joint probability

Consider two events A and B that are disjoint, no elements in common, $A \cap B = \emptyset$

↝ The occurrence of one event rules out the occurrence of the other one

We extend the experiment of picking one molecule to the selection of two molecules

↝ For the first molecule, we have variable $Y_1 = \{y_1 = 0, y_1 = 1\}$

↝ For the second one, we have variable $Y_2 = \{y_2 = 0, y_2 = 1\}$

For the two molecules, we have the sample space $\Omega = \Omega_{Y_1} \times \Omega_{Y_2}$

↝ The set of all possible pairs of labels

• $\Omega = \{(0, 0), (0, 1), (1, 1), (1, 0)\}$

Consider the event $Y_1 = y_1 \cap Y_2 = y_2$ and the number of elements in this event space

$$\#(Y_1 = y_1 \cap Y_2 = y_2) = \#(Y_1 = y_1) \times \#(Y_2 = y_2)$$

(True IFF the first selected molecule is placed back before the second selection occurs)

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Random variables | Joint probability (cont.)

Using the relative-size interpretation of probability, we get the joint probability

$$\mathbb{P}\left[Y_1 = y_1 \cap Y_2 = y_2\right] = \frac{\#(Y_1 = y_1) \times \#(Y_2 = y_2)}{\#(\Omega_{Y_1}) \times \#(\Omega_{Y_2})}$$

$$= \frac{\#(Y_1 = y_1)}{\#(\Omega)} \times \frac{\#(Y_2 = y_2)}{\#(\Omega)}$$

$$= \mathbb{P}\left[Y_1 = y_1\right] \times \mathbb{P}\left[Y_2 = y_2\right]$$

The selection sequences $(0, 0)$, $(0, 1)$, $(1, 1)$, and $(1, 0)$ have the likelihoods

↝ For $(0, 0)$, we have $\mathbb{P}\left[Y_1 = 0, Y_2 = 0\right] = \underbrace{\mathbb{P}\left[Y_1 = 0\right]}_{1 - p_u} \times \underbrace{\mathbb{P}\left[Y_2 = 0\right]}_{1 - p_u}$

↝ For $(0, 1)$, we have $\mathbb{P}\left[Y_1 = 0, Y_2 = 1\right] = \underbrace{\mathbb{P}\left[Y_1 = 0\right]}_{1 - p_u} \times \underbrace{\mathbb{P}\left[Y_2 = 1\right]}_{p_u}$

↝ For $(1, 1)$, we have $\mathbb{P}\left[Y_1 = 1, Y_2 = 1\right] = \underbrace{\mathbb{P}\left[Y_1 = 1\right]}_{p_u} \times \underbrace{\mathbb{P}\left[Y_2 = 1\right]}_{p_u}$

↝ For $(1, 0)$, we have $\mathbb{P}\left[Y_1 = 1, Y_2 = 0\right] = \underbrace{\mathbb{P}\left[Y_1 = 1\right]}_{p_u} \times \underbrace{\mathbb{P}\left[Y_2 = 0\right]}_{1 - p_u}$

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Random variables | Joint probability (cont.)

The assumption of independence is the consequence of placing back the first molecule

- (Without replacement, the joint sample space would be smaller, $\overline{n}(\overline{n}-1)$)
- (Also, the size of the joint events would depend on the first outcome)

Without independence, we have the equivalent factorisations of the joint probability

$$\begin{aligned}\mathbb{P}\left[Y_1=y_1 \cap Y_2=y_2\right] &= \mathbb{P}\left[Y_2=y_2 \mid Y_1=y_1\right] \times \mathbb{P}\left[Y_1=y_1\right]\\ &= \mathbb{P}\left[Y_1=y_1 \mid Y_2=y_2\right] \times \mathbb{P}\left[Y_2=y_2\right]\end{aligned}$$

The factorisation of the joint probability $\mathbb{P}\left[A \cap B\right]=\mathbb{P}\left[B\right]\mathbb{P}\left[A|B\right]$ has useful consequences if the sample space Ω can be partitioned into disjoint collections B_1 and B_2

Then, each event $A \cap B_{n_b}$ represents the joint occurrence of A and associated B_{n_b}

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Random variables | Joint probability (cont.)

Summing up the joint occurrences of event A and B_{n_r} gives the probability of event A

$$\begin{aligned}\mathbb{P}\left[A\right] &= \sum_{n_r=1}^{N_r} \mathbb{P}\left[A \cap B_{n_r}\right]\\ &= \sum_{n_r=1}^{N_r} \mathbb{P}\left[B_{n_r}\right]\mathbb{P}\left[A|B_{n_r}\right]\end{aligned}$$

The probability of event A can be represented as the sum of probabilities of the joint occurrence of A with a collection of disjoint events B_{n_r} that cover the sample space Ω

- This relationship is known as the total law of probability

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Random variables | Joint probability (cont.)

We can use the total probability to determine p_u

We defined the probability of picking an unmodified molecule, given $n_u \, \mathcal{U}$ molecules

$$\mathbb{P}\left[Y=1|n_u\right]=n_u/\overline{n}$$

Let N_u be the number of ummodified molecules, a random variable with values n_u

Summing up the probabilities of event $Y=1 \cap N_u=n_u$, over all possible n_u

$$\begin{aligned}\mathbb{P}\left[Y=1\right] &= \sum_{n_u}\mathbb{P}\left[Y=1 \cap N_u=n_u\right]\\ &= \sum_{n_u}\mathbb{P}\left[Y=1|N_u=n_u\right]\mathbb{P}\left[N_u=n_u\right]\\ &= \sum_{n_u}\frac{n_u}{\overline{n}}\mathbb{P}\left[N_u=n_u\right]\\ &= \frac{1}{\overline{n}}\langle N_u \rangle\end{aligned}$$

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Random variables | Sum of random variables

The sum of two or more random variables is also a random variable

The sum $Y_1 + Y_2 = Y$ is a random variable

- $\rightsquigarrow$ $Y=0$ with sequence $(0,0)$
- $\rightsquigarrow$ $Y=1$ with sequences $(1,0)$ and $(0,1)$
- $\rightsquigarrow$ $Y=2$ with sequence $(1,1)$

We know the probabilities of each of those sequences,

$$\mathbb{P}\left[Y=y\right]=\begin{cases}(1-p_u)^2, & y=0\\ 2p_u(1-p_u), & y=1\\ p_u^2, & y=2\end{cases}$$

The expected value $\sum_y y\mathbb{P}\left[Y=y\right]$

$$\begin{aligned}\langle Y \rangle &= (0)(1-p_u)^2 + (1)[2p_u(1-p_u)] + (2)p_u^2\\ &= 2p_u^2\end{aligned}$$

The variance $\sum_y (y-\langle Y \rangle)^2\mathbb{P}\left[Y=y\right]$

$$\begin{aligned}&= (0-2p_u)^2(1-p_u)^2 + (1-2p_u)^2[2p_u(1-p_u)] + (2-2p_u)^2p_u^2\\ &= 2p_u(1-p_u)\end{aligned}$$

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Random variables | Sum of random variables (cont.)

The average of the sum is the sum of the averages

$$\left\langle \sum_{n_y} Y_{n_y} \right\rangle = \sum_{n_y} \left\langle Y_{n_y} \right\rangle$$

The variance of the sum is the sum of the variances

$$\left\langle \left(\sum_{n_y} Y_{n_y} - \left\langle \sum_{n_y} Y_{n_y} \right\rangle \right)^2 \right\rangle = \sum_{n_y} \left\langle \left(Y_{n_y} - \left\langle Y_{n_y} \right\rangle \right)^2 \right\rangle$$

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Random variables | Probability distributions

Consider a further extension of the experiment of selecting molecules $\mathcal{U} = 1$ and $\mathcal{M} = 0$

⤳ We selected a single molecule, then we selected two molecules

• While always keeping the same p_u

We now consider the case of selecting $\overline{n}$-long sequences of molecules, with replacement

Variable $N = \sum_{n=1}^{\overline{n}} Y_n$ models the number of unmodified molecules in the sequence

The probability of a sequence of n_u (1)s first and then $(\overline{n} - n_u)$ (0)s

$$\mathbb{P}\left[Y = \left(\underbrace{(1) \cdots (1)}_{n_u \text{ times}} \underbrace{(0) \cdots (0)}_{(\overline{n}-n) \text{ times}} \right) \right] = p_u^n (1 - p_u)^{\overline{n} - n_u}$$

There are a known number of sequences of n_u (1)s and $(\overline{n} - n_u)$ (0)s

$$\binom{\overline{n}}{n_u} = \frac{\overline{n}!}{n_u! \, (\overline{n} - n_u)!}$$

Each is equally probable, thus

$$\mathbb{P}[N = n_u] = \binom{\overline{n}}{n_u} \left[p_u^{n_u} (1 - p_u)^{\overline{n} - n_u} \right]$$

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Random variables | Probability distributions (cont.)

Random variable N has a binomial distribution $\mathbb{P}[N = n_u] = \binom{\overline{n}}{n_u} \left[p_u^{n_u} (1 - p_u)^{\overline{n} - n_u} \right]$

• The parameters of the distribution are $\overline{n}$ and p_u

The expected value,

$$\langle N \rangle = \overline{n} p_u$$

The variance,

$$\left\langle \left(n - \langle N \rangle \right)^2 \right\rangle = \overline{n} p_u \left(1 - p_u \right)$$

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Random variables | Probability distributions (cont.)

Consider the problem of increasing the length $\overline{n}$ of the sequence while decreasing p_u

$$\uparrow \overline{n} \times p_u \downarrow = \underbrace{\text{constant}}_{\mu}$$

The limiting behaviour of the binomial, for infinitely large $\overline{n}$ and infinitely small p_u

For $\overline{n} \to \infty$, we have

$$\binom{\overline{n}}{n_u} p_u^n = \frac{\overline{n}(\overline{n} - 1)(\overline{n} - 2) \cdots (\overline{n} - n_u + 1)}{n!} p_u^{n_u}$$

$$= \frac{\overline{n} p_u}{n_u!} \left(1 - \frac{1}{\overline{n}} \right) \cdots \left(1 - \frac{n_u - 1}{\overline{n}} \right)$$

$$\to \frac{\mu^{n_u}}{n_u!}$$

For $\overline{n} \to \infty$, we have

$$(1 - p_u)^{\overline{n}} = \left(1 - \frac{\mu}{\overline{n}} \right)^{\overline{n}}$$

$$\to e^{-\mu}$$

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Random variables | Probability distributions (cont.)

$$\mathbb{P}\left[N = n_u\right] = \underbrace{\binom{\overline{n}}{n_u} p_u^{n_u}}_{\dfrac{\mu^{n_u}}{n_u!}} \underbrace{\left(1 - p_u\right)^{\overline{n} - n_u}}_{e^{-\mu}}$$

Substituting, we get

$$\mathbb{P}\left[N = n_u\right] = \frac{\mu^{n_u} e^{-\mu}}{n_u!}$$

This is called the Poisson distribution with parameter μ and Y is a Poisson variable
- Parameter μ substitutes $\overline{n} \times p_u$
- Model for rare events

The expected value,

$$\left\langle N \right\rangle = \mu$$

The variance,

$$\left\langle \left(N - \left\langle N \right\rangle\right)^2 \right\rangle = \mu$$

For infinitesimally small p_u, average and the variance of the distribution are the same

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Random variables | Poisson processes

Suppose we repeat the experiment of picking a sequence of $\overline{n}$ molecules at each time t
- At each time t, we determine how many of them are in unmodified form

We have a random process $(N(t))_{t \geq 0}$ and $\left\langle (N(t))_{t \geq 0} \right\rangle$ is its expected time course

Consider the zeroth-order reaction in which molecules of a certain protein $\mathcal{S}$ are produced from some uninteresting reactants, here $\emptyset$, at a constant conversion rate $\lambda = \widehat{k}$

$$\emptyset \xrightarrow{\lambda} \mathcal{S}$$

In the deterministic setup, the time-dependent abundance $n(t)$ has kinetics $\dot{n}(t) = \widehat{k}$

$$n(t) = \widehat{k}t$$

In the stochastic setting, the time-dependent abundance can be seen as mean trajectory

$$\left\langle N(t) \right\rangle = \lambda t$$

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Random variables | Poisson processes (cont.)

$$\emptyset \xrightarrow{\lambda} \mathcal{S}$$

We are interested in the random process $N(t + s) - N(t)$ representing the random increment in abundance of species $\mathcal{S}$ in the time interval $[t, t + s)$, from a known $N(t)$

Consider the average increment

$$\begin{aligned}
\left\langle N(t + s) - N(t) \right\rangle &= \left\langle N(t + s) \right\rangle - \left\langle N(t) \right\rangle \\
&= \lambda(t + s) - \lambda t \\
&= \lambda s
\end{aligned}$$

The expected increment is independent of time t when the measurement is performed
  ⇝ This is an important result

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Random variables | Poisson processes (cont.)

$$[t, t + s)$$

Suppose that we divide the time interval $[t, t+s)$ in K subintervals of length $\Delta s = s/K$
  ⇝ The intervals Δs are so small that only one reaction (production) occurs
  ⇝ We let the probability of occurrence of the reaction in Δs to be $\lambda \Delta s$
  ⇝ (This probability is thus a Bernoulli random variable)

Each subinterval Δs contributes an increment ΔN to the abundance current $N(t)$

The expected contribution from each subinterval,

$$\left\langle \Delta N \right\rangle = \lambda \Delta s$$

$$= \lambda \frac{s}{K}$$

The subincrement is a Bernoulli variable, as only one of two events can occur in Δs
- A production reaction occurs and $\Delta N = 1$, with probability $p = \lambda \Delta s$
- No reaction occurs and $\Delta N = 0$, with probability $q = 1 - p$

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Random variables | Poisson processes (cont.)

$$\langle \Delta N \rangle = \lambda \frac{s}{K}$$

As $p = \lambda \Delta s$, we interpret conversion rates λ as reaction probabilities in the unit time
  ⤳ Importantly, note that the probability $\lambda \Delta s$ does not depend on s or $N(t)$

$$\emptyset \xrightarrow{\lambda} \mathcal{S}$$

For the production reaction, we have defined the random process

$$N(t + s) - N(t) = K \Delta N(s)$$

This is a sum of K Bernoulli variables, hence a binomial variable
  ⤳ The parameters of the distribution are K and p

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Random variables | Poisson processes (cont.)

$$N(t + s) - N(t) = K \Delta N(s)$$

K must be large for the subinterval to be small to allow only one rare reaction event
  • For $K \to \infty$ and $p \to 0$, a binomial variable becomes Poissonian

$$\mathbb{P}\left[N(t + s) - N(t) = n\right] = \mathbb{P}\left[N(s) = n\right]$$
$$= \frac{(\lambda s)^n \mathrm{e}^{-\lambda s}}{n!}$$

We have a time-dependent (on s) probability, a Poisson process with rate parameter λ
  • The average and the variance of the process are equal to $\mu = \lambda s$

Independence on t implies that increments in non-overlapping intervals are stationary
  • Lack of dependence on $N(t)$ implies that increments are identically distributed

$$\emptyset \xrightarrow{\lambda} \mathcal{S}$$

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Random variables | Poisson processes (cont.)

$$\mathbb{P}\left[N(t + s) - N(t) = n\right] = \mathbb{P}\left[N(s) = n\right]$$
$$= \frac{(\lambda s)^n \mathrm{e}^{-\lambda s}}{n!}$$

Let us consider the case of $n = 0$, we get

$$\mathbb{P}\left[N(s) = 0\right] = \frac{(\lambda s)^0 \mathrm{e}^{-\lambda s}}{0!}$$
$$= \mathrm{e}^{-\lambda s}$$

The time S until the next reaction has probability $\mathrm{e}^{-\lambda s}$ of being greater than s

$$\mathbb{P}\left[S > s\right] = \mathrm{e}^{-\lambda s}$$

It implies that time S is an exponentially distributed variable, with parameter λ
  • The distribution does not depend on t or $N(t)$
The times between reactions are independent and identically distributed variables

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Random variables | Poisson processes (cont.)

The time S until the next reaction is exponentially distributed

$$p(s) = \lambda \mathrm{e}^{-\lambda s} \qquad (s \geq 0)$$

The probability of the next reaction between $[t, t + s]$

$$\mathbb{P}\left[S_n \leq s\right] = 1 - e^{-\lambda s}$$
$$= \int_{-\infty}^{s} p(s) \mathrm{d}s$$

The exponential distribution does not remember its past

$$\mathbb{P}\left[S > t + s \mid S > t\right] = \frac{\mathbb{P}\left[S > t + s \cap S > t\right]}{\mathbb{P}\left[S > t\right]}$$
$$= \frac{\mathbb{P}\left[S > t + s\right] \mathbb{P}\left[S > t\right]}{\mathbb{P}\left[S > t\right]}$$
$$= \frac{\mathbb{P}\left[S > t + s\right]}{\mathbb{P}\left[S > t\right]}$$
$$= \frac{\mathrm{e}^{-\lambda(t+s)}}{\mathrm{e}^{-\lambda s}}$$
$$= \underbrace{e^{-\lambda s}}_{\mathbb{P}[S>s]}$$

Random variables | Poisson processes (cont.)

$$\mathbb{P}\left[S > t + s \mid S > t\right] = \mathbb{P}\left[S > s\right]$$

Given that an event has not occurred until time t, the probability that it will not occur in an additional time s equals the probability of the event no occurring until a time s

⤳ This is the memoryless property of the exponential distribution

⤳ Any variable satisfying the property is an exponential variable

---

Random variables | Poisson processes (cont.)

$$\emptyset \xrightarrow{\lambda} \mathcal{S}$$

We may be interested in characterising the time S_n of occurrence of the n-th reaction

• This is the time the process needs to reach state n

• The arrival time of the n-th reaction

We consider the likelihood that the n-th reaction occurs in some interval $[s, s + \Delta s]$

1 $n - 1$ reactions must have occurred in $[0, s]$

2 The n-th reaction in the interval Δs

The event of interest is a joint event that involves two non-overlapping time intervals

$$\begin{aligned}
\mathbb{P}\left[s \le S_n \le s + \Delta t\right] &= \mathbb{P}\left[(N(t) = n - 1) \cap (\Delta N(t) = 1)\right] \\
&= \mathbb{P}\left[N(t) = n - 1\right] \times \mathbb{P}\left[\Delta N(t) = 1\right] \\
&= \frac{e^{-\lambda s}(\lambda s)^{n-1}}{(n-1)!} \times (\lambda \Delta s)
\end{aligned}$$

Random variables | Poisson processes (cont.)

$$\emptyset \xrightarrow{\lambda} \mathcal{S}$$

That is, the probability density of the n-th arrival time S_n

$$p(s) = \frac{\lambda^n s^{n-1}}{(n-1)!} e^{-\lambda s}$$

The distribution of an Erlang variable with rate parameter λ and shape parameter n

Because arrival times can be described as sums $\sum_{n=0}^{n-1} S_n$ of n inter-reaction times, all exponentially distributed with the rate parameter λ, their sum are Erlang variables

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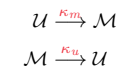## Random variables | Reactions

Poisson processes describe time-dependent abundances $N(t)$ for zeroth-order reactions

⤳ The conversion rate λ was interpreted as probability per unit time

We are interested in whether a similar interpretation is valid for arbitrary reactions (?)

Consider the usual modification/demodification reaction of a protein between two forms

$$\mathcal{U} \xrightarrow{\kappa_m} \mathcal{M}$$
$$\mathcal{M} \xrightarrow{\kappa_u} \mathcal{U}$$

In the deterministic set up, we have the two conversion rates

$$\dot{z}_m(t) = k_m n(t)$$
$$\dot{z}_u(t) = k_u \left[\overline{n} - n(t)\right]$$

The reaction count increments during a small interval $[t, t + \Delta t]$

$$\Delta z_m(t) = k_m n(t) \Delta t$$
$$\Delta z_u(t) = k_u \left[\overline{n} - n(t)\right] \Delta t$$

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Random variables | Reactions (cont.)

$$\mathcal{U} \xrightarrow{\kappa_m} \mathcal{M}$$
$$\mathcal{M} \xrightarrow{\kappa_u} \mathcal{U}$$

In the stochastic setup, the count increments are replaced by two stochastic processes

- Both counts are Bernoulli variables, as at most one event occurs in Δt
- The average of a Bernoulli variable is the success probability

The deterministic increments can only be interpreted in an average sense

$$\langle \Delta Z_m(t) \mid N(t) = n(t) \rangle = k_m n(t) \Delta t$$
$$\langle \Delta Z_u(t) \mid N(t) = n(t) \rangle = k_u \left[\overline{n} - n(t) \right] \Delta t$$

That is,
- $\rightsquigarrow$ $k_m n(t) \Delta t$ is the success probability for the modification
- $\rightsquigarrow$ $k_u \left[\overline{n} - n(t) \right] \Delta t$ is the success probability for demodification

Then, $k_m n(t)$ and $k_u \left[\overline{n} - n(t) \right]$ are probabilities per unit time of the respective reaction

Differently from the Poisson process, this process have a state-dependent probability

- A Markov process

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Random variables | Reactions (cont.)

$$\mathcal{U} \xrightarrow{\kappa_m} \mathcal{M}$$
$$\mathcal{M} \xrightarrow{\kappa_u} \mathcal{U}$$

Let $T_m(n)$ and $T_u(n)$ be times until the next modification and demodification reaction

The probability of a modification in Δt is $k_w n \Delta t$
- If n is constant, a Poisson arrival
- $T_m(n)$ is an exponential variable
- The rate parameter is $k_m n$

The probability of a demodification in Δt is $k_u \left[\overline{n} - n \right] \Delta t$
- If $\left[\overline{n} - n \right]$ is constant, a Poisson arrival
- $T_u(n)$ is an exponential variable
- The rate parameter $k_u \left[\overline{n} - n \right]$

We could draw both times and use the shortest one to deduce which reaction occured

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Random variables | Reactions (cont.)

Alternatively, we can determine the time $T_n(n)$ until the next reaction
- Irrespective of which one it will be

As long as n does not change, the next reaction is a Poisson arrival
- $T_n(n)$ is an exponential variable
- Parameter $k_m \left[n \right] + k_u \left[\overline{n} - n \right]$

The type of the next reaction

- Modification, with probability $\dfrac{k_m \left[n \right]}{k_m \left[n \right] + k_u \left[\overline{n} - n \right]}$

- De-modification, with probability $\dfrac{k_u \left[\overline{n} - n \right]}{k_m \left[n \right] + k_u \left[\overline{n} - n \right]}$ or $1 - \dfrac{k_m \left[n \right]}{k_m \left[n \right] + k_u \left[\overline{n} - n \right]}$

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Stochastic formulation

Reaction networks

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Stochastic formulation

We show how the notion of propensity, the chemical master equation, and the stochastic simulation algorithm can be seen as emerging as consequence of the Markov property

The presentation is based on the stochastic formulation of an arbitrary reaction network

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We started acknowledging that modelling the occurrence of reactions involves discrete and random events that arise from a system that is not described microscopically

- It is not possible to predict deterministically the progress of a reactive system, starting from (macroscopic) variables (copy number and relative concentration)
- The processes $(N(t))_{t \geq 0}$, $(Z(t))_{t \geq 0}$, or $(X(t))_{t \geq 0}$ must be stochastic

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Stochastic formulation (cont.)

Say, we choose the copy-number $N(t)$, then the sample value $n(t)$ is the system's state
- ⤳ The objective is to determine the evolution of the process $(N(t))_{t \geq 0}$

Starting at time $t = 0$, from some initial state $N(t = 0) = N(0)$, the system remains in state $N(0)$ for a random amount of time, S_1, until the occurrence of a reaction event
- ⤳ Then, the state changes from $N(t = 0)$ to become $N(t = S_1)$

The system remains in state $N(S_1)$ for another random amount of time, say S_2
- ⤳ Until the occurrence of a new reaction, then $N(t = S_1 + S_2)$

The collection $(N(t))_{t \geq 0}$ of time-dependent copy-numbers is a stochastic process
- A collection of state probabilities and state-transition probabilities
- This specific stochastic process is called a jump process

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Stochastic formulation (cont.)

$$(N(t))_{t \geq 0}$$

The state probability is the probability that the process is in state n at certain time t

$$\text{Prob}\left[N(t) = n\right] = \mathbb{P}(n, t)$$
$$= \mathbb{P}(n(t))$$
$$= \mathbb{P}_n(t)$$

If one species, $N_s = 1$
$$N(t) = n \in \{0, 1, 2, \dots\}$$
If two species, $N_s = 2$
$$N(t) = (n_1, n_2) \in \{0, 1, 2, \dots\} \times \{0, 1, 2, \dots\}$$
If N_s species
$$N(t) = (n_1, n_2, \dots, n_{N_s}) \in \underbrace{\{0, 1, 2, \dots\} \times \{0, 1, 2, \dots\} \times \cdots \times \{0, 1, 2, \dots\}}_{N_s \text{ times}}$$

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Stochastic formulation (cont.)

$$(N(t))_{t \geq 0}$$

The state-transition probability is the conditional probability that the process, during the time interval $[t, t + s)$, evolves to state n, given that it started in state n' at t

$$\text{Prob}\left[N(t + s) = n \mid N(t) = n'\right] = \mathbb{P}(n, t + s \mid n', t)$$
$$= \mathbb{P}(n(t + s) \mid n'(t))$$
$$= \mathbb{P}_{n|n'}(t + s \mid t)$$

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Stochastic formulation (cont.)

We assume that the state-transition probability depends only on state n at t, not on earlier ones, and that the duration s of the interval does not depend on initial time t

⤳ Markovianity (first assumption)

⤳ Time-homogeneity (second assumption)

When the molecules in the reaction system are well-mixed and available everywhere for reaction, then $(N(t))_{t \geq 0}$ can be formulated as time-homogeneous Markov process

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Stochastic formulation (cont.)

We can write state and state-transition probability functions using a simplified notation

$$\text{Prob}\left[N(t) = n\right] = \mathbb{P}_n(t)$$
$$\text{Prob}\left[N(t+s) = n \mid N(t) = n'\right] = \mathbb{P}_{n|n'}(t+s|t)$$

The initial condition is often, although not necessarily, fixed to be $N(t=0) = n^0$

Thus, the state probability can always be given as transition probability

$$\mathbb{P}_{n|n^o}(t|0) = \text{Prob}\left[N(t) = n \mid (N(0) = n^0\right]$$

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Chapman-Kolmogorov

Stochastic formulation

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Chapman-Kolmogorov

Markovianity sets a consistence condition on the transition probabilities $\mathbb{P}_{n|n'}(t+s|t)$

Consider the probability of being at state n' at some time $t+s$, given initial state n^0

$$\mathbb{P}_{n|n^0}(t+s|0) = \sum_{n'} \mathbb{P}_{n|n',n^0}(t+s|t,0)\mathbb{P}_{n'|n^0}(t|0)$$
$$= \sum_{n'} \mathbb{P}_{n|n'}(t+s|t)\mathbb{P}_{n'|n^0}(t|0)$$

Because of first-order Markovianity, we can ignore information about the initial state

We can write the Chapman-Kolmogorov equation for continuous-Markov processes

$$\mathbb{P}_{n|n^0}(t+s|0) = \sum_{n'} \mathbb{P}_{n|n'}(t+s|t)\mathbb{P}_{n'|n^0}(t|0)$$

Spelling the equation, the probability of a transition $n^0 \to n'$ can be computed as the summation of probabilities of all transitions $n^0 \to n \to n'$ via intermediate states n'

To characterise the equation to a specific process, we need relations between variables

- Form the local behaviour of transition probabilities over a short interval Δs

$$\mathbb{P}_n(t+\Delta s) = \sum_{n'} \mathbb{P}_{n|n'}(t+\Delta s|t)\mathbb{P}_{n'}(t)$$
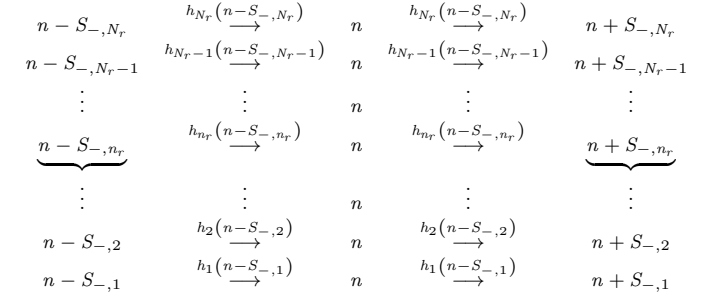
Master equation

Stochastic simulation

Master equation

The occurrence of any reaction event moves the system from some state to another one

The possible state transitions to state n and from state n

$$
\begin{array}{ccccc}
n - S_{-,N_r} & \xrightarrow{h_{N_r}\left(n - S_{-,N_r}\right)} & n & \xrightarrow{h_{N_r}\left(n - S_{-,N_r}\right)} & n + S_{-,N_r} \\
n - S_{-,N_r-1} & \xrightarrow{h_{N_r-1}\left(n - S_{-,N_r-1}\right)} & n & \xrightarrow{h_{N_r-1}\left(n - S_{-,N_r-1}\right)} & n + S_{-,N_r-1} \\
\vdots & \vdots & n & \vdots & \vdots \\
\underbrace{n - S_{-,n_r}} & \xrightarrow{h_{n_r}\left(n - S_{-,n_r}\right)} & n & \xrightarrow{h_{n_r}\left(n - S_{-,n_r}\right)} & \underbrace{n + S_{-,n_r}} \\
\vdots & \vdots & n & \vdots & \vdots \\
n - S_{-,2} & \xrightarrow{h_2\left(n - S_{-,2}\right)} & n & \xrightarrow{h_2\left(n - S_{-,2}\right)} & n + S_{-,2} \\
n - S_{-,1} & \xrightarrow{h_1\left(n - S_{-,1}\right)} & n & \xrightarrow{h_1\left(n - S_{-,1}\right)} & n + S_{-,1}
\end{array}
$$

The transition rate of a state transition from a single reaction equals the propensity of that reaction and the transition rate from more reaction is the sum of their propensities

---

Master equation (cont.)

$$
\underbrace{n - S_{-,n_r}} \xrightarrow{h_{n_r}\left(n - S_{-,n_r}\right)} n \xrightarrow{h_{n_r}\left(n - S_{-,n_r}\right)} \underbrace{n + S_{-,n_r}}
$$

We used

$$
\underbrace{\begin{bmatrix} n_1 \\ \vdots \\ n_s \\ \vdots \\ N_s \end{bmatrix}}_{n} - \underbrace{\begin{bmatrix} S_{1,n_r} \\ \vdots \\ S_{n_s,n_r} \\ \vdots \\ S_{N_s,n_r} \end{bmatrix}}_{S_{-,n_r}} \quad \text{and} \quad \underbrace{\begin{bmatrix} n_1 \\ \vdots \\ n_s \\ \vdots \\ N_s \end{bmatrix}}_{n} + \underbrace{\begin{bmatrix} S_{1,n_r} \\ \vdots \\ S_{n_s,n_r} \\ \vdots \\ S_{N_s,n_r} \end{bmatrix}}_{S_{-,n_r}}
$$

The stoichiometric matrix

$$
S = \begin{bmatrix}
\left(\overline{S}_{1,1} - \underline{S}_{1,1}\right) & \cdots & \left(\overline{S}_{n_s,1} - \underline{S}_{n_s,1}\right) & \cdots & \left(\overline{S}_{N_s,1} - \underline{S}_{N_s,1}\right) \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
\left(\overline{S}_{1,n_r} - \underline{S}_{1,n_r}\right) & \cdots & \left(\overline{S}_{n_s,n_r} - \underline{S}_{n_s,n_r}\right) & \cdots & \left(\overline{S}_{N_s,n_r} - \underline{S}_{N_s,n_r}\right) \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
\left(\overline{S}_{1,N_r} - \underline{S}_{1,N_r}\right) & \cdots & \left(\overline{S}_{n_s,N_r} - \underline{S}_{n_s,N_r}\right) & \cdots & \left(\overline{S}_{N_s,N_r} - \underline{S}_{N_s,N_r}\right)
\end{bmatrix}^T
$$

Master equation (cont.)

The probability to be at state $n = (n_1, \ldots, n_s, \ldots, N_s)$ at time t changes with time

$$
\mathbb{P}_n(t)
$$

To understand how $\mathbb{P}_n(t)$ changes in time, we need to determine $\mathbb{P}_n(t + \Delta t)$

⤳ The probability of being in state n after a short interval Δt

For vanishingly small Δt, we could then use $\mathbb{P}_n(t)$ and $\mathbb{P}_n(t + \Delta t)$ to get

$$
\frac{\mathbb{P}_n(t) - \mathbb{P}_n(t + \Delta t)}{\Delta t} \rightsquigarrow \frac{\mathrm{d}\mathbb{P}_n(t)}{\mathrm{d}t}
$$

The resulting equation of motion can be integrated, from an initial condition $\mathbb{P}_n(t_0)$

- The solution $\left(\mathbb{P}_n(t) \mid \mathbb{P}_n(t_0)\right)_{t \geq 0}$ is the transition probability kernel

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Master equation (cont.)

We must determine how to reach state n at $t + \Delta t$, given that at t the state is n'

→ State n can be reached any state n' such that $n' = n - S_{-,1 \rightsquigarrow N_r}$

→ State n can be reached any state n' such that $n' = n$

For each of the options, we know also the probability of occurrence in a small Δt

$$\mathbb{P}_{n|n'}(\Delta t) = \begin{cases} h_1\left(n - S_{-,1} \mid \kappa_1\right)\Delta t, & n' = n - S_{-,1} \\ h_2\left(n - S_{-,2} \mid \kappa - 2\right)\Delta t, & n' = n - S_{-,2} \\ \cdots, & \cdots \\ h_{n_r}\left(n - S_{-,n_r} \mid \kappa_{n_r}\right)\Delta t, & n' = n - S_{-,n_r} \\ \cdots, & \cdots \\ h_{N_r-1}\left(n - S_{-,N_r-1} \mid \kappa_{N_r-1}\right)\Delta t, & n' = n - S_{-,N_r-1} \\ h_{n_r}\left(n - S_{-,N_r} \mid \kappa_{N_r}\right)\Delta t, & n' = n - S_{-,N_r} \\ 1 - \sum_{n_r=1}^{N_r} h_{n_r}\left(n|\kappa_{n_r}\right)\Delta t, & n' = n \\ 0, & \text{elsewhere} \end{cases}$$

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Master equation (cont.)

Substituting the expressions for $\mathbb{P}_{n|n'}(\Delta t)$ into Chapman-Kolmogorov, we get

$$\mathbb{P}_n(t + \Delta t) = \sum_{n'} \mathbb{P}_{n|n'}(\Delta t)\mathbb{P}_{n'}(t)$$

$$= h_1\left(n - S_{-,1}\right)\Delta t \mathbb{P}_{n-S_{-,1}}(t)$$
$$+ h_2\left(n - S_{-,2}\right)\Delta t \mathbb{P}_{n-S_{-,2}}(t)$$
$$+ \cdots$$
$$+ h_{n_r}\left(n - S_{-,n_r} \mid \kappa_{n_r}\right)\Delta t \mathbb{P}_{n-S_{-,n_r}}(t)$$
$$+ \cdots$$
$$+ h_{N_r-1}\left(n - S_{-,N_r-1} \mid \kappa_{N_r-1}\right)\Delta t \mathbb{P}_{n-S_{-,N_r-1}}(t)$$
$$+ h_{n_r}\left(n - S_{-,N_r} \mid \kappa_{N_r}\right)\Delta t \mathbb{P}_{n-S_{-,N_r}}(t)$$
$$+ \left[1 - \sum_{n_r=1}^{N_r} h_{n_r}\left(n|\kappa_{n_r}\right)\Delta t\right]\mathbb{P}_n(t)$$

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Master equation (cont.)

$$\mathbb{P}_n(t + \Delta t) = \mathbb{P}_n(t)\left[1 - \sum_{n_r=1}^{N_r} h_{n_r}\left(n \mid \kappa_r\right)\Delta t\right]$$
$$+ \sum_{n_r=1}^{N_r} \mathbb{P}_{n-S_{-,n_r}} h_{n_r}\left(n - S_{-,n_r} \mid \kappa_{n_r}\right)\Delta t + \text{h.o.t.}$$

Neglecting the higher-order terms and rearranging, we can write

$$\frac{\mathbb{P}_n(t + \Delta t) - \mathbb{P}_n(t)}{\Delta t} = -\sum_{n_r=1}^{N_r} \mathbb{P}_n(t)h_{n_r}\left(n \mid \kappa_r\right) + \sum_{n_r=1}^{N_r} \mathbb{P}_{n-S_{-,n_r}} h_{n_r}\left(n - S_{-,n_r} \mid \kappa_{n_r}\right)$$

$$= \sum_{n_r=1}^{N_r} \left[\mathbb{P}_{n-S_{-,n_r}} h_{n_r}\left(n - S_{-,n_r} \mid \kappa_{n_r}\right) - \mathbb{P}_n(t)h_{n_r}\left(n \mid \kappa_r\right)\right]$$

For a vanishingly small time interval Δt, we get the chemical master equation

$$\frac{\mathrm{d}\mathbb{P}_n(t)}{\mathrm{d}t} = \sum_{n_r=1}^{N_r} \left[\underbrace{h_{n_r}\left(n - S_{-,n_r} \mid \kappa_{n_r}\right)\mathbb{P}_{n-S_{-,n_r}}(t)} - \underbrace{h_{n_r}\left(n \mid \kappa_{n_r}\right)\mathbb{P}_n(t)}\right]$$