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Aalto University

Higher-order reactions
Stochastic analysis and simulation of reactive and diffusive systems

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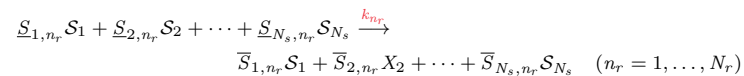

Stochastic kinetics
Reaction networks

Stochastic mass-action kinetics

We considered the molecules of N_s chemical species homogeneously distributed in a volume V, at thermal equilibrium, interacting through N_r irreversible reaction channels

We symbolised the n_s-th species with $\mathcal{S}_{n_s}$ and its abundance in the reaction compartment at time t with copy-numbers $N_{n_s}(t)$, the reaction channels were denoted by $\mathcal{R}_{n_r}$

For any n_r-th reaction channel involving the N_s species, we have the chemical equation

$$\underline{S}_{1,n_r}\mathcal{S}_1 + \underline{S}_{2,n_r}\mathcal{S}_2 + \cdots + \underline{S}_{N_s,n_r}\mathcal{S}_{N_s} \xrightarrow{k_{n_r}}$$
$$\overline{S}_{1,n_r}\mathcal{S}_1 + \overline{S}_{2,n_r}X_2 + \cdots + \overline{S}_{N_s,n_r}\mathcal{S}_{N_s} \quad (n_r = 1, \ldots, N_r)$$

At time t, the state of the system of size Ω is the collection of abundances of all species

$$N(t) = (N_1(t), N_2(t), \ldots, N_{N_s}(t))$$
$$X(t) = (X_1(t), X_2(t), \ldots, X_{N_s}(t))$$

Stochastic mass-action kinetics (cont.)

Often, we have deterministic rate laws with definite orders, in which the conversion rate $\widehat{v}_{n_r}\left(N^c(t)\right)$ is proportional to the copy-number of reactants raised to some power

$$\widehat{v}_{n_r}\left(X^c(t)\right) = \widehat{k}_{n_r} \prod_{n_s=1}^{N_s} N_{n_s}^c(t)^{\underline{S}_{n_s,n_r}}$$

The conversion rate $\widehat{v}(X^c(t) \mid \widehat{k}_{n_r})$ is the reaction count per unit of time

- The conversion rate constant $\widehat{k}_{n,r}$ has always units $\sec^{-1}$

Similarly, we have deterministic rate laws with definite orders, in which the reaction rate $v_{n_r}\left(X^c(t)\right)$ is proportional to the concentration of reactants raised to some power

$$v_{n_r}\left(X^c(t)\right) = k_{n_r} \prod_{n_s=1}^{N_s} X_{n_s}^c(t)^{\underline{S}_{n_s,n_r}}$$

The reaction rate $v\left(X^c(t) \mid k_{n_r}\right)$ is the reaction count per unit of time and system size

- The reaction rate constant $k_{n,r}$ has units that depend also on Ω

Stochastic mass-action kinetics (cont.)

There exists a relationship that combines reaction rate and conversion rate constants

By equating the conversion rate and the (overall) reaction rate, we get

$$\underbrace{\widehat{k}_{n_r} \prod_{n_s=1}^{N_s} N_{n_s}^c(t)^{\underline{S}_{n_s,n_r}}}_{\widehat{v}(\cdot)} = \underbrace{\Omega k_{n_r} \prod_{n_s=1}^{N_s} X_{n_s}^c(t)^{\underline{S}_{n_s,n_r}}}_{\Omega v(\cdot)}$$

Because we have that $N_{n_s} = \Omega X_{n_s}$, we get

$$\widehat{k}_{n_r} = \frac{k_{n_r}}{\Omega^{\sum_{n_s=1}^{N_s} \underline{S}_{n_s,n_r} - 1}}$$

Stochastic mass-action kinetics (cont.)

At time t, we have the collection of copy-numbers of all species

$$N(t) = (N_1(t), N_2(t), \ldots, N_{N_s}(t))$$

The progress $Z_{n_r}(t)$ of the n_r-th channel is the reaction count

$$Z(t) = (Z_1(t), \ldots, Z_{N_r}(t))$$

When a reaction occurs, the state is updated

$$N(t) = N(t = 0) + SZ(t)$$

Stochastic mass-action kinetics (cont.)

The basis for the stochastic analysis and simulation is the probability per unit time of occurrence of reaction $\mathcal{R}_{n_r}$, or the reaction propensity, given the system state $N(t)$

$$\underline{S}_{1,n_r}\mathcal{S}_1 + \underline{S}_{2,n_r}\mathcal{S}_2 + \cdots + \underline{S}_{N_s,n_r}\mathcal{S}_{N_s} \xrightarrow{\kappa_{n_r}}$$
$$\overline{S}_{1,n_r}\mathcal{S}_1 + \overline{S}_{2,n_r}X_2 + \cdots + \overline{S}_{N_s,n_r}\mathcal{S}_{N_s} \quad (n_r = 1, \ldots, N_r)$$

Each reaction $\mathcal{R}_{n_r}$ is equipped with a rate constant κ_{n_r} and a rate law $\nu_{n_r}(N(t) \mid \kappa_{n_r})$
  ⤳ We can think of the stochastic rate law as an hazard or propensity function

$$\nu_{n_r}(N(t) \mid \kappa_{n_r})$$

  ⤳ With associated stochastic rate constant, an hazard or propensity constant

$$\kappa_{n_r}$$

The rate law and the interpretation of the constant is determined by the reaction order

The dependence of the rate law only on state $N(t)$ is linked to modelling assumption
  - (The relationship reflects our assumption about the system)
  - (Elementary reactions | well-mixed | thermal equilibrium)

Stochastic mass-action kinetics (cont.)

For a well-mixed system in thermal equilibrium, each combination of molecules involved in the $\mathcal{R}_{n_r}$ channel is assumed to have the same probability per unit time to react, κ_{n_r}

$\kappa_{n_r} dt$ is the probability that a particular combination of molecules reacts in $[t, t+dt)$
  ⤳ κ_{n_r} is thus the hazard or stochastic rate constant

When at state $n(t)$, there are $h_{n_r}(n(t))$ combinations of molecules for reaction $\mathcal{R}_{n_r}$

Conditional on the state of system $N(t)$ being $n(t)$, the probability that a reaction $\mathcal{R}_{n_r}$ occurs in the time interval $[t, t+dt)$ is given by the function $\nu_{n_r}(n(t) \mid \kappa_{n_r}) dt$

Thus, we can write the propensity function, or stochastic rate law

$$\nu_{n_r}(n(t) \mid \kappa_{n_r}) = \kappa_{n_r} h_{n_r}(n(t))$$

The specific form of function $h_{n_r}(n(t))$ depends on the reaction order of channel $\mathcal{R}_{n_r}$

Stochastic mass-action kinetics (cont.)

In the absence of other reactions taking place, the time until one such reaction event

$$\text{Exp}\left(\nu_{n_r}\left(n(t) \mid \kappa_{n_r}\right)\right)$$

However, other reactions may occur in $[t, t + \mathrm{d}t]$ and change $n(t)$ during the interval

- Thus, this time is only assumed to be exponentially distributed

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Zeroth-order reactions

Reaction networks

Zeroth-order reaction

We consider a zeroth-order reaction (production of species $\mathcal{S}_{n_s}$) for the n_r-th channel

$$\emptyset \xrightarrow{\kappa_{n_r}} \mathcal{S}_{n_s}$$

The equation does not state that $\mathcal{S}_{n_s}$ is created from nothing, but rather that it is produced from uninteresting species, or that there is an influx from another compartment

Rate constant κ_{n_r} denotes the hazard that a molecule of $\mathcal{S}_{n_s}$ undergoes reaction $\mathcal{R}_{n_r}$

- The abundance $N_{n_s}(t)$ of $\mathcal{S}_{n_s}$ is irrelevant

At any time t, for zeroth-order reaction we have the propensity function

$$\nu_{n_r}\left(N(t) \mid \kappa_{n_r}\right) = \kappa_{n_r} h_{n_r}\left(N(t)\right)$$
$$= \kappa_{n_r}$$

In this case, the deterministic reaction rate $\widehat{v}_{n_r}(N(t) \mid \widehat{k}_{n_r}) = \widehat{k}_{n_r}$ is also constant
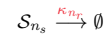

First-order reactions

Reaction networks

First-order reaction | Unimolecular

We consider a first-order reaction (degradation of species $\mathcal{S}_{n_s}$) through n_r-th channel

$$\mathcal{S}_{n_s} \xrightarrow{\kappa_{n_r}} \emptyset$$

The equation does not state that $\mathcal{S}_{n_s}$ is degraded into nothing, but rather that it is degraded into uninteresting species, or that there is an outflux to another compartment

Rate constant κ_{n_r} denotes the hazard that a molecule of $\mathcal{S}_{n_s}$ undergoes reaction $\mathcal{R}_{n_r}$

⤳ There are $N_{n_s}(t)$ distinct molecules of $\mathcal{S}_{n_s}$ at t

• Each subject to hazard κ_{n_r} of reacting

At time t, for first-order/unimolecular reactions we have the propensity function

$$\nu_{n_r}\left(N_{n_s}(t) \mid \kappa_{n_r}\right) = \kappa_{n_r} h_{n_r}\left(N_{n_s}(t)\right)$$
$$= \kappa_{n_r} N_{n_s}(t)$$

In this case, the deterministic reaction rate is $\widehat{v}_{n_r}(N(t) \mid \widehat{k}_{n_r}) = \widehat{k}_{n_r} N_{n_s}(t)$

Second-order reactions

Reaction networks

Second-order reaction | Bimolecular

We consider a second-order reaction between species $\mathcal{S}_{n_s}$ and $\mathcal{S}n_s'$ in the n_r-th channel

$$\mathcal{S}_{n_s} + \mathcal{S}_{n_s'} \xrightarrow{\kappa_{n_r}} \emptyset$$
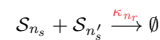
Rate constant κ_{n_s} is the hazard that a pair of molecules of $\mathcal{S}_{n_s}$ and $\mathcal{S}_{n_s'}$, while moving around the compartment, collide with sufficient energy and undergoes reaction $\mathcal{R}_{n_r}$

⤳ There are $N_{n_s}(t)$ molecules of $\mathcal{S}_{n_s}$ and $N_{n_s'}(t)$ molecules of $\mathcal{S}_{n_s'}$ at time t

⤳ There are $\dfrac{N_{n_s}(t) \times N_{n_s'}(t)}{2}$ distinct pairs

• Each pair subject to reaction hazard κ_{n_r}

At time t, for second-order/bi-molecular reactions we have the propensity function

$$\nu_{n_r}\left(N(t) \mid \kappa_{n_r}\right) = \kappa_{n_r} h_{n_r}\left(n(t)\right)$$
$$= \kappa_{n_r} \frac{N_{n_s}(t) \times N_{n_s'}(t)}{2}$$
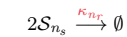$$= \overline{\kappa_{n_r}}\left[N_{n_s}(t) \times N_{n_s'}(t)\right]$$

In this case, the deterministic reaction rate is $\widehat{v}_{n_r}(N(t) \mid \widehat{k}_{n_r}) = \widehat{k}_{n_r} N_{n_s}(t) N_{n_s'}(t)$

Second-order reaction | Bimolecular (cont.)

We consider also second-order reaction between species $\mathcal{S}_{n_s}$ only, in the n_r-th channel

$$2\mathcal{S}_{n_s} \xrightarrow{\kappa_{n_r}} \emptyset$$

Rate constant κ_{n_s} is the hazard that any pair of molecules of $\mathcal{S}_{n_s}$, while moving around the compartment, collide with sufficient energy and undergoes reaction $\mathcal{R}_{n_r}$

⤳ There are $N_{n_s}(t)$ molecules of $\mathcal{S}_{n_s}$ at time t

⤳ $\dfrac{N_{n_s}(t) \times (N_{n_s}(t) - 1)}{2}$ distinct pairs

• Each pair subject to hazard κ_{n_r}

At time t, for second-order/bi-molecular reactions have the propensity function

$$\nu_{n_r}\left(N_{n_s}(t) \mid \kappa_{n_r}\right) = \kappa_{n_r} h_{n_r}\left(n(t)\right)$$
$$= \kappa_{n_r} \frac{N_{n_s}(t) \times (N_{n_s}(t) - 1)}{2}$$
$$= \overline{\kappa_{n_r}}\left[N_{n_s}(t) \times (N_{n_s}(t) - 1)\right]$$

In this case, the deterministic reaction rate is $\widehat{v}_{n_r}(N(t) \mid \widehat{k}_{n_r}) = \widehat{k}_{n_r} \underbrace{N_{n_s}(t) N_{n_s}(t)}_{N_{n_s}(t)^2}$

Higher-order reactions

Reaction networks

Higher-order reactions

Based on combinatorial considerations about the number of available combinations of reacting molecules, it is straightforward to extend the theory to higher-order reactions

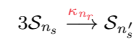$$\underline{S}_{1,n_r}\mathcal{S}_1 + \underline{S}_{2,n_r}\mathcal{S}_2 + \cdots + \underline{S}_{N_s,n_r}\mathcal{S}_{N_s} \xrightarrow{\kappa_{n_r}} \overline{S}_{1,n_r}\mathcal{S}_1 + \overline{S}_{2,n_r}X_2 + \cdots + \overline{S}_{N_s,n_r}\mathcal{S}_{N_s}$$

For rate constant κ_{n_r}, we have the general form of the propensity function at time t

$$\nu_{n_r}\left(N(t) \mid \kappa_{n_r}\right) = \kappa_{n_r} \prod_{n_s=1}^{N_s} \binom{N_{n_s}(t)}{\underline{S}_{n_r,n_s}}$$

$$= \kappa_{n_r}\left[\binom{N_1(t)}{\underline{S}_{n_r,1}} \times \binom{N_2(t)}{\underline{S}_{n_r,2}} \times \cdots \times \binom{N_{N_s}(t)}{\underline{S}_{n_r,N_s}}\right]$$

Higher-order reactions | Third-order

For example, consider the tri-merisation reaction

$$3\mathcal{S}_{n_s} \xrightarrow{\kappa_{n_r}} \mathcal{S}_{n_s'}$$

The rate constant κ_{n_r} represents the hazard that three distinct molecules of species $\mathcal{S}_{n_s}$ come together simultaneously and react to produce one molecule of species $\mathcal{S}_{n_s'}$

For a system with $N_{n_s}(t)$ molecules of $\mathcal{S}_{n_s}$ at time t, the number of distinct triples

$$\binom{N_{n_s}(t)}{3}$$

At time t, these third-order/tri-molecular reactions have propensity function

$$\nu_{n_r}\left(N_{n_s}(t) \mid \kappa\right) = \kappa_{n_r} \binom{N_{n_s}(t)}{3}$$

$$= \kappa_{n_r} \frac{N_{n_s}(t)!}{3!(N_{n_s}(t)-3)!}$$

$$= \kappa_{n_r} \frac{N_{n_s}(t) \times (N_{n_s}(t)-1) \times (N_{n_s}(t)-2)}{6}$$

In this case, the deterministic reaction rate is $\widehat{v}_{n_r}(N(t) \mid \widehat{k}_{n_r}) = \widehat{k}_{n_r} \underbrace{N_{n_s}(t)N_{n_s}(t)N_{n_s}(t)}_{N_{n_s}(t)^3}$

Higher-order reactions | Third-order (cont.)

Rather than modelling higher-order reaction, we often treat them as simple reactions

Consider again the tri-merisation reaction as an example

$$3\mathcal{S}_{n_s} \xrightarrow{\kappa_{n_r}} \mathcal{S}_{n_s'}$$
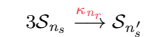
We can, perhaps more realistically, model the process as a pair of second-order reactions

$$2\mathcal{S}_{n_s} \xrightarrow{\kappa_{n_r}''} \mathcal{S}_{n_s''}$$

$$\mathcal{S}_{n_s} + \mathcal{S}_{n_s''} \xrightarrow{\kappa_{n_r}'} \mathcal{S}_{n_s'}$$
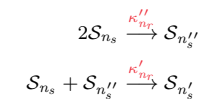
Importantly, notice that the two system may be characterised by different dynamics

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Higher-order reactions | Third-order (cont.)

Another example of tri-molecular reaction
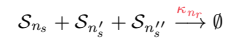
$$\mathcal{S}_{n_s} + \mathcal{S}_{n_s'} + \mathcal{S}_{n_s''} \xrightarrow{\kappa_{n_r}} \emptyset$$

At time t, these third-order/tri-molecular reactions have propensity function

$$\nu_{n_r}\left(N_{n_s}(t) \mid \kappa\right) = \kappa_{n_r} N_{n_s}(t) \times N_{n_s'}(t) \times N_{n_s''}(t)$$

Another example of tri-molecular reaction
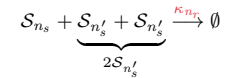
$$\mathcal{S}_{n_s} + \underbrace{\mathcal{S}_{n_s'} + \mathcal{S}_{n_s'}}_{2\mathcal{S}_{n_s'}} \xrightarrow{\kappa_{n_r}} \emptyset$$

At time t, these third-order/tri-molecular reactions have propensity function

$$\nu_{n_r}\left(N_{n_s}(t) \mid \kappa\right) = \kappa_{n_r} N_{n_s}(t) \times \frac{N_{n_s'}(t) \times (N_{n_s'}(t) - 1)}{2}$$

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Rate constants

Literature on chemical reactions is dominated by the continuous and deterministic view

- Rate constants are documented as deterministic rate constants $\{k_{n_r}\}_{n_r=1}^{N_r}$

To carry out correct stochastic simulations, these constants must be properly converted

⤳ The rates used in simulation must reflect molecular reaction hazards

There exist relationships between stochastic and deterministic rates

- They can can be used to convert between the two forms

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Rate constants (cont.)

In a stochastic model, the amount of a species is represented by an integer (the number of molecules of that species), as (some kind of) concentration in a deterministic model

Say we want to convert concentrations $\{X_{n_s}\}$ (moles per litre) to copy-numbers $\{N_{n_s}\}$

⤳ We need to know the volume V of the compartment (in litres)

For a concentration of X_{n_s} moles of some species $\mathcal{S}_{n_s}$ in a volume of V litres, we have

$$X_{n_s} \times V \quad \text{moles of } \mathcal{S}_{n_s}$$

Because each mole contains $N_A \simeq 6.023 \times 10^{23}$ molecules of $\mathcal{S}_{n_s}$, we have

$$X_{n_s} \times V \times N_A \quad \text{molecules of } \mathcal{S}_{n_s}$$

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Rate constants (cont.)

Example (E. coli)

A typical tubular cell of *Escherichia coli* is $l = 2\mu$m long and of diameter $d = 1\mu$m

$\rightsquigarrow 1\mu\text{m} = 1 \times 10^{-6}\text{m}$

We can compute the volume V of a bacterium

$$V = \pi \left(\frac{d}{2}\right)^2 \times l$$

$$= \pi \left(\frac{1 \times 10^{-6}}{2}\right)^2 \times \left(2 \times 10^{-6}\right)$$

$$= \frac{\pi}{2} \times 10^{-18}\text{m}^3$$

$$= \frac{\pi}{2} \times 10^{-15}\text{L}$$

Suppose that species $\mathcal{S}_{n_s}$ exists inside the cell with concentration $X_{n_s} = 10^{-5}\text{M}$

We can compute the number of molecules of species $\mathcal{S}_{n_s}$ inside the cell

$$X_{n_s} \times V \times \text{N}_\text{A} = 10^{-5} \times (\pi/2) \times 10^{-15} \times (6.023 \times 10^{23})$$

$$\simeq 9461$$

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Rate constants | Zeroth-order reaction

$$\emptyset \xrightarrow{\kappa_{n_r}} \mathcal{S}_{n_s}$$

Consider a zeroth-order reaction (production of species $\mathcal{S}_{n_s}$) for the n_r-th channel

$\rightsquigarrow$ The deterministic rate law

$$v_{n_r}\left(X^c(t)\right) = \frac{\widehat{v}_{n_r}\left(N^c(t)\right)}{\Omega}$$

$$= k_{n_r}$$

$\rightsquigarrow$ The deterministic rate constant k_{n_r} has dimensions $\left[\underbrace{\text{moles} \times \text{L}^{-1}}_{1\text{M}} \times \text{s}^{-1}\right]$

In a vessel of size $\Omega = V$, $k_{n_r} \times \text{N}_\text{A} \times V$ molecules $\mathcal{S}_{n_s}$ are produced per second
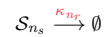
$\rightsquigarrow$ The stochastic rate law

$$\nu_{n_r}\left(N(t)\right) = \kappa_{n_r}$$

$\rightsquigarrow$ The stochastic rate constant κ_{n_r} has dimensions $\left[\text{molecules} \times \text{s}^{-1}\right]$

For values $\kappa_{n_r} = k_{n_r}\text{N}_\text{A}V$, the deterministic and the stochastic rate laws are equal

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Rate constants | First-order reaction

$$\mathcal{S}_{n_s} \xrightarrow{\kappa_{n_r}} \emptyset$$

Consider a first-order reaction (degradation of species $\mathcal{S}_{n_s}$) for the n_r-th channel

$\rightsquigarrow$ The deterministic rate law

$$v_{n_r}\left(X^c(t)\right) = \frac{\widehat{v}_{n_r}\left(N^c(t)\right)}{\Omega}$$

$$= k_{n_r}X^c_{n_s}(t)$$

$\rightsquigarrow$ The deterministic rate constant k_{n_r} has dimensions $\left[\underbrace{\text{moles} \times \text{L}^{-1}}_{1\text{M}} \times \text{s}^{-1}\right]$

In a container of size $\Omega = V$, $X_{n_s}(t)$ corresponds to $N_{n_s}(t) = X^c_{n_s}(t)V\text{N}_\text{A}$ molecules

- The stochastic rate law
$$\nu_{n_r}\left(N(t)\right) = \kappa_{n_r}N_{n_s}(t)$$

- The stochastic rate constant κ_{n_r} has dimensions $\left[\text{molecules} \times \text{s}^{-1}\right]$

For values $\kappa_{n_r} = k_{n_r}$, the deterministic and the stochastic rate laws are equal

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Propensity function

We defined the propensity function $\nu(t)$ of a certain reaction event as that function such that $\nu(t)\mathrm{d}t$ defines the probability that that reaction occurs in the interval $[t, t + \mathrm{d}t]$

For zeroth- and first-order reactions, the occurrence of events with zero or one molecule

Chemical reaction	Order	Propensity function	Units of κ
$\emptyset \xrightarrow{\kappa} \mathcal{A}$	0-th	κV	$\mathrm{m}^{-3} \ \mathrm{sec}^{-1}$
$\mathcal{A} \xrightarrow{\kappa} \emptyset$	1-st	$N_{\mathcal{A}}(t)\kappa$	sec^{-1}

For second-order reactions, we require the occurrence of events involving two molecules

Chemical reaction	Order	Propensity function	Units of κ
$\mathcal{A} + \mathcal{B} \xrightarrow{\kappa} \emptyset$	2-nd	$N_{\mathcal{A}}(t)N_{\mathcal{B}}(t)\dfrac{\kappa}{V}$	$\mathrm{m}^{3} \ \mathrm{sec}^{-1}$
$\mathcal{A} + \mathcal{A} \xrightarrow{\kappa} \emptyset$	2-nd	$N_{\mathcal{A}}(t)\left(N_{\mathcal{A}}(t) - 1\right)\dfrac{\kappa}{V}$	$\mathrm{m}^{3} \ \mathrm{sec}^{-1}$

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Propensity function (cont.)

For third-order reactions we require the occurrence of events involving three molecules

Chemical reaction	Order	Propensity function	Units of κ
$\mathcal{A} + \mathcal{B} + \mathcal{C} \xrightarrow{\kappa} \emptyset$	3-rd	$N_{\mathcal{A}}(t)N_{\mathcal{B}}(t)N_{\mathcal{C}}(t)\dfrac{\kappa}{V^2}$	$\mathrm{m}^{6} \ \mathrm{sec}^{-1}$
$\mathcal{A} + \mathcal{A} + \mathcal{B} \xrightarrow{\kappa} \emptyset$	3-rd	$N_{\mathcal{A}}(t)\left(N_{\mathcal{A}}(t) - 1\right)N_{\mathcal{B}}(t)\dfrac{\kappa}{V^2}$	$\mathrm{m}^{6} \ \mathrm{sec}^{-1}$
$\mathcal{A} + \mathcal{A} + \mathcal{A} \xrightarrow{\kappa} \emptyset$	3-rd	$N_{\mathcal{A}}(t)\left(N_{\mathcal{A}}(t) - 1\right)\left(N_{\mathcal{A}}(t) - 2\right)\dfrac{\kappa}{V^2}$	$\mathrm{m}^{6} \ \mathrm{sec}^{-1}$