



Exact and approximate solutions for spatial stochastic models of chemical systems

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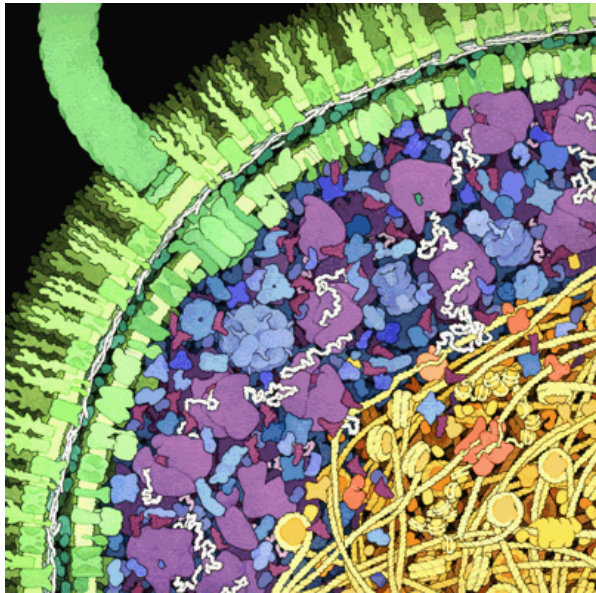
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- ◆ The intracellular environment: noisy chemical reactions in a crowded diffusion-limited space
- ◆ Current stochastic approaches often ignore space and assume dilute conditions
- ◆ Noise + space in dilute conditions
- ◆ Noise + space in non-dilute conditions

What is macromolecular crowding?

- ◆ It is estimated that between 5-40% of the intracellular volume is occupied by macromolecules. Hence the intracellular medium is **NON-DILUTE** and CROWDED.



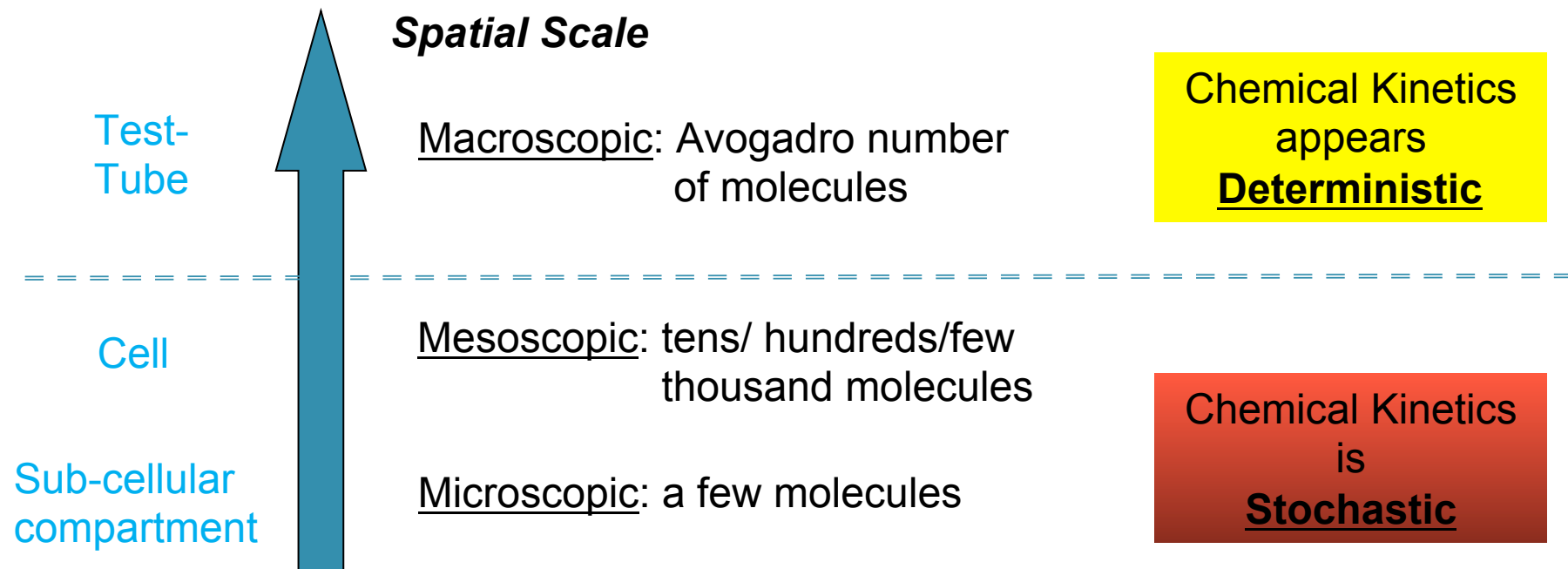
- ◆ The vast majority of these macromolecules do not participate in a given chemical reaction. However they still influence kinetics via **volume exclusion (steric) effects**.

Cross Section of an E. Coli Cell. Image is built using structure analysis, electron microscopy, and biochemical analysis to have the proper number of molecules in the proper place and with proper size and shape.

D. S. Goodsell 1999

What is intrinsic noise?

- ◆ The **time** between successive biochemical reaction events, e.g. dissociation and binding, **is a random variable**.
- ◆ This randomness leads to fluctuations in the chemical concentrations, also called **intrinsic noise**.



The standard stochastic description: Chemical Master Equation (CME)

Major Assumptions:

The system is well-stirred – guarantees that the molecules are randomly distributed throughout the volume and that hence we can describe them just by the molecule numbers, i.e. ignore molecular position & velocity.

The molecules are point-particles – molecules do not experience volume exclusion effects, an assumption true in the dilute limit.

These assumptions imply that the time between successive reactions is exponentially distributed and hence the system is Markovian.

$P(n_A, n_B, \dots, t)$ = probability that the system has n_A molecules of A, n_B of B, etc ..., at time t .

The CME is a set of ODEs for $P(n_A, n_B, \dots, t)$ which is derived by modeling chemical reactions as a continuous-time Markov process.

Noise + space
in dilute conditions

Spatial stochastic description: Reaction-Diffusion Master Equation (RDME)

Major Assumptions:

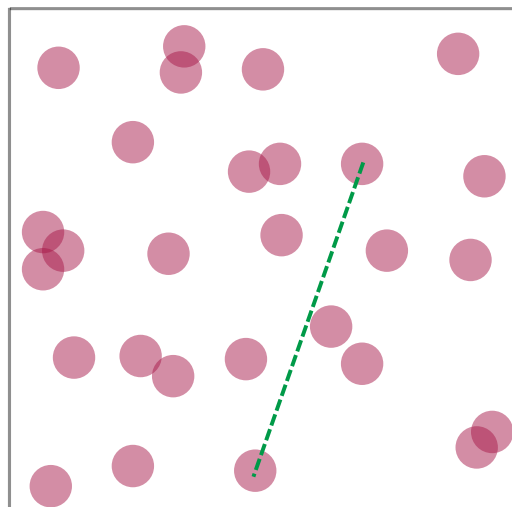
The system is well-stirred in small regions of space – specifically space is divided into small boxes (voxels) and in each box we assume well-mixed conditions but NOT throughout the whole space.

The molecules are point-particles

Diffusion is modeled as hopping from particles from one voxel to a neighboring one.

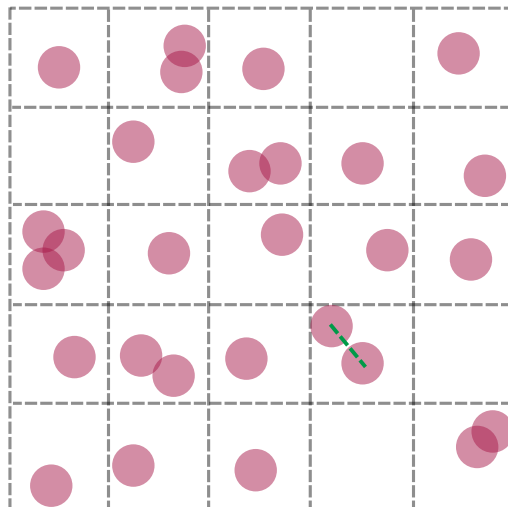
$P(n_A^i, n_B^i, \dots, t)$ = probability that there are n_A^i molecules of A, n_B^i of B, etc ..., at time t in voxel i .

The RDME is a set of ODEs for $P(n_A^i, n_B^i, \dots, t)$ which is derived by modeling chemical reactions inside each voxel + diffusion between voxels as a continuous-time Markov process.



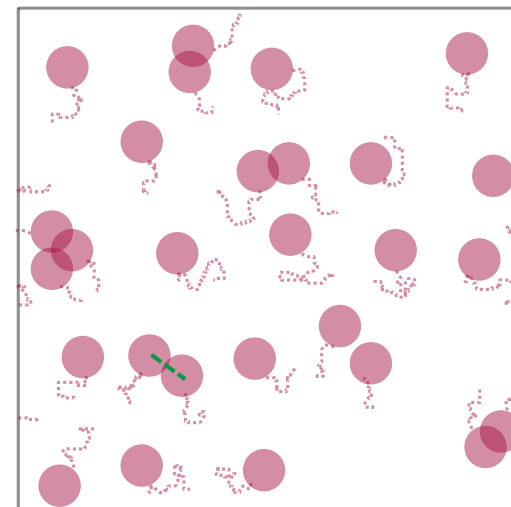
(a)

CME
(well-mixing
across space)



(b)

RDME
(well-mixing
locally only)



(c)

Brownian dynamics
(no length scale on which
well-mixing occurs)

Problem: the high dimensionality of the RDME

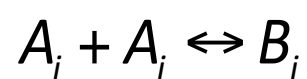
Consider a simple dimerisation reaction where two molecules of the same type A bind to form a second type of molecule B:

The CME describes the chemical reaction in the whole space:



The RDME describes the set of chemical & diffusive reactions in each of the N^2 voxels on a grid with coordination number z :

$2N^2$ species + $2N^2$ chemical reactions + $2zN^2$ diffusion reactions



Chemical reaction in voxel i



Species A diffusing between two neighboring voxels (i and j)



Species B diffusing between two neighboring voxels (i and j)

Approximation of the RDME of a multi-species system

Steps of the calculation:

1. Starting from a multi-species RDME **reduce to an effective single-species** RDME using time-scale separation or other methods.
2. Specify **steady-state** conditions and assume the *same reactions occur all over space with some finite diffusion coefficient*.
3. **Derive coupled equations for the first and second moments** of the number of molecules in each voxel.
4. **Expand each moment as a Taylor series** in a small parameter ... the inverse volume of each voxel.
5. Simplify resulting expressions by assuming *number of voxels is large*.

Approximation of the 2D RDME of a multi-species system

The general approximative solution for the mean concentration in each voxel:

$$\psi \sim \phi + \underbrace{\left(\phi + \frac{\beta}{\alpha} \right) \frac{1}{2V\alpha} \frac{d\alpha}{d\phi}}_{\text{Correction for finite molecule numbers}} + \underbrace{\left(\phi + \frac{\beta}{\alpha} \right) \frac{(N^2 - 1)}{2V\alpha} \frac{d\alpha}{d\phi} \frac{|\alpha|}{|\alpha| + k_D}}_{\text{Correction for finite diffusion coefficient}}$$

Deterministic solution

α = Jacobian of non-spatial rate equations

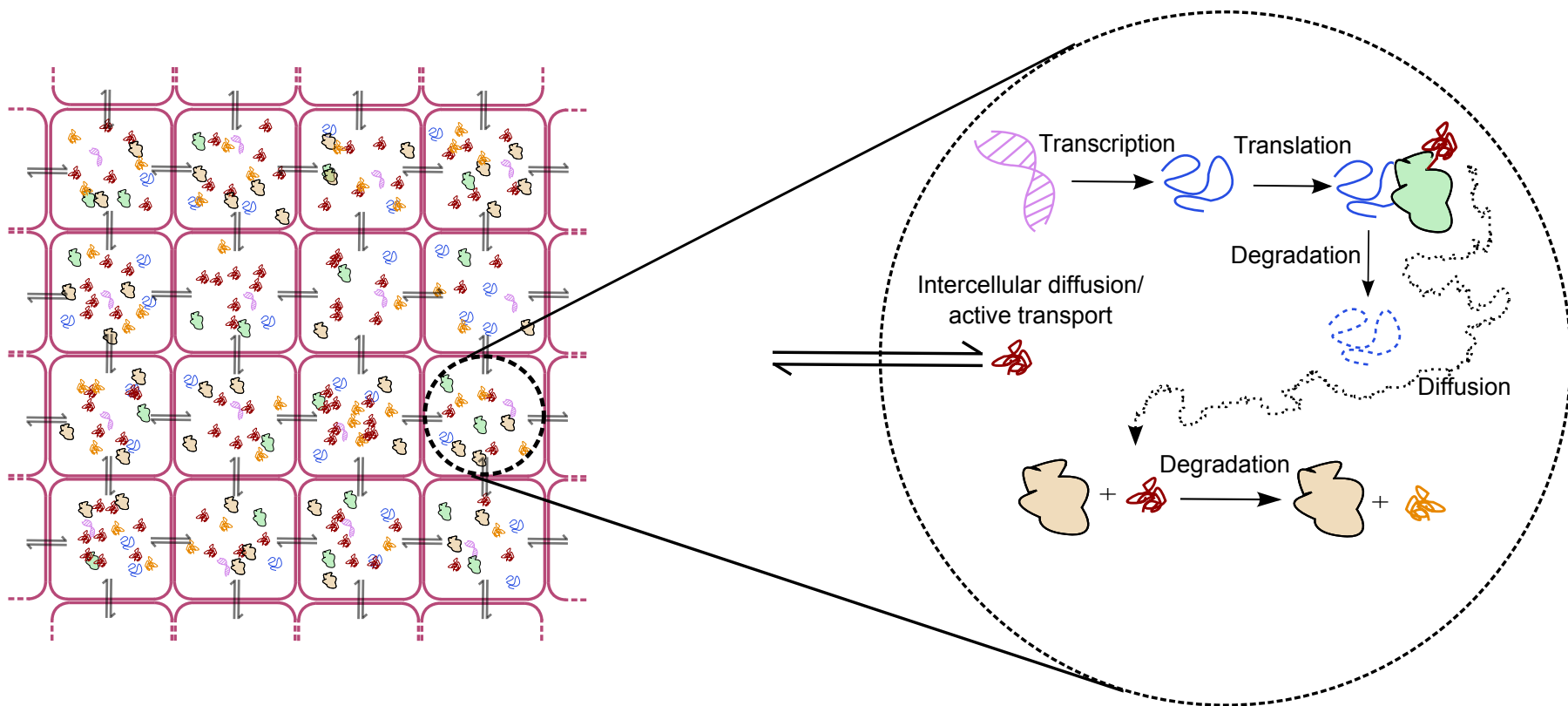
β = function of stoichiometric & rate constants

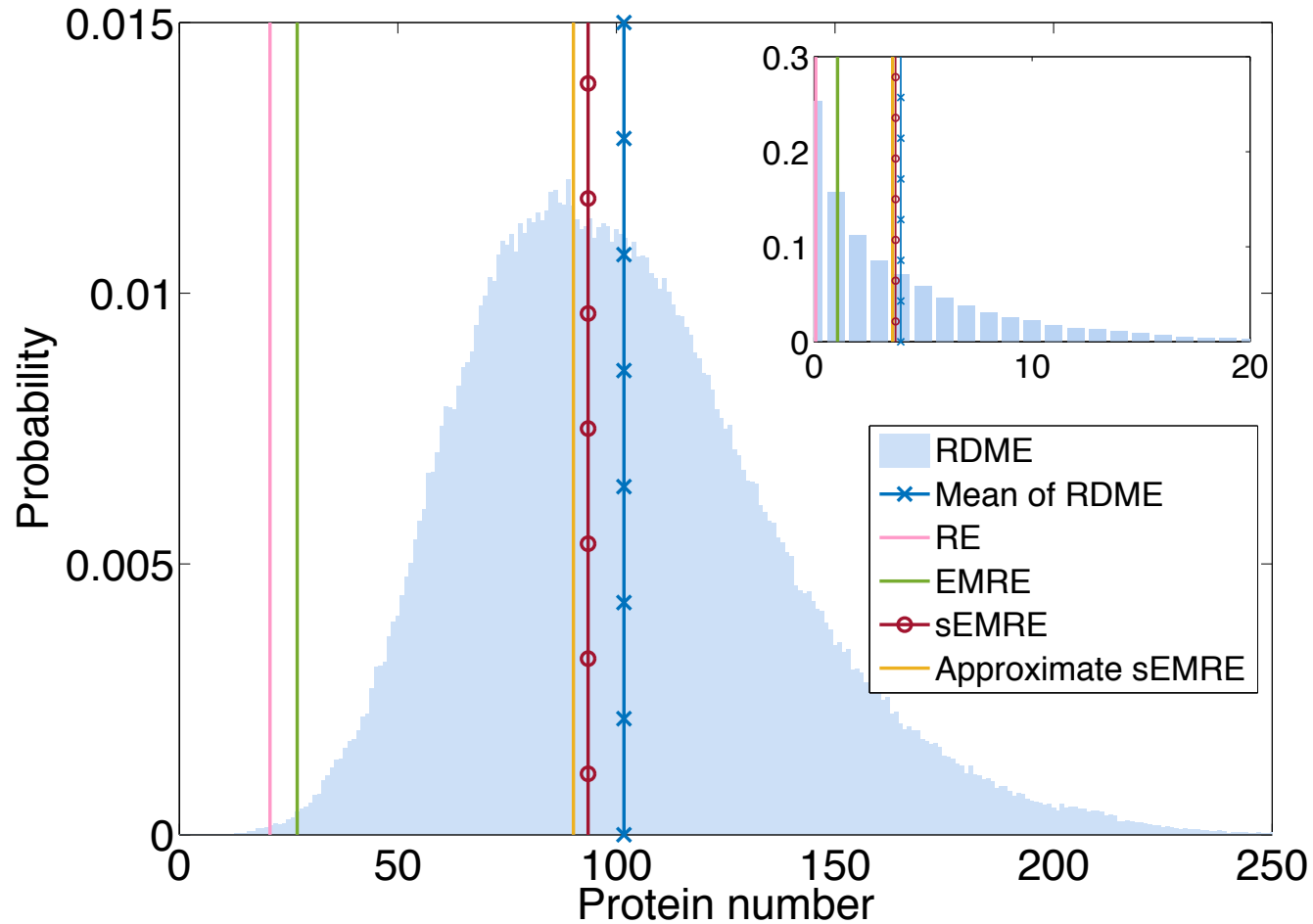
k_D = Diffusion rate between voxels

N^2 = Total number of voxels in 2D space

V = Total area of all space

Application: modeling a tissue, wherein each cell has a gene regulatory network + it is well-mixed + it communicates with neighbouring cells





RE: deterministic rate equations

EMRE: RE + correction due to finite molecule numbers

sEMRE: EMRE + correction due to finite diffusion coefficients

Noise + space
in crowded conditions

Spatial crowded stochastic description: cRDME

Major Assumption: Molecules all have the same finite size

Features:

A description at the molecule level – space is divided into voxels whose size is that of one molecule.

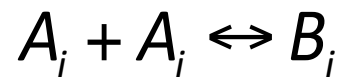
Volume exclusion is included – Molecules can hop between neighboring voxels only if there is an empty space. Each voxel can hold at most 1 molecule.

Chemical reactions occur between molecules in neighboring voxels – this is a natural outcome of modeling at the scale of a single molecule.

Empty space is explicitly tracked and modeled – this is a natural requirement needed to impose volume exclusion

Illustration of RDME vs cRDME modeling

The RDME describing a dimerisation reaction in non-crowded conditions:



Chemical reaction in voxel i

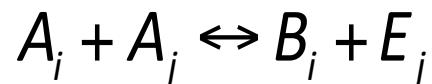


Species A diffusing between two neighboring voxels (i and j)



Species B diffusing between two neighboring voxels (i and j)

The cRDME describing a dimerisation reaction in crowded conditions:



Chemical reaction in between 2 A's in neighboring voxels

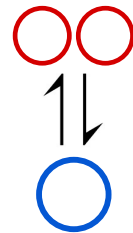
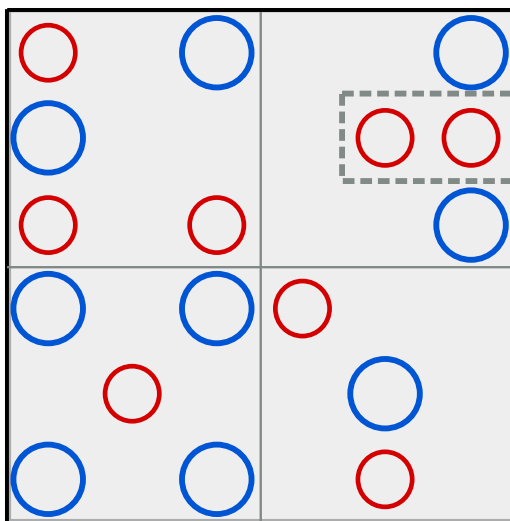


Species A diffusing between two neighboring voxels (i and j). E_i stands for empty space in voxel i

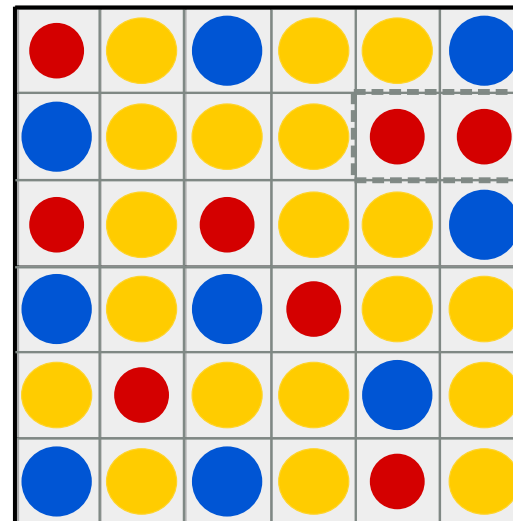


Species B diffusing between two neighboring voxels (i and j)

RDME



cRDME



Exact solution of the cRDME in equilibrium conditions

Global solution = probability distribution for the number of molecules of each species in the whole compartment

We consider a chemical system of reversible chemical reactions in a closed compartment. In steady-state such a system obeys **detailed-balance**, i.e., one can write a master equation for each pair of states and this allows an exact local and global solution of the cRDME (and RDME).

Exact global solution of the cRDME in equilibrium conditions

Exact mean concentrations for a system with M chemical species

For each reversible reaction j, one has the relation:

$$\prod_{i=1}^{M+1} \tilde{\phi}_i^{S_{ij}} = \frac{\tilde{k}_j}{\tilde{k}_j'}$$

where

$\tilde{\phi}_i$ is the mean concentration of species i (Species M+1 is space)

S_{ij} is the change in the number of molecules of species i when reaction j occurs

\tilde{k}_j and \tilde{k}_j' are the reaction rate constants for the forward & backward reactions of the reversible pair j

Exact global solution of the cRDME in equilibrium conditions

The global equilibrium distribution is a constrained multivariate Poisson distribution:

$$P(n_1, \dots, n_{M+1}) = C \prod_{j=1}^{M+1} \frac{(\Omega \tilde{\phi}_j)^{n_j}}{n_j!}$$

together with the two sets of constraints:

$$\sum_{i=1}^{M+1} n_i = N$$

The volume exclusion constraint: N is maximum number of molecules allowed in the compartment

$$f_k(\vec{n}) = K_k, \quad k = 1, \dots, Y$$

These are the Y chemical conservation laws which characterize a chemical system

Exact global solution of the RDME in equilibrium conditions (same as CME)

The global equilibrium distribution is a constrained multivariate Poisson distribution:

$$P(n_1, \dots, n_M) = C \prod_{j=1}^M \frac{(\Omega \phi_j)^{n_j}}{n_j!}$$

together with the single set of constraints:

$$f_k(\vec{n}) = K_k, \quad k = 1, \dots, Y$$

These are the Y chemical conservation laws which characterize a chemical system

Note that $\phi_i = \tilde{\phi}_i$ in the **dilute limit** $N \rightarrow \infty$ at constant compartment volume Ω

Chemical systems with no chemical conservation laws

Example: $\emptyset \leftrightarrow A, A + A \leftrightarrow B$

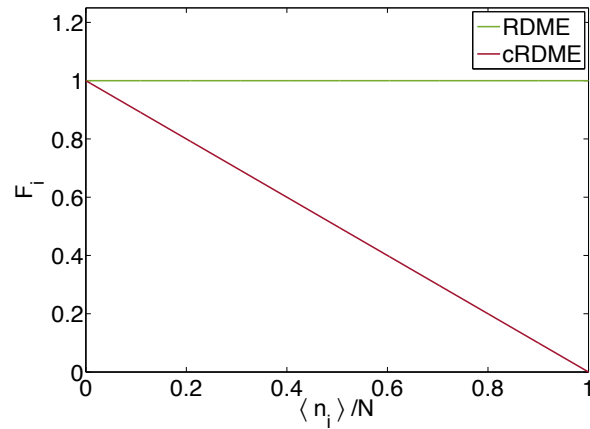
The global equilibrium distribution according to the RDME is a **multivariate Poisson distribution**.

The global equilibrium distribution according to the cRDME is a **multinomial distribution**.

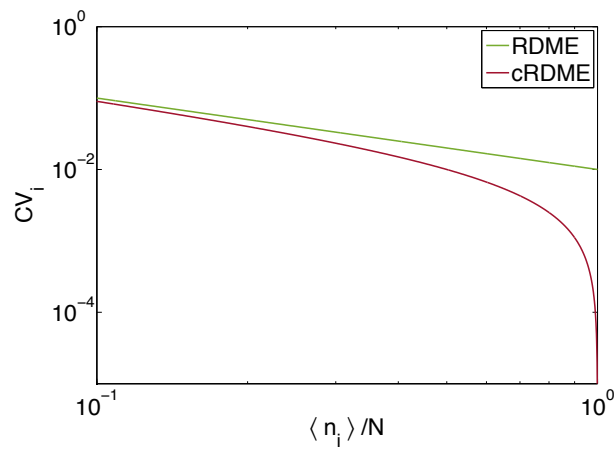


The marginal distribution of a chemical species according to the RDME is a **Poisson distribution**.

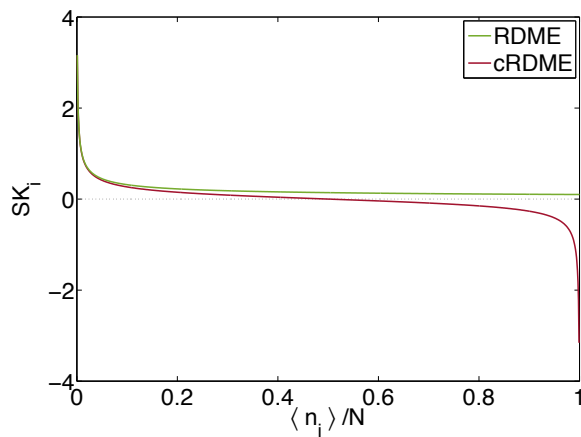
The marginal distribution of a chemical species according to the cRDME is a **Binomial distribution**.



Crowding leads to **sub-Poissonian fluctuations**



Crowding leads to **deviations from the standard inverse square root law** for the size of fluctuations.



Crowding can lead to a **flip in the skewness of the distribution (right-skew to left-skew)**

Chemical systems with a special type of chemical conservation laws

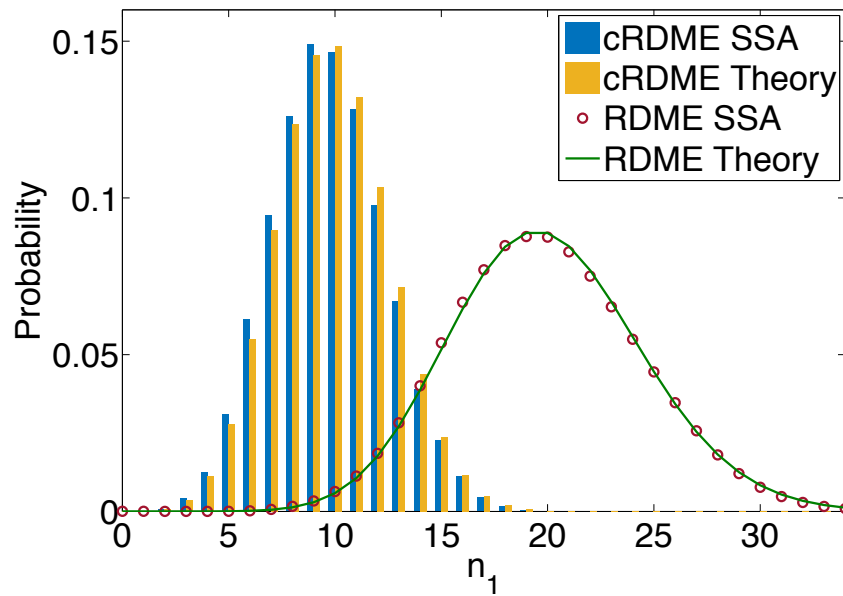
We consider a chemical conservation law of the form:

$$\sum_{i=L}^M n_i = k, \quad L < M$$

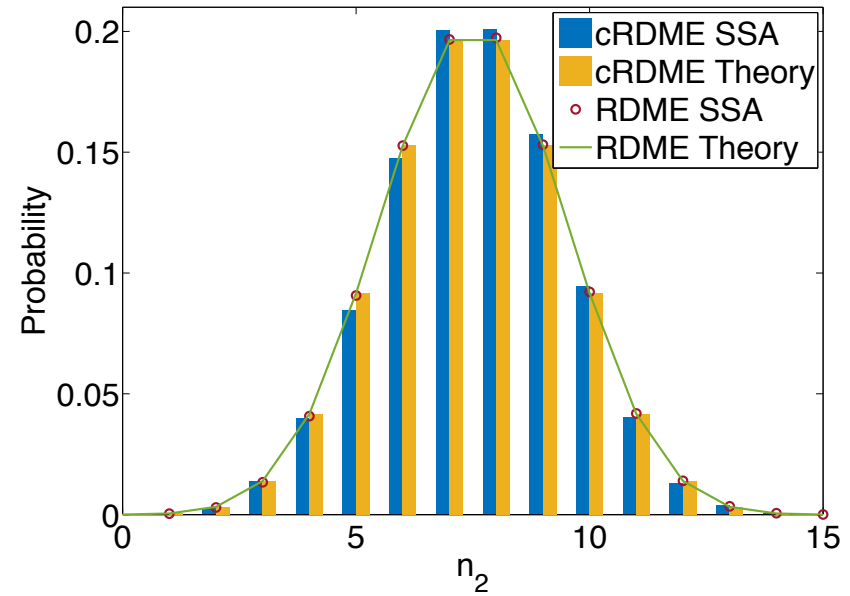
Example: $\emptyset \leftrightarrow A, A + B \leftrightarrow C$ has the conservation law $n_B + n_C = k$

	Species not involved in a chemical cons law e.g. A	Species involved in a chemical cons law e.g. B, C
Marginal dist (RDME)	Poisson	Binomial
Marginal dist (cRDME)	<i>Binomial</i>	<i>Binomial</i>

Crowding typically has a much larger effect on the marginals of species not involved in the chemical conservation law



Marginal distribution of A

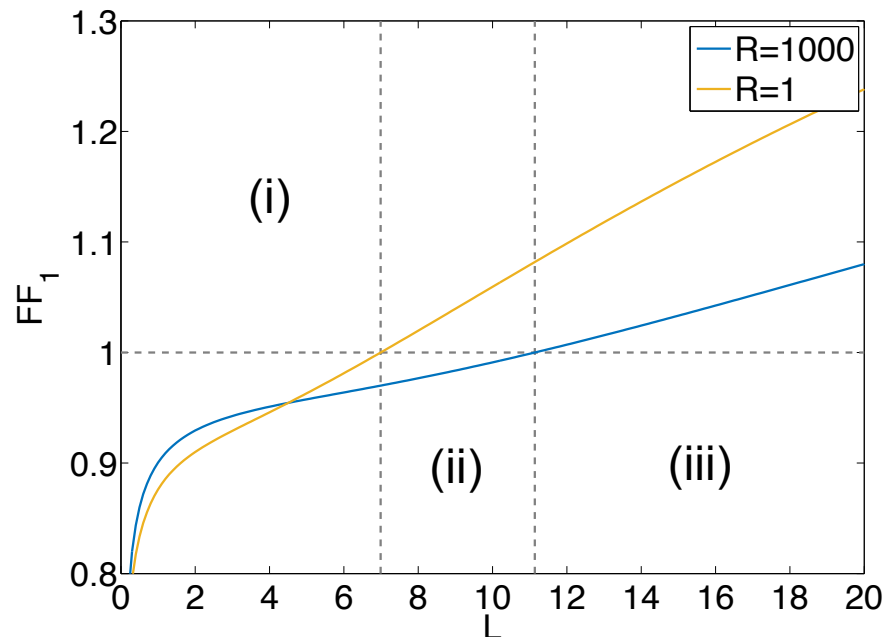


Marginal distribution of B

Chemical systems with other types of chemical conservation laws

Although exact solution applies to these systems as well, their **probability distribution is not of the form of a well known distribution and hence no general results can be easily deduced.**

Example: $A + A \leftrightarrow B$ has the conservation law $n_B + 2n_A = k$



- (i) Fluctuations are sub-Poissonian for both RDME and cRDME
- (ii) Fluctuations are sub-Poissonian (RDME) and super-Poissonian (cRDME)
- (iii) Fluctuations are super-Poissonian for both RDME and cRDME



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