MIXED PARTITION OF UNITY METHODS AND STOCHASTIC GILLESPIE ALGORITHMS FOR TRANSPORT-REACTION EQUATIONS

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Abstract. We introduce a new type of model framework which is part stochastic and part deterministic. The starting point is a finite size particle system within a single reaction volume, with type exchanges modelled by a contact process. Inside the reaction volume, each particle can interact with every other particle with the same probability. This is the setting of a classical reaction system simulated with a Gillespie algorithm. Such systems can be used to describe other than chemistry type exchanges, like an infection process, and therefore are already very versatile. Their advantage is that they are able to be used where small size effects can play a role, like extinction events, which are impossible to model with differential equations, including stochastic differential equations. However finite size and single reaction volume settings for reaction systems are too restrictive in other ways. We might like to add internal or external states to the particles. These states are coordinates in a position space. An example of an internal position/state space is age (since entering the system), an example for an external position/state space is geographical location. The particles then can also change their positions in these state spaces, according to some probability distribution which evolution is modelled deterministically. The classical example for a transport process is a partial differential equation like the heat equation, or more general parabolic advection-diffusion equations. We assume that the distribution of the particles in position space is not influencing the evolution of the probability distribution driving in turn the evolution of the particles' positions. The model framework with its finite-size particle population approach can very accurately model situations where finite-size effects take place, however provides in addition detailed descriptions of both internal and external particle state spaces where needed. The framework can therefore be used in addition to traditional established models, like transport PDEs or internally structured population models, when the computation of the statistics of finite-size effects is important.

1 INTRODUCTION

We introduce a new type of model class which is part deterministic and part stochastic. These hybrid models conceptually start their construction by first establishing a rule-based model (see Figure 1), which is derived from reaction kinetics. The number of particles, here called **basic objects**, is assumed finite. Via a stochastic process, realised via the Gillespie algorithm known from reaction kinetics, the basic objects classified into different types and can have type transformations. One can just think of types as subsets of the basic object population creating a partition, every object has exactly one type. No new types can be created in the process. All of this description so far takes place in a single so-called reaction volume, see Figure 2. A reaction volume is characterised by the fact that each object can meet every other object with the same probability, hence allowing the use of a Gillespie algorithm to have type changes according to the rules.
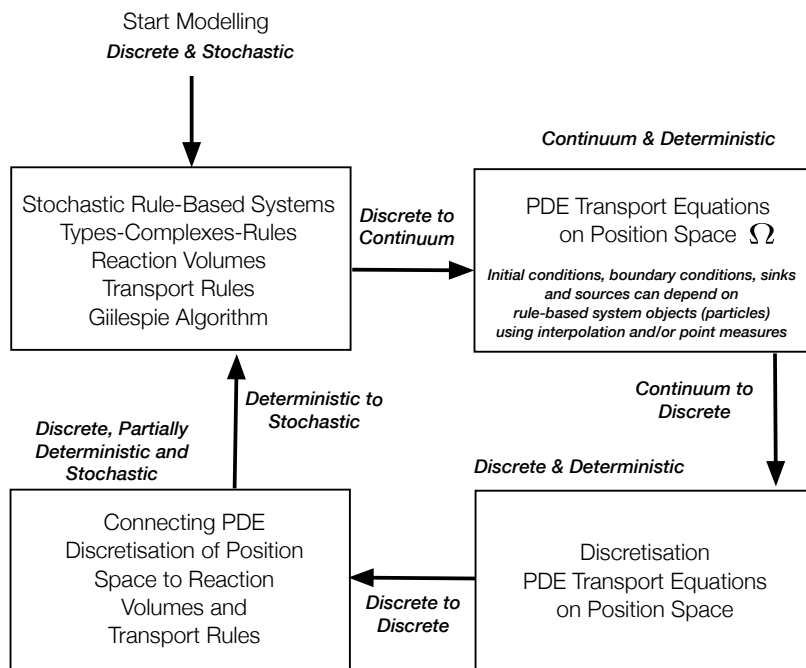
Start Modelling
Discrete & Stochastic

Continuum & Deterministic

Stochastic Rule-Based Systems
Types-Complexes-Rules
Reaction Volumes
Transport Rules
Giilespie Algorithm

Discrete to Continuum

PDE Transport Equations
on Position Space Ω

Initial conditions, boundary conditions, sinks and sources can depend on rule-based system objects (particles) using interpolation and/or point measures

Continuum to Discrete

Deterministic to Stochastic

Discrete, Partially Deterministic and Stochastic

Discrete & Deterministic

Connecting PDE
Discretisation of Position
Space to Reaction
Volumes and
Transport Rules

Discrete to Discrete

Discretisation
PDE Transport Equations
on Position Space

Figure 1: The conceptual modelling steps using the hybrid method proposed.

This part of the model allows therefore the inorporation of small-size stochastic effects, very important for many applications. As we are mostly interested in objects or particles which have some kind of additional coordinates, like physical space, we necessarily must discuss the possibility of multiple reaction volumes covering some physical space. The concept of a reaction volume can be either physical or natural, like a well-mixed chemical reactor with robust boundary walls, or more conceptual, like a part of physical space where the objects approximately can meet each other with the same probability. As we

will consider mainly transport processes, the focus more on the latter. As reaction volumes are not naturally allowing particles to have coordinates, the proposed hybrid method will have to discuss how coordinate changes are driven by the transport equation. We use the discretisation (grid or patches) of the position space denoted by Ω to connect the concept of reaction volume needed for the particle system to the concept of grid element or patch for the discretisation of the transport equation.

2 START MODELLING WITH RULE-BASED PARTICLE SYSTEMS

A classification, or category (we use the two words here synonymously), consists of finitely many discrete types, or classes. The list, mathematically a set of types, becomes

$$\mathcal{T} = \{T_1, \ldots, T_s\}, s \in \mathbb{N}.$$

The classical example from chemistry is $\mathcal{T}$ describing the set of different chemical species, or the disease states in epidemiology, with $\mathcal{T} = \{S, I, R, D\}$, with S the 'susceptible' individuals, I the 'infected' individuals, R the 'recovered' individuals, and D the 'diseased' individuals.

2.1 General Classification

Identifying every atom and molecule as a certain type is an example of a **single category classification**. This is the usual approach in classical reaction kinetics. However, many scientific areas work usually with several categories simultaneously, or even a hierachy of categories. The best example of the latter is biological taxonomy. Here every organism is attached a species (like for atoms and molecules), but then also a genus, family, order , class etc. Rule-based systems can also be formulated for such cases, either **parallel** categorisation, of **hierachical** classification. However, this is beyond the scope of this article.

2.2 The System State

The basic assumption is that every type T introduced forms a group of so-called **basic objects**. In the chemistry example the basic objects were chosen to be single atoms, ions or molecules. In population dynamics or epidemiology the basic objects are individuals. We also assume we can **count** the basic objects of any type. The **state space** $\mathbb{S}$ of the system can be defined as follows: let $N_i(t)$ be a random variable that represents the number of particles of type T_i in the reaction volume (see below), all measured at time $t \in \mathbb{R}$. Let $\mathbf{N}$ denote the vector of all N_i's, i.e.

$$\mathbf{N} = (N_1, \ldots, N_s)(t).$$

Then $\mathbf{N}$ is the **system state** or **configuration** at time t, and the state space $\mathbb{S}$ becomes $\mathbb{N}^s$. The next component needed is an exact system boundary. There are several scientific

reasons for this. The most important one is empirical: as outlined there is a need to exactly count the number of particles at a certain well-defined place, at a certain well-defined time. Only then the prediction task will be well-defined. We need, for example, to know initial conditions, i.e. the number of elements and molecules at some initial reference time. For this we will need some more basic physical assumptions, for example the separability of time and space, we assume no relativistic effects. At fixed time, we assume there is a part of space, called the **reaction volume**, in which our particles reside and can be counted. The following assumptions are essential:

1. In each reaction volume there are infinitely many particles allowed to reside. Therefore, we impose no restriction on capacity, or, in other words, there is no physical restriction of particle size of any type.

2. Inside a reaction volume, any particle of any type can interact with any other particle with equal probability. This can also be expressed by way of introducing the contact graph, where the particles form the vertices, and the edges describing possible contacts between particles. In our case the contact graph must be the complete graph.

2.3   The Reaction Volume

The collision-based contact network of molecules is illustrated in Figure 2. Of course, in principle, there might be several reaction volumes describing the system. Then transport rules need to be introduced, in case basic objects can switch between reaction volumes. In chemical reaction systems, the reaction volume is typically a chemical reactor with well-defined boundaries. However, sometimes such an easy system boundary is not available and is only defined approximately. In case of continuum space, one can think about the reaction volume as a discretisation, for example a finite volume control volume. We will come back to this later. If both the particle size becomes infinite, i.e. we have a mass-action system, and space becomes continuous as well, the result is a classical reaction-transport equation, a partial differential equation. However, in our hybrid approach, we will not take a continuum limit, and the particle numbers will stay **finite**.

2.4   Rules

In this section we introduce rule-based systems, where we introduce rules to describe the evolution in state space. Each rule describes a possible event in the system and will be written in the form (1):

$$\sum_{i=1}^{s} \alpha_{ij} T_i \rightarrow \sum_{i=1}^{s} \beta_{ij} T_i. \tag{1}$$

We assume the set of all possible rules of the system is finite, and we can enumerate rules and assemble them into a set $\mathcal{R} := \{R_1, R_2, \ldots, R_r\}$. Each rule R_j, $1 \leq j \leq r$,
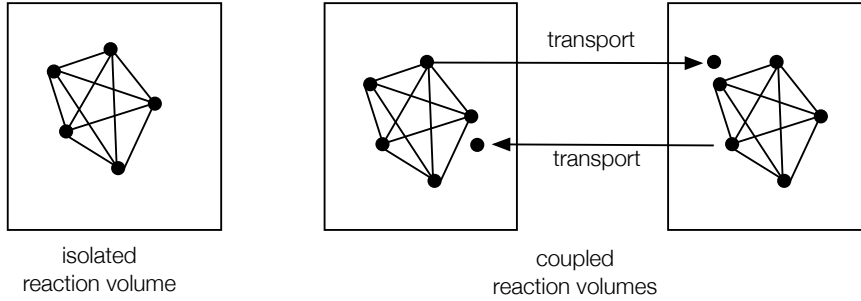
Figure 2: An isolated reaction volume, **left**. Dots represent single elements or molecules, and an edge between them indicates they can take part in a contact process. Note that the assumption of everyparticle can meet every otherparticle in the reaction volume leads to a complete graph, usually called the **contact graph**. The complete graph indicates that the volume is 'well-mixed'. Two coupled reaction volumes, **right**. Same as for the isolated reaction volume, but now there is an additional transport process, particles can swap locations. After swapping places, it is again assumed that each particle in the contact process can meet every other particle at the same location, i.e. reaction volume.

has a **source complex** $C_j^s := \sum_{i=1}^s \alpha_{ij} T_i$ and a **target complex** $C_j^t := \sum_{i=1}^s \beta_{ij} T_i$. The interpretation is that the source complex determines how many objects of different types need to be in the system for the event to happen, and the target complex describes the outcome how many objects of different types will be created during the event. We can assemble different complex sets, the set of all source complexes $\mathcal{C}^s$, the set of all target complexes $\mathcal{C}^t$, and the set of all complexes $\mathcal{C} := \mathcal{C}^s \cup \mathcal{C}^t$.

2.5 Gillespie's Algorithm

The most important stochastic update idea for rule-based models is *Gillespie's Stochastic Simulation Algorithm (SSA)* and its generalisation. This evolution arises due to the interactions of basic objects having different types $\mathcal{T}$ and, in the language of reaction schemes, can be expressed as a reaction network. Reaction R_j is given by Equation (1) for $j = 1, \ldots, r$, where k_j denotes the rate constant of reaction R_j. Interpreting a reaction as a rule, we will use the terms *reaction* and *rule* interchangeably. Each process occurs with a *propensity* $\kappa_j(n)$, defined as

$$\kappa_j(n) := k_j \, h_j(n), \tag{2}$$

where

$$h_j(n) := \prod_{i=1}^s \binom{n_i}{\alpha_{ij}}.$$

Here, the combinatorial factor h_j describes the number of ways in which reaction R_j takes place. As in the original paper [6] by Gillespie, we make the following assumption: Reaction R_j occurs within a time interval Δt with probability $\kappa_j(n)\Delta t$.

For a given population with system configuration $n \in \mathbb{R}^s$, one can show (see [6]) that the probability density associated with the occurrence of R_j is given by

$$\Phi_j(n, t) = \kappa_j(\vartheta(n), n) \exp\left(-\sum_{l=1}^{r} \kappa_l(\vartheta(n), n)\, t\right) \tag{3}$$

as a function of time t. The probability that reaction R_j ever occurs is given by

$$\rho_j(n) = \int_0^\infty dt'\, \Phi_j(n, t') = \frac{\kappa_j(\vartheta(n), n)}{\sum_{l=1}^{r} \kappa_l(\vartheta(n), n)} \tag{4}$$

for $j \in \{1, ..., r\}$. The rules given by Equation (1) generate a stochastic process which satisfies the Markov property due to our assumption. This process is the starting point for the derivation of the master equation, describing the time evolution of the probability distribution of the system as a whole (see [5]). The probability density in (3) can be interpreted in terms of reaction waiting times and, in fact, instead of Assumption **??**, we can equivalently assume that reaction R_j occurs with an *exponentially distributed* reaction waiting time. In [6] Gillespie showed that the master equation can be exactly solved through the construction of realisations of the stochastic process associated to (1). This is achieved through the following algorithm, where ::= denotes replacement:

Algorithm 2.1 [Gillespie Algorithm]

0 *Initialize the starting time t, the system configuration $n = (n_1, \ldots, n_s)$ and the rate constants k_j for $j = 1, \ldots, r$.*

1 *Generate two random numbers r_1, r_2 uniformly distributed in $[0, 1]$.*

2 *Set $\Phi := \sum_{l=1}^{r} \kappa_l(n)$ and compute $\tau := -\frac{1}{\Phi} \ln r_1$.*

3 *Set $t ::= t + \tau$ as the time of the next rule execution.*

4 *Determine the reaction R_i which is executed at time t by finding i such that*

$$\frac{1}{\Phi} \sum_{l=1}^{i-1} \kappa_l(n) < r_2 \le \frac{1}{\Phi} \sum_{l=1}^{i} \kappa_l(n). \tag{5}$$

5 *Execute rule R_i and update the new system configuration n.*

6 *Go to step **1** if $t < T$, otherwise stop.*

The random numbers generated in Algorithm 2.1 are used for determining the index i of the next rule to be triggered, and the time interval τ for reaction R_i to occur. By the definition of $\rho_l(n)$ in (4) we have

$$\frac{1}{\Phi} \sum_{l=1}^{i} \kappa_l(n) = \sum_{l=1}^{i} \int_0^{\infty} \mathrm{d}t'\, \Phi_l(n, t') = \sum_{l=1}^{i} \rho_l(n)$$

in step **4** in Algorithm 2.1. We use Gillespie's algorithm to simulate the model dynamics, based on the assumption that the processes have exponentially distributed waiting times or, equivalently, that they are all Poisson processes, like atomic or molecular mixtures of gases or liquids. In complex systems formed by types which are heterogeneous and evolve through diverse interactions that cannot be always characterised by *exponentially distributed waiting times*, therefore the Gillespie approach is not fully adequate. It is thus very important to have a generalisation of Gillespie's algorithm that allows us to study systems driven by processes with different waiting time distributions and not necessarily exponentially distributed waiting times. Several generalisations exist in the literature, see [1], [7], [8] and [2] for instance, where a generalised Gillespie algorithm based on a generalised master equation in the form of an integro-differential equation [1] may be considered.

3   TRANSPORT EQUATIONS ON POSITION SPACE

We describe a dynamical process of redistribution of probability mass in a position space. The idea will be that the particles, or basic objects, are not only interacting by rules as described in Section 2, but also follow a re-positioning in position space according to a redistribution process. Each particle or basic object for that purpose will get attached coordinates in a postulated **position space**. The position space can be either an **internal state space** for the particles, describing something like age of the particle, or its size, or it can be a spatial position, then better described as an **external state space**. In this introduction to hybrid systems we are focussing the discussion on a spatial position space, denoted $\Omega \subset \mathbb{R}^d$, as usually domains in PDE theory are denoted. Important for the discussion will be that the particles can be located in different reaction volumes, see Figure 2. Therefore we will have to discuss in a later section the relationship between the position space Ω and the different reaction volumes. Recall that inside a reaction volume the particles have no positions, and each particle interacts with every other particle with the same probability. A natural way to connect reaction volumes and position space consistently will be to introduce a **discretisation** of the position space. Then we can associate a discretisation point (finite differences), control volume (finite volumes) or finite element (finite elements) to a reaction volume, all depending on the discretisation method that has been chosen. We assume, for example, there are a finite number of general conservation laws defined on Ω like

$$q_t(x,t) + \text{div}F(x,t) = f(x,t), \tag{6}$$

with F defining a general flux, a transport mechanism, with $F = (F_1, \ldots, F_d)$, and q being some transported quantity. Recall

$$\text{div}F = \frac{\partial}{\partial x_1}F_1 + \ldots + \frac{\partial}{\partial x_d}F_d,$$

and f is a well-behaving source term. Let $F = vq$, with v a smooth vector field defined on $\mathbb{R}^d$. The basic objects or particles introduced in Section 2 will have now obtain positions in Ω to start closing the model. We allow initial conditions, sinks or sources, or boundary conditions to be dependent on the particles, so in principle the particles can have an influence on the transport process. This can either be achieved by introducing particle concentrations as **point measures**, or using a continuum approach by introducing **interpolation**. The primary idea of this hybrid approach is that now transported quantities like q can appear as changing kinetic rates of the transport rules for the particle system.

4 TRANSPORT EQUATION DISCRETIZATION

We are now discretising the transport equation on position space Ω. This is not only to be able to solve the transport equation numerically, but in this hybrid approach is also a step towards the discrete number of particles and associated reaction volumes. This will later allow us to close the hybrid model, and make it well-defined. All common simple discretisation techniques will work.

4.1 Finite Differences

In this case the discrete grid will only allow particle coordinates in position space to be located at the discretisation points of the finite difference discretisation.

4.2 Finite Volumes

In this case there is some modelling freedom to have particle coordinates in the different control volumes forming a partition of position space Ω.

4.3 Finite Elements

In the classic finite element context we discuss a two dimensional example. We can tessellate the position space Ω into triangles:

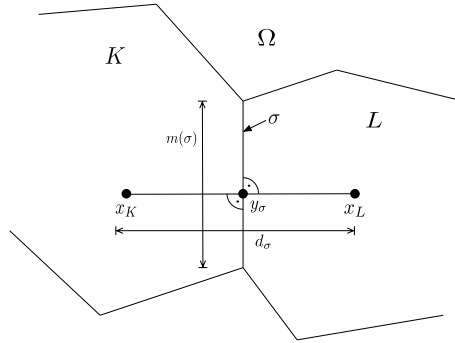$$\overline{\Omega} \;=\; \bigcup_{K \in T_h} K$$

Figure 3: A generic finite volume discretisation showing neighbouring control volumes in two dimensions.

where $T_h = \{K_1, \ldots, K_{E_h}\}$ is a set of $E_h \in \mathbb{N}$ closed triangles such that $K_i \cap K_j$ is an edge, a vertex, or empty if $i \neq j$. We denote the vertices of the triangulation by $\{X_1, \ldots, X_{N_h}\}$ where N_h is the number of vertices. The discrete positioning of particles has the same degree of freedom as in the finite volume case.

4.4 Mesh-Free Methods, Partition of Unity Method

We are especially interested in the partition of unity method (PUM), which is closely related to generalised finite elements (GFEM). This will allow us to define hybrid models with arbitrary complex domains, a huge advantage in many applications. for example in cell biology, or material science. Mesh-free methods based on the PUM share many basic approximation results of classic FEM which can be carried over directly or extended appropriately. Moreover, the distinct approach of constructing function spaces with the PUM exhibits some unique features which makes it especially attractive for particular problems that classical FEM cannot deal with efficiently. Some important properties of the PUM are:

- Approximation spaces of arbitrary smoothness can be created. Moreover, special functions suited for approximating the sought solution are incorporated and adapted easily.

- No mesh has to be created for the discretisation. It is instead based on an unconnected set of patches covering the domains, see Figure 4. Patches can be redistributed or the density of patches changed without geometrical constraints as would be the case with triangulations.

- Adaptivity by *hp*-refinement can be carried out without any complications induced by the domain or function spaces.

- Mathematical results from Galerkin methods and the Finite Elements Method (FEM) in particular can often be transferred or taken as a basis for extended results in the
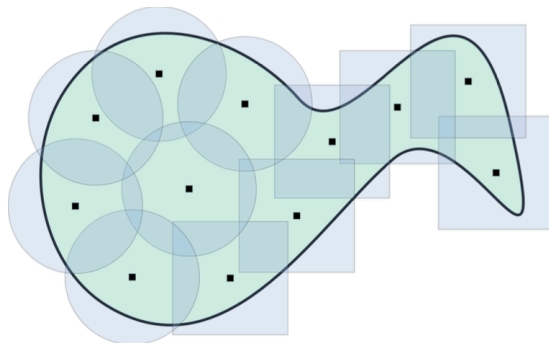
PUM context.

Figure 4: Domain covered with square and circular patches; dots marking patch centres

There is the same degree of freedom for defining particle coordinates like in the finite volume or finite element case. However not that whereas finite volume and finite element grids are partitions of the position space Ω, the patches of the PUM cover can overlap. This means for the hybrid method that particles can have coordinates in multiple patches, see also Figure 5.

5 CONNECTING TRANSPORT EQUATION DISCRETISATION TO RE-ACTION VOLUME

We now come to the last step in the definition of the hybrid method, connecting **reaction volumes** of a rule-based system to the **discretisation** of the transport equation defined on position space Ω.

5.1 Finite Differences

Finite difference discretisations of the transport equation defined on position space are straightforward to interpret. Every discretisation point is also a point measure reaction 'volume', particles can only jump from a discretisation point to neighbouring discretisation points, inheriting their coordinates.

5.2 Finite Volumes

The finite volume method is from its construction principles perhaps the generic case for the proposed hybrid method. **We can in fact define control volumes to be identical to reaction volumes.** Particles are transported from control volume to neighbouring control volumes by transport rules driven by the transport equation defined on Ω. The

coordinate change of the particles by jumping from one control volume to the next can be, for example, computed by the advective and diffusive regime imposed by the transport equation.

5.3 Finite Elements

Similar discussion as for finite volumes. Conservation relations for the transported quantity q (see Section 3) on the discrete level are typically harder to achieve for finite element grids of the position space.

5.4 Mesh-Free Methods, Partition of Unity Method

This is an extremely interesting discretisation with respect to the hybrid method. We can identify reaction volumes (Figure 2) with patches created for the PUM method (Figure 4). This implies, by the definition of the reaction volume, and the set-up of the Gillespie algorithm, that reaction volumes can overlap, and the Gillespie algorithm is not working on sets of particles which would be necessarily disjoint. For reaction volumes that are not having natural boundaries, like chemical reactors, this is a more convincing setting. For example, if larger particles are passively transported by some fluid, their reaction volumes are not properly defined, reaction volumes are not fixed but conceptually transported along the flow. This effect can be very well reconstructed with static overlapping patches, as particles close to each other in position are not necessarily separated by an artificial boundary between them. This is illustrated in Figure 5.

Again the re-positioning of particles can be adapted via the computed advection and diffusion via transport rules.

6 CONCLUSIONS

The proposed hybrid method is constructed for systems which (a) have an underlying medium in which larger particles get transported, (b) the particles can have type changes by stochastic collision events, and (c) the transport taking place in the medium is approximately deterministic. Such systems are relatively widespread, making the hybrid method attractive. We give a few examples:

Reaction-Diffusion Equations: For an introduction see [4]. We can treat reactions as stochastic, whereas the transport part can be more efficiently computed via a transport PDE.

Process Engineering: There are many problems close to our concept. A good example is gas bubble extraction. The bubbles get passively transported by a fluid flow and can collide and split stochastically.

Epidemiology: We can model geographic mobility efficiently deterministically, however we can keep the infection process stochastic.
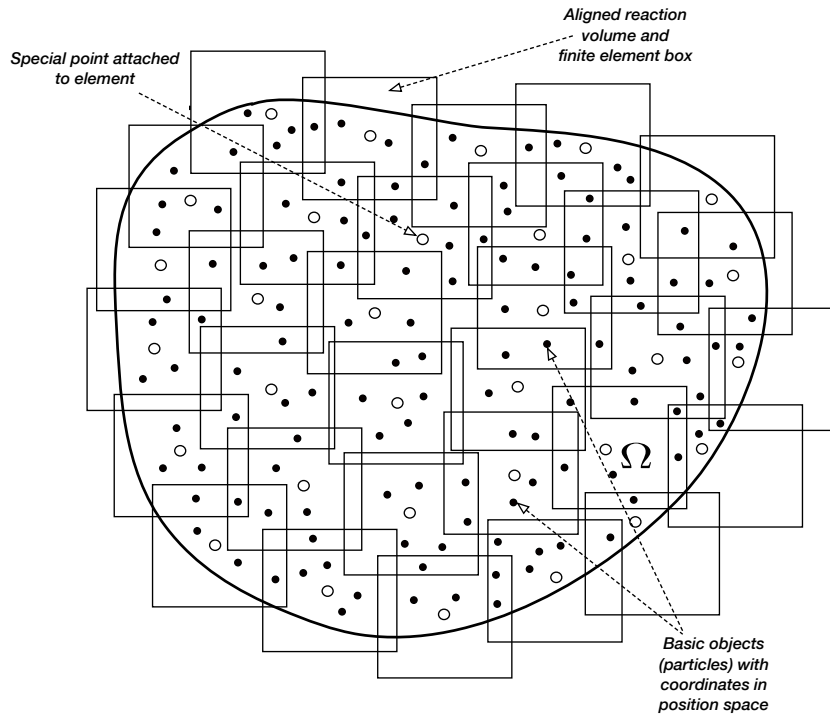
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Figure 5: Patches covering the position space, and the distribution of particles in Ω.

Demography: The position space is simply age-structure of individuals, therefore the transport is an ordinary differential equation in age-space. However, for example, the important process of couple formation can be modelled stochastically.

Cell Biology: Larger molecules like proteins can be modelled individually and stochastically with repect to their catalytic properties in metabolism, whereas their transport in the cell follows a transport equation.

Agent-based Modelling: The hybrid approach is ideal for agnt-nased modelling in both economics and finance.

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