On the Formalisation of Gradient Diffusion Models of Biological Systems

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Abstract

Many formal models for biological systems include a notion of topological space in the form of compartments. We consider the problem of modelling gradient diffusion systems that require a notion of metric space. We define diffusive *slots*, which govern local interactions and the diffusion from and to adjacent slots, and *areas*, which comprise one or more slots. We propose that a generic formalism is not suitable for modelling gradient diffusion systems, rather we tailor formalisms to particular scenarios, e.g. to biological systems with a given shape. An example of diffusion of nitric oxide in blood vessels illustrates the approach.

1 Introduction

Numerous languages and frameworks for discrete representation and reasoning about biological interactions have been developed over the last decade. The main contributions have been in the area of *process algebras* [15, 14, 9, 4, 3, 7], where a biochemical system is modelled by interacting processes representing molecules or species; *rewriting rules* [8, 2], where a system is modelled by molecules and their binding sites and state change is governed by rules that rewrite parts of the system; and *high level languages* [5, 13], where a biochemical system is specified by a list of parameters, reactions and additional grammatical features, which can be converted to any other formalism.

Here, we consider the problem of representing and reasoning about *space* in a discrete formalisation and in particular, we consider *gradient diffusion systems*. While the formalisms above have been extended to include a notion of space, it is usually by means of a topological space with *compartments* that are private locations, each of which is governed by a specific set of reactions and between which interactions are prohibited. Compartments are delimited by membranes that are static or dynamic, i.e. they change through time, leading to changes in the configuration of the compartmental structure.

In models of gradient diffusion systems, so far formalised mainly by *cellular automata* [1], notions like position and distance between molecules are required. These models apply, for example, to biological systems where proteins are translated in specific areas of tissues or

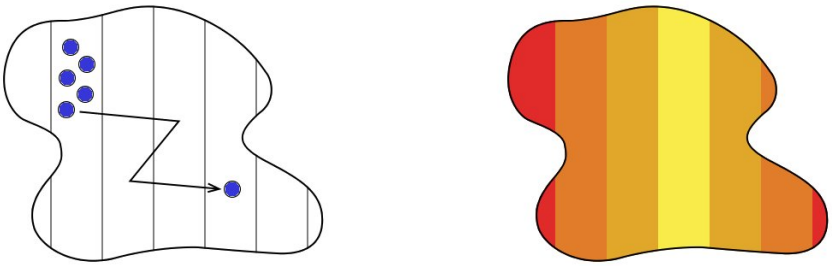

Figure 1: Two spatial approaches: single unit tracking (on the left) and average unit amount in an area (on the right).

organs. The diffusion distance, i.e. the ability of proteins to migrate far from the source, is fundamental for the correct functioning of the system: very precise phenotypes might be connected to areas where different proteins meet. An example of this phenomenon is pattern formation during morphogenesis of the Drosophila embryo [12].

The paper is organised as follows. In the next section we consider modelling choices for spatial models and in section 3 we propose a framework for the formalisation of gradient diffusion models. In section 4 we give an overview of a gradient diffusion model example: diffusion of nitric oxide in blood vessels. Our conclusions and future work are in section 5.

2 Modelling choices for space

In this section we give an overview of modelling choices for the formalisation of biological systems when a notion of location is required.

Individual and population view: in formal models of biochemical interactions, an elementary unit is either a single molecule, a fixed number of molecules, or a fixed amount of concentration. Formalising these elementary units in space, one has a choice between labelling

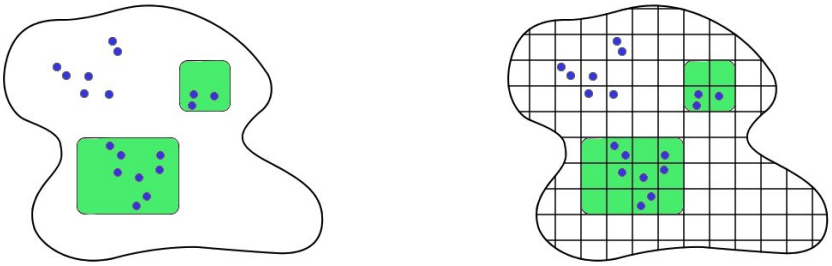

Figure 2: Compartments can be extended with a notion of position.

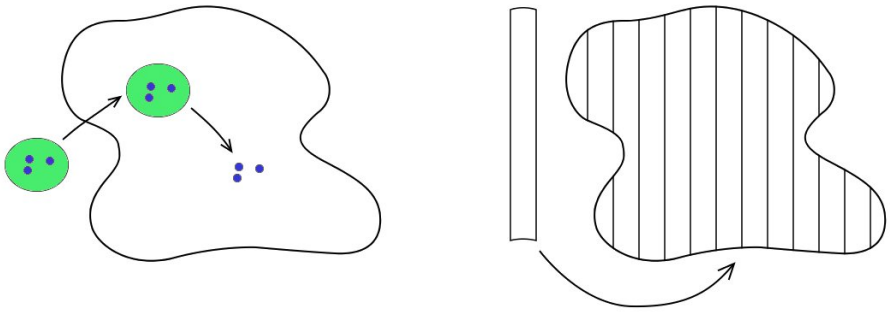

Figure 3: Modification of the compartmental structure or of the spatial shape.

a unit with its position, or simply tracking the number of units of the same type that are at a specific position. This is illustrated in Figure 1.

Many formalisms, such as Bioambients [16], Brane Calculi [6], bioκ-calculus [11] and stochastic bigraphs [10], although capable of implementing the individual view, choose the population view, primarily to reduce the state space explosion problem. An example of a process algebra based on the population view is Bio-PEPA [7].

Topological and metric space: as previously mentioned, compartments delimit areas where different molecules or different interactions take place. This is often suitable when considering a cell: typical compartments are cytoplasm and nucleus. But in diffusion systems, one often considers tissues or organs, at an higher organisational level. The notion of compartment is no longer sufficient. One needs to distinguish between diffusive *slots*, which govern local interactions and the diffusion from and to adjacent slots, and *areas*, usually comprising one or more slots, which encompass the delimiting function of compartments. This is illustrated in Figure 2. Models that include a notion of diffusion in a metric space are usually continuous and based on or derived from partial differential equations (PDEs). We note that in these models, the shape of the biological entity being modelled and the coordinate system used are critical factors.

Compartments and shape modification: some of the above mentioned formalisms, e.g. Bioambients, Brane Calculi and stochastic bigraphs, allow compartment manipulation. When the shape and the position of a biological entity is taken into consideration, other modifications might be necessary, such as the addition of new slots or the reassignment of a slot to a different area. This is illustrated in Figure 3. Examples of when these additional modifications might be required are tumour growth and organ morphogenesis.

Clearly a form of metric space is required for modelling gradient diffusion. Our preliminary investigations have led us to believe that a generic formalism will not be useful because there is huge variety of overall shape of the biological entity, and consequently the chosen coordinate system. We therefore concentrate on particular scenarios, as defined in the next section.

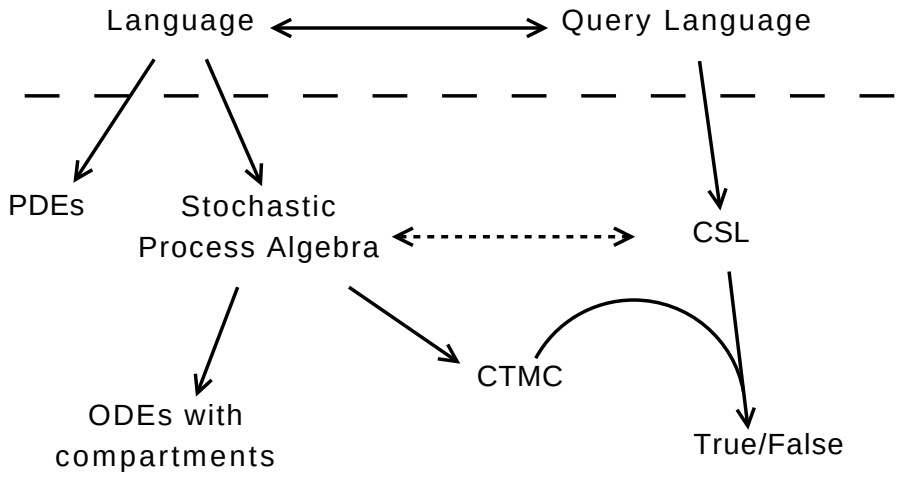

Figure 4: Translation and query for a description of a given scenario

3 High level languages for specific scenarios

We define a *scenario* as a biological system and a set of assumptions about shape, compartmentalisation and equations governing diffusion. The difference between models of a scenario will be in the level of detail, the types of molecules and biochemical interactions.

In order to formalise gradient diffusion models, we propose a high level descriptive language that is designed specifically for a single scenario. These are the main advantages:

Improved readability and maintenance: a scenario specific language is compact, it states only the information that distinguish models belonging to the same scenario. Notions and assumptions that are shared by models of the same scenario do not need to be stated explicitly in the language. Consequently descriptions are easy to read, write and maintain by modellers that are familiar with the scenario.

Modularity and translations: a formal language can be parsed and translated to other formalisms, such as process algebras or rewriting rules, if these are suitable for the scenario. The translation is automatic and ensures reliability of model formulation. If new mathematical models or formalisms that are more suitable are later defined, then new translations can be used while the high level language is unaltered.

High level queries: it is possible to formulate queries based on the high level language. Results are computed depending on the underlying formalism.

4 Example: nitric oxide bioavailability in blood vessels

In this section we briefly present an example scenario: diffusion in blood vessels.

Consider modelling nitric oxide (NO) bioavailability in blood vessels. Models of this scenario aim to determine the diffusion distance of NO along the radius of a vessel, where NO is produced in a narrow region on the internal wall of the vessel. Numerous models have been developed over the last decade (see [17] for a complete review) and almost all of them share

the same assumptions and use the same diffusion governing equations. In particular, a vessel is modelled as a cylinder with partial differential equations (PDEs), using Fick's law of diffusion in cylindrical coordinates. Compartments define areas such as endothelium (where NO is produced), vascular wall, and lumen (i.e. where the blood flows). Another common assumption is that the diffusion operates only in the radial direction, while it can be considered negligible in other directions.

We have defined a high level language from which both a traditional PDE and a stochastic process algebra (SPA) model can be derived. The SPA in this case is Bio-PEPA with static compartments: the space (in this case the radius) has to be divided into a number of slots defined by the modeller. The Bio-PEPA model is derived according to the implicit assumptions of the scenario and to information in the high level description. This means that the characteristics of each compartment, given by the rates of transport between compartments, the volume and the associated reactions, are derived automatically. From the Bio-PEPA description thus derived, other modelling approaches become accessible, such as ordinary differential equations (ODEs) with compartments, and continuous time markov chains (CTMCs with levels) (see [7] for details). Finally, a high level query language can be mapped to continuous stochastic logic (CSL), for reasoning about the states of the chain. A schematic representation of these translations is given in Figure 4.

5 Conclusions and Future Work

We have considered the problem of modelling gradient diffusion systems requiring a notion of metric space. In order to model space, we introduced diffusive *slots*, which govern local interactions and the diffusion from and to adjacent slots, and *areas*, comprising one or more slots, which encompass the function of compartments. We outlined an approach for modelling based on a high level language description for a given scenario and gave a brief overview of modelling an example gradient diffusion system: bioavailability of nitric oxide in blood vessels.

Future work includes formal proof the relationship between the underlying models, i.e. between PDEs, ODEs and CTMCs with levels, and further investigation of suitable query languages for gradient diffusion models.

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