

Spatial Modeling in the Attributed Pi Calculus

Mathias John

University of Rostock
Institute of Computer Science, Modeling and Simulation Group

Abstract. In the context of signaling pathways, the distribution of molecules in intracellular space is of basic interest, since dependencies between the functioning of proteins and their locations is often observed. Recently, the attributed π -calculus $\pi(\mathcal{L})$ was introduced; a modeling language based on the π -calculus, where reaction rates can be made dependent on attributes that are assigned to π processes. The aim of this work, is to discuss the applicability of the approach to spatial modeling. Therefore, common spatial effects in cells are presented and expressed in $\pi(\mathcal{L})$.

1 Introduction

In signaling pathways the functioning of proteins is strongly influenced by their location. Consider e.g. the Wnt-pathway [1]; an essential part of the signaling process is the complex formation of *Frizzled* proteins and *LRP6* receptors. Since both reactants are part of the cell membrane, binding can only be achieved by transbilayer motion. As in signaling cascades some molecules are in low abundance, equal spatial distribution cannot be presumed. Therefore, the modeling has to take spatial aspects into account.

The investigation of protein locations, requires modeling languages to provide two main concepts. First, it must be possible to make the reaction capability of molecules dependent on their location. Second, concepts for describing molecular motion are needed. In principle, molecular motion is regarded as a diffusion process. However, it can be strongly influenced by active transport, semipermeable membranes, or molecular crowding. Active transport and semipermeable membranes lead to similar effects just with opposite signs. Whereas membranes hamper the motion of molecules in some direction, active transport supports it. Both mechanisms show specificity for molecule sorts. Molecular crowding describes the interference of molecular motion caused by high molecular density and slow moving macro molecules [2].

The aim of this work is to present concepts for applying attributed π to spatial modeling. Therefore, the formalism is outlined in Section 2. Then, in Section 3, the integration of spatial aspects into attributed π models is discussed by means of some examples. This leads to some conclusions, as described in Section 4.

2 The Attributed π -calculus

The attributed π -calculus $\pi(\mathcal{L})$ [3] extends the π -calculus [4] by the parameter \mathcal{L} that refers to some functional programming language. \mathcal{L} is used to define values of process attributes and also to specify reaction constraints that take these values into account. The main idea can be depicted by an example; a system with two sorts of reactants, R_1 and R_2 , that can be located in two different compartments and are capable of binding. They have an attribute called `comp`, which can either be set to `'nucleus'` or `'cytosol'`, indicating the containing compartment. An $R_1(\text{comp})$ should only be able to bind to an $R_2(\text{comp})$, if their `comp` values equal. In $\pi(\mathcal{L})$ this can be expressed as

$$\begin{aligned} R_1(\text{comp}) &\triangleq \text{bind}[\text{comp}]!() . R_1\text{Bound}(\text{comp}) \\ R_2(\text{comp}) &\triangleq \text{bind}[\lambda r_1 \text{comp} . r_1 \text{comp} = \text{comp}]?() . R_2\text{Bound}(\text{comp}) \end{aligned}$$

The binding of $R_1(\text{comp})$ and $R_2(\text{comp})$ is constrained by the application of $R_1(\text{comp})$'s location to the expression $[\lambda r_1 \text{comp} . r_1 \text{comp} = \text{comp}]$. Assuming $R_1(\text{comp}: \text{'nucleus'})$ and $R_2(\text{comp}: \text{'nucleus'})$, application yields `'nucleus'='nucleus'`, which, given an appropriate semantics of \mathcal{L} , evaluates to the truth value `true`. This enables the binding reaction such that the reactants turn into their bound states (not further described here). Notice, that `true` is assumed to be a successful value whereas `false` is not. The set of successful values is specified by \mathcal{L} and can therefore vary. In particular, it can be the set of stochastic rates $\mathbb{R}^+ \cup \infty$. Based on the stochastic semantics of $\pi(\mathcal{L})$, this facilitates stochastic simulation [5].

3 Spatial Modeling in the Attributed π -calculus

As illustrated in Section 2, space can be modeled in $\pi(\mathcal{L})$ by introducing attributes that indicate discrete locations, like `'cytosol'`, and restricting interactions accordingly. The latter requires the definition of reaction constraints that check location equality. A more general spatial model is considered by introducing two reactants that move on a rectangular grid with $m \times n$ volumes, see Figure 1. $R_1(\mathbf{p}_x, \mathbf{p}_y)$ and $R_2(\mathbf{p}_x, \mathbf{p}_y)$ describe the reactants with coordinates \mathbf{p}_x and \mathbf{p}_y . Summation (+) denotes, that they can either bind or move. Binding is encoded similar to the preceding example. However, the λ expression for checking equality assigned to the channel `bind` and accessed via the constant `'val'`. The reactants interact via `move` with $V(\mathbf{p}_x, \mathbf{p}_y, f_l, f_r, f_u, f_d)$, which represents a grid's single volume. Apart from its position, V provides additional attributes with values $\in \{0, 1\}$, that are used to scale the motion of reactants to one of V 's four neighbors (left, right, up, down). For volumes at the grid border some of these attributes are set to 0 to assure that reactants do not move out of model space, see `Initial solution`. When acting on `move`, the position coordinates of reactants are set to \mathbf{p}'_x and \mathbf{p}'_y , whose values are provided by V .

Notice, that the model can be extended to an irregular n -dimensional grid by simply changing the neighborhood relation. Furthermore, the effort for introduc-

Global channel definitions

```
bind: λxy. if (x=px) and (y=py) then rate else 0
move: λxyf. if (x=px) and (y=py) then f*d else 0
```

Process definitions

```
R1(px, py, d) ≜ bind [px py]!() .R1Bound(px, py)
+move ['val' move]?(p'x, p'y) .R1(p'x, p'y)
R2(px, py, d) ≜ bind ['val' bind]?() .R2Bound(px, py)
+move ['val' move]?(p'x, p'y) .R2(p'x, p'y)
V(px, py, fl, fr, fu, fd) ≜
move [px py fl]!(px-1, py) .V(px, py, fl, fr, fu, fd)
+move [px py fr]!(px+1, py) .V(px, py, fl, fr, fu, fd)
+move [px py fu]!(px, py-1) .V(px, py, fl, fr, fu, fd)
+move [px py fd]!(px, py+1) .V(px, py, fl, fr, fu, fd)
```

Initial solution

```
V(0, 0, 0, 1, 0, 1) | V(0, n-1, 0, 1, 1, 0) | V(m-1, 0, 1, 0, 0, 1) |
V(m-1, n-1, 1, 0, 1, 0) | %corners
∏j=1m-2 ∏i=1n-2 V(m, n, 1, 1, 1, 1) | %grid center
∏i=1m-2 V(i, 0, 1, 1, 0, 1) | ∏i=1m-2 V(i, n, 1, 1, 1, 0) | %horizontal borders
∏i=1n-2 V(0, i, 0, 1, 1, 1) | ∏i=1n-2 V(m, i, 1, 0, 1, 1) | %vertical borders
%reactants with some position and diffusion constant
∏∏R1(xpos, ypos, diff) | ∏∏R2(xpos, ypos, diff)
```

Fig. 1. A spatial model in $\pi(\mathcal{L})$ with two reactants and a regular, two-dimensional grid. $\prod_{i=1}^n P_i$ denotes $P_1|\dots|P_n$, which says that n instances of P are called in parallel.

ing new reactants or reactions is rather low, since no additional logic regarding space is required.

3.1 Adding further Spatial Features

The preceding model illustrates the basic concepts of spatial modeling in $\pi(\mathcal{L})$. In the following, it is discussed how further features of interest can be added.

Varying Size of Volumes The basic effect of volume sizes is that they influences reaction rates. A model with variable volume sizes needs to map them to an additional attribute of V . Furthermore, reactants are required to provide the size of their containing volume, which is used to parameterize the rates of reactions and updated accordingly with priority, i.e. with infinite rate. The following encoding shows the basic concept of integrating variable volumes, where s is the volume size, s_V the size of the containing volume, and **size** the update channel:

```
%additional channel
size:  $\lambda xys. \text{if } (x=p_x) \text{ and } (y=p_y) \text{ and } (s!=s_V)$ 
  then  $\infty$  else 0
%additional summands in definitions
 $R(p_x, p_y, d, s_V) \triangleq \text{size}[\text{'val' } \text{size}]?(s'_V) \cdot R(p_x, p_y, d, s'_V) + \dots$ 
 $V(p_x, p_y, f_l, f_r, f_u, f_d, s) \triangleq$ 
   $\text{size}[p_x \ p_y \ s]!(s) \cdot V(p_x, p_y, f_l, f_r, f_u, f_d) + \dots$ 
```

Notice, that this also allows for the modeling of volumes with sizes varying over time.

Molecular Crowding Molecular crowding hampers the motion of reactants depending on the position of some macro molecules. In the basic model, V provides attributes that are used to parameterize the rate of motion reactants (f_l, f_r, f_u, f_d) . Molecular crowding can be integrated by introducing macro molecules that decrease the values of these attributes when they enter a volume and reset them to status quo when they leave.

Semipermeable Membranes and Active Transport The effects of semipermeable membranes and active transport can be integrated by modifying reaction constraints and attribute values accordingly. E.g. to integrate the notion of semipermeable membranes the following constraint is assigned to **move**:

```
 $\lambda xyf. \text{if } (x=p_x) \text{ and } (y=p_y) \text{ then}$ 
   $\text{if}(sort \in f) \ d \text{ else } 0$ 
else 0
```

The constraint assumes that **sort** indicates the reactant's sort and **f** is a set which is provided by V and contains all sorts of reactants that are allowed to move in a particular direction.

4 Conclusion

As discussed in [6], the concept of constraining reaction by additional equality checks (poly-synchronization) to express locations, forms the basis of the majority of formalisms addressing spatial modeling, e.g. BioAmbients [7] or Brane Calculi [8]. In deed, it could be shown in [3], that all these languages can be encoded in $\pi(\mathcal{L})$. However, as illustrated in Section 3, additional spatial effects of basic interest, like active transport or molecular crowding, can be model in $\pi(\mathcal{L})$. To the best of my knowledge, this is the first time these have been expressed in a formal stochastic modeling language.

References

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