Multi-scale Models of Pattern Formation with Process Algebra

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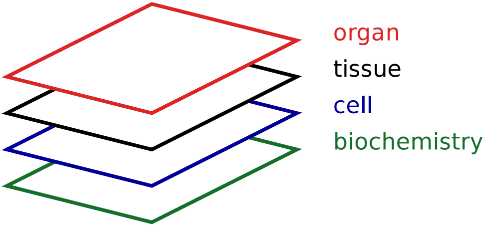
Stirling, 6th of July 2010

Multi-scale Modelling



- Each layer has a current state;
- Biochemistry drives the action, it's timing and likelihood;
- Information flows bottom up;
- We want to focus on one layer at a time, abstracting away from the other layers.

Motivations

We want to study *pattern formation* in biological systems with the theory of process algebra and automated reasoning.

What is pattern formation?

An area with equivalent and uniformly distributed cells, produces transient or steady complex forms and functions.

Why do we care?

Development of organs and limbs, tumour growth, basic mechanisms are preserved in different animals.

Morphogenesis (1950s)

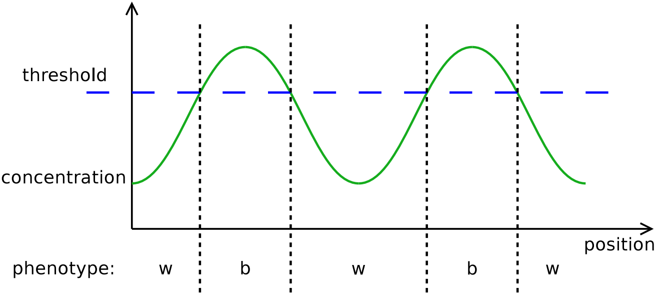
Key assumption: there is a direct dependence between a phenotype and the concentration of one or more chemicals (*morphogens*) at a certain position.

Key elements for morphogenesis (Turing 1952):

1. Two or more chemical species (activator and inhibitor);
2. Different rates of diffusion for the species;
3. Chemical interactions.

A combination of these factors can result in chemical patterns.

Concentration and Tissue Phenotypes



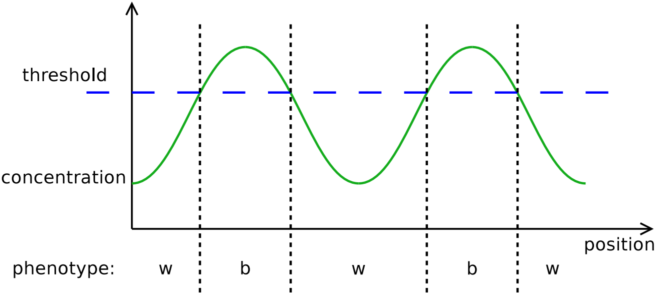
Formalisation of mathematical models with process algebra

We use features from other process algebras that have been proved effective in modelling biological systems. Mainly from PEPA and Bio-PEPA [Hillston 1996, Ciocchetta and Hillston 2008].

To mention a few:

- multiway synchronisation;
- functional rates;
- processes as levels of concentration;
- parsimony, i.e. absence of unnecessary constructs in the language.

Concentration and Tissue Phenotypes



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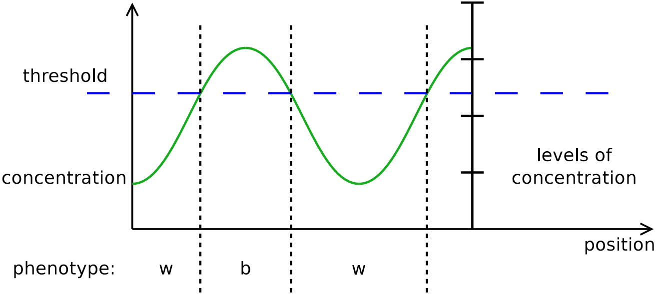
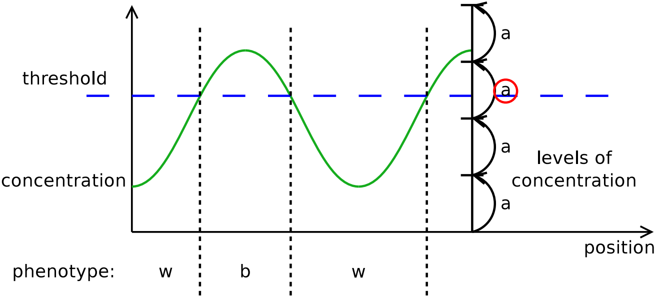


Concentration and Tissue Phenotypes



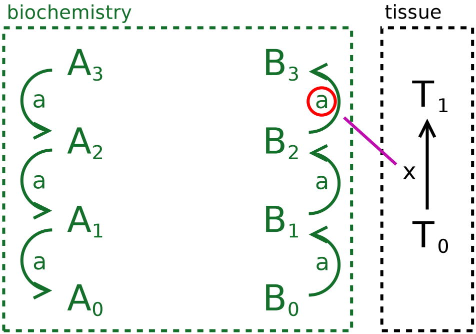
The Synchronisation Issue

$A_3 \triangleq a.A_2$
$A_2 \triangleq a.A_1$
$A_1 \triangleq a.A_0$
$A_0 \triangleq nil$

$B_3 \triangleq nil$
$B_2 \triangleq a.B_3$
$B_1 \triangleq a.B_2$
$B_0 \triangleq a.B_1$

$T_1 \triangleq nil$
$T_0 \triangleq x.T_1$

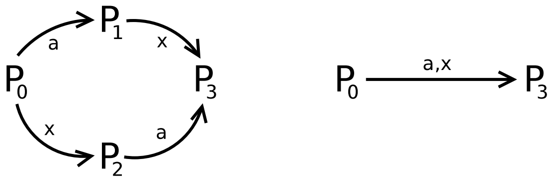
$$(A_3 \underset{\{a\}}{\bowtie} B_0) \underset{\{x\}}{\bowtie} T_0$$



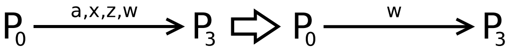
Interleaving and Filtering

a and *x* are not two different actions, but **the same action** seen from different layers of abstraction.

Thus, we avoid interleaving and compress different names of the same action on a single label.



Which requires a filtering of the labels of the transition system, to focus on a layer of abstraction.



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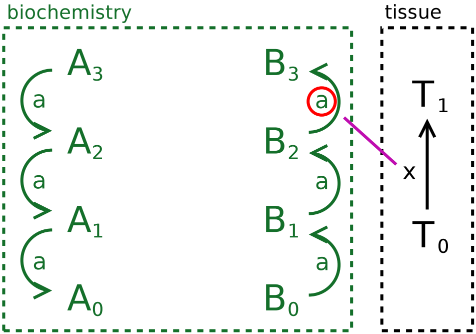
$$(A_3 \underset{\{a\}}{\bowtie} B_0) \underset{\{x\}}{\bowtie} T_0$$



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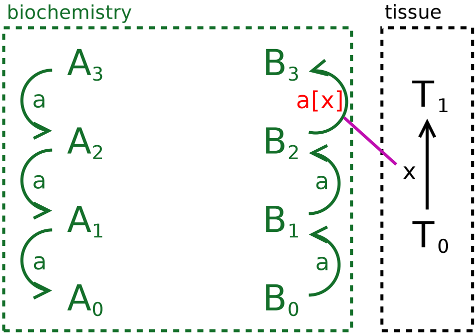
$A_1 \triangleq a.A_0$
$A_0 \triangleq nil$

$B_3 \triangleq nil$
$B_2 \triangleq a[x].B_3$
$B_1 \triangleq a.B_2$
$B_0 \triangleq a.B_1$

$T_1 \triangleq nil$
$T_0 \triangleq x.T_1$

$(A_3 \underset{\{a\}}{\bowtie} B_0) \underset{\{x\}}{\lhd} T_0$



Example 1

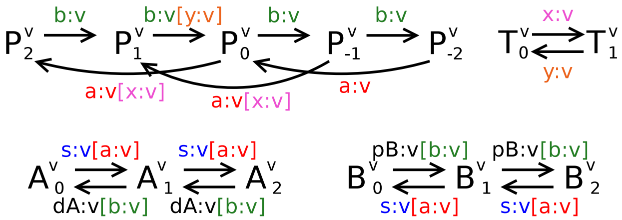
Tissue changes when morphogen passes the threshold.

$$\mathrm{M}_0^{\mathrm{v}} \underset{\mathrm{b:v}}{\overset{\mathrm{a:v}}{\rightleftarrows}} \mathrm{M}_1^{\mathrm{v}} \underset{\mathrm{b:v}[\mathrm{y:v}]}{\overset{\mathrm{a:v}[\mathrm{x:v}]}{\rightleftarrows}} \mathrm{M}_2^{\mathrm{v}} \underset{\mathrm{b:v}}{\overset{\mathrm{a:v}}{\rightleftarrows}} \mathrm{M}_3^{\mathrm{v}} \qquad \mathrm{T}_0^{\mathrm{v}} \underset{\mathrm{y:v}}{\overset{\mathrm{x:v}}{\rightleftarrows}} \mathrm{T}_1^{\mathrm{v}}$$

$$M_1^v \underset{x:v,y:v}{\lhd} T_0^v \xrightarrow{a:v,x:v[x:v]} M_2^v \underset{x:v,y:v}{\lhd} T_1^v$$

Example 2

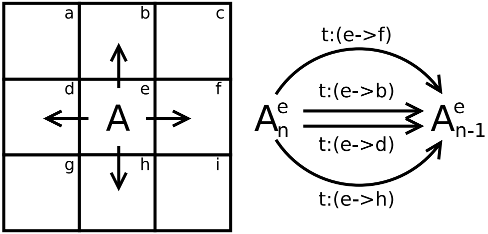
Tissue changes when the concentration of A becomes more than the concentration of B.



$$((A_1^v \underset{s:v}{\bowtie} B_2^v) \underset{a:v,b:v}{\lhd} P_{-1}^v) \underset{x:v,y:v}{\lhd} T_0^v \xrightarrow{s:v,a:v,x:v[a:v,x:v]} ((A_2^v \underset{s:v}{\bowtie} B_1^v) \underset{a:v,b:v}{\lhd} P_1^v) \underset{x:v,y:v}{\lhd} T_1^v$$

Example 3

Use of space: many actions have the same effect.



PAH: Syntax

Sequential Component:

$$S ::= nil \mid \mathcal{L}'[\mathcal{L}''].C^v \mid S + S$$

Constant Definition:

$$C^v \triangleq S$$

Model Component:

$$P ::= P \underset{\mathcal{L}}{\bowtie} P \mid P \underset{\mathcal{L}'}{\lhd} C^v \mid C^v$$

Other details:

$$\mathcal{L} ::= ø \mid \mathcal{L}' \qquad \mathcal{L}' ::= a{:}m \mid a{:}m, \mathcal{L}' \qquad \mathcal{L}'' ::= ø \mid a{:}m$$

$$m ::= v \mid (v \rightarrow v) \qquad v ::= (z, z, z)$$

Regular Cooperation

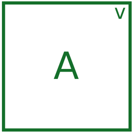
$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{E}]} P_3 \qquad P_2 \xrightarrow{\mathcal{B}[\mathcal{F}]} P_4}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{\mathcal{A}\cup\mathcal{B}[\mathcal{E}\cup\mathcal{F}]} P_3 \underset{\mathcal{L}}{\bowtie} P_4}, \mathcal{A} \cap \mathcal{B} \cap \mathcal{L} \neq \emptyset$$

Hook Synchronisation

$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{E}]} P_2 \qquad C_{\prime}^{v} \xrightarrow{\mathcal{B}[\mathcal{F}]} C_{\prime\prime}^{v}}{P_1 \underset{\mathcal{L}}{\lhd} C_{\prime}^{v} \xrightarrow{\mathcal{A}\cup\mathcal{B}[\mathcal{E}\cup\mathcal{F}]} P_2 \underset{\mathcal{L}}{\lhd} C_{\prime\prime}^{v}}, \quad \mathcal{B}[\mathcal{F}]\ cond$$

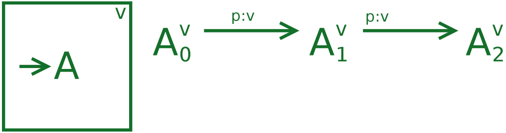
$\mathcal{B}[\mathcal{F}]$ *cond*: given $C_{\prime}^{v} \triangleq \mathcal{B}_1[\mathcal{F}_1].C_1^v + \mathcal{B}_2[\mathcal{F}_2].C_2^v + ... + \mathcal{B}_n[\mathcal{F}_n].C_n^v$, let $\mathcal{B}$ be a $\mathcal{B}_i$ in $\mathcal{B}_1, \mathcal{B}_2, ..., \mathcal{B}_n$ such that $\mathcal{B}_i \subseteq \mathcal{E}$ and $\mathcal{B}_i \subseteq \mathcal{L}$ (i.e. $\mathcal{B}_i \subseteq \mathcal{E} \cap \mathcal{L}$) and there is no B_j in $\mathcal{B}_1, \mathcal{B}_2, ..., \mathcal{B}_n$ with larger cardinality than $\mathcal{B}_i$ such that $\mathcal{B}_j \subseteq \mathcal{E} \cap \mathcal{L}$.

Example 4 - Building up



A_0^v A_1^v A_2^v

Example 4 - Building up



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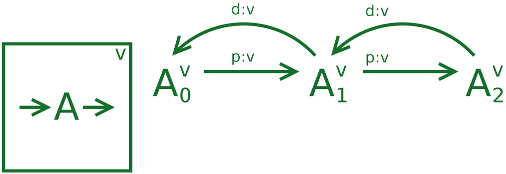

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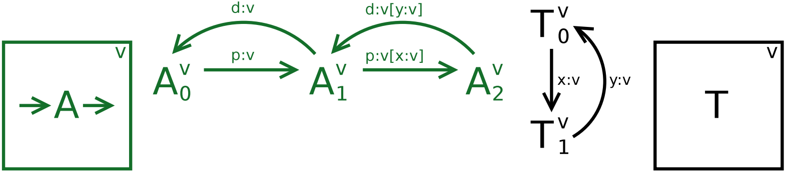

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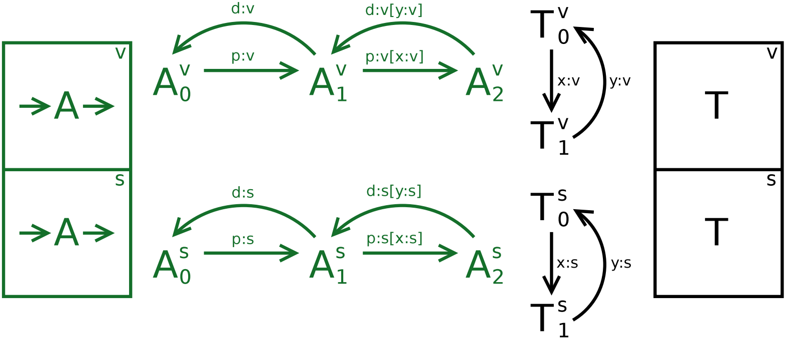

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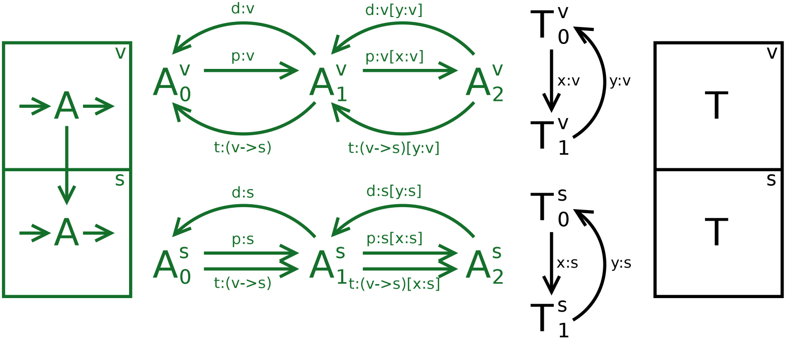
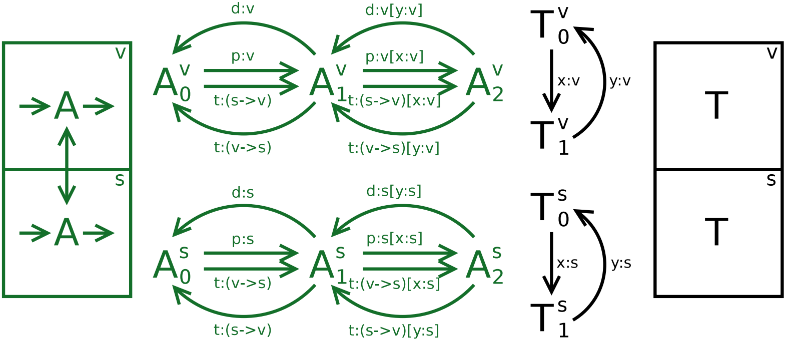
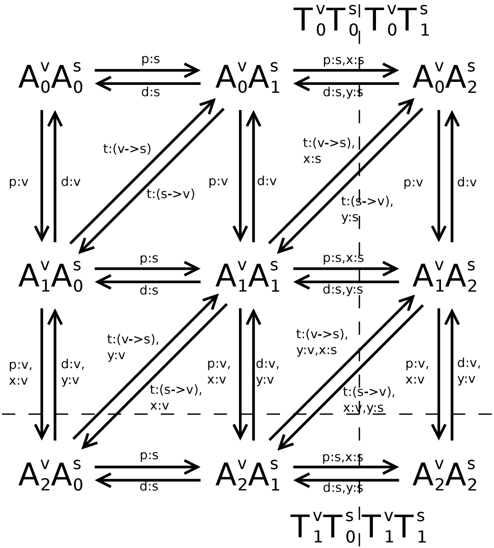


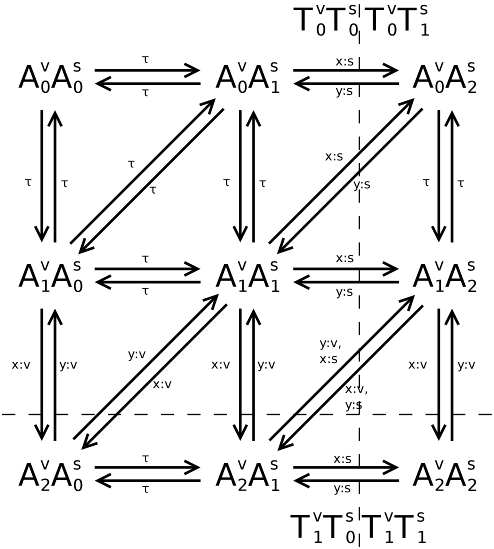
Example 4 - Processes



Example 4 - temporary LTS



Example 4 - Filtered LTS



Conclusions

Done:

- definition of a non stochastic version of PAH that generates LTS;
- extension of PAH to support functional rates and to generate stochastic LTS;
- abstract machine for PAH and proved soundness, completeness and termination with respect to the operational semantics;
- abstract machine implemented in OCaml, along with a bisimulation minimisation algorithm.

Planned:

- export models in PRISM;
- identification of suitable bisimulations and their implementation;
- model rewriting to simulate growth or other spatial modifications.