

# Multi-cell Modelling Using Coloured Petri Nets Applied to Planar Cell Polarity

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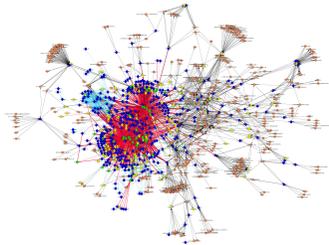
**Brunel**  
UNIVERSITY  
LONDON

# Overview

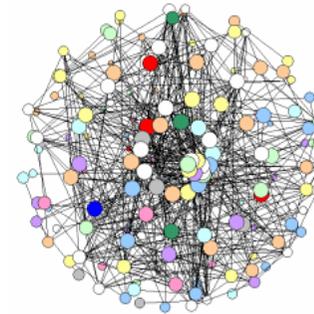
1. Petri Nets
2. Coloured Petri Nets
3. Planar Cell Polarity
4. Analysis Results
5. Summary

# Networks

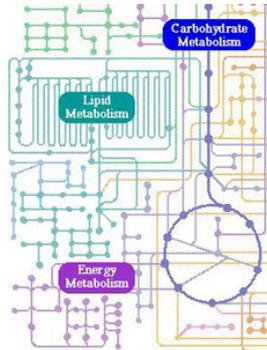
- Gene regulation



- Protein-protein interaction

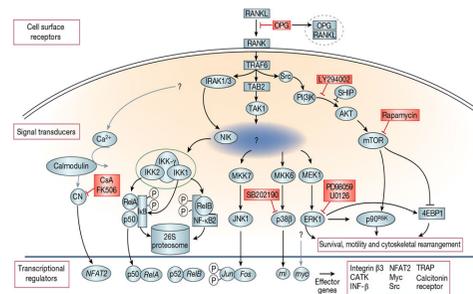


- Metabolic

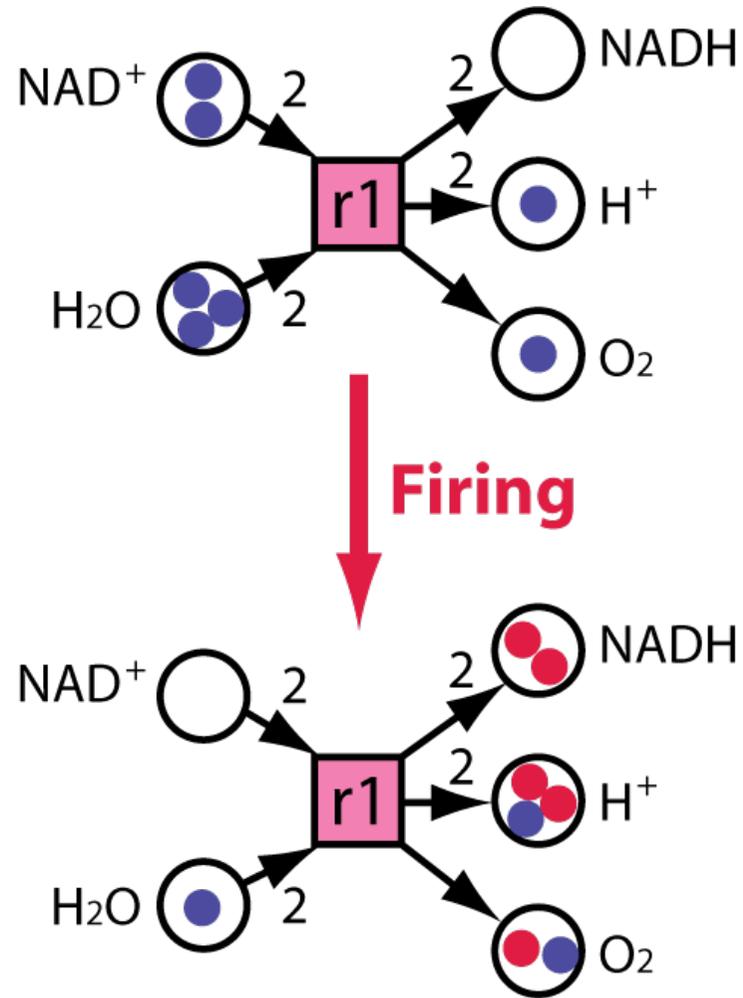


- Developmental

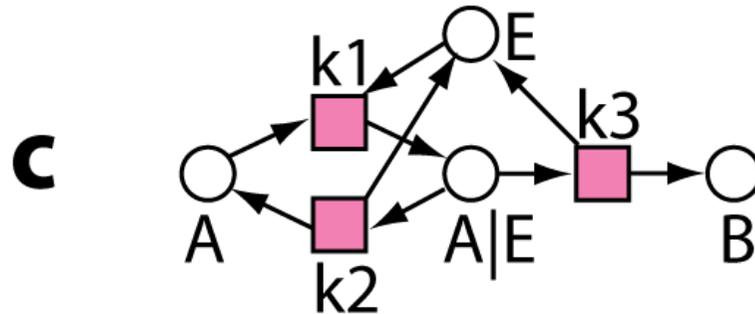
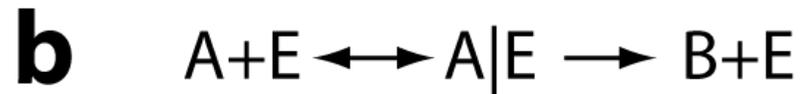
- Signalling



# Petri Nets



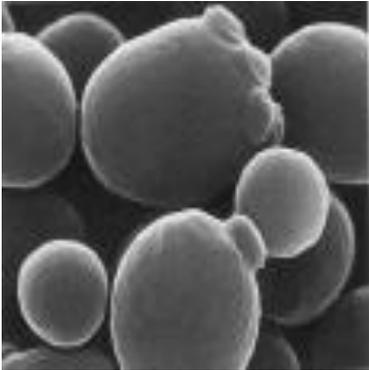
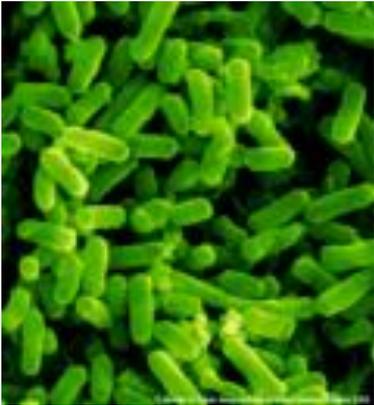
# Simple enzymatic reaction



**d**

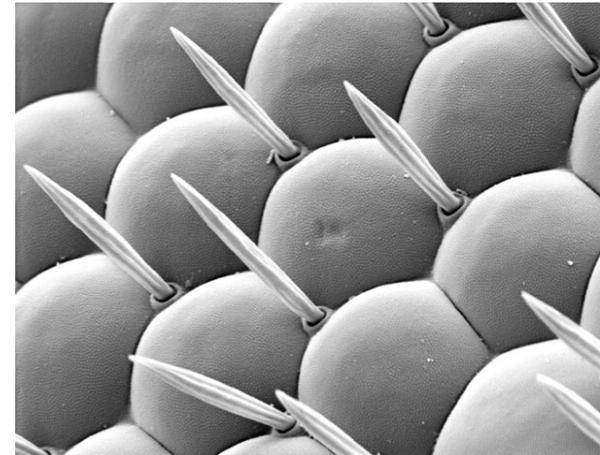
$$\frac{d[A]}{dt} = -k_1[A][E] + k_2[A|E]$$
$$\frac{d[E]}{dt} = -k_1[A][E] + k_2[A|E] + k_3[A|E]$$
$$\frac{d[A|E]}{dt} = k_1[A][E] - k_2[A|E] - k_3[A|E]$$
$$\frac{d[B]}{dt} = k_3[A|E]$$

# Scaling up?



# Multiscale modelling challenges

- **Repetition** – multiple cells with similar definitions
- **Variation** – mutants.
- **Organisation** - regular or irregular patterns over spatial networks in one, two or three dimensions.
- **Communication** – between neighbours constrained by neighbour relation, and the position in spatial network.
- **Hierarchical organisation** – cells containing compartments. Enables abstraction over level of detail of components.



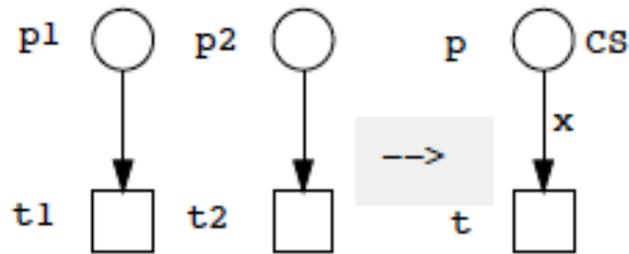
# Coloured Petri nets

- Tokens distinguished via their colours.
- Each place gets a colour set, specifying the kind of tokens which can reside on the place.
- Each transition gets a guard, specifying which coloured tokens are required for firing.
- Each arc gets an arc expression specifying the kind of tokens flowing through it
  
- Allows for the discrimination of species (molecules, metabolites, proteins, secondary substances, genes, etc.).
- Colours can be used to distinguish between sub-populations of a species in different locations (cytosol, nucleus and so on).

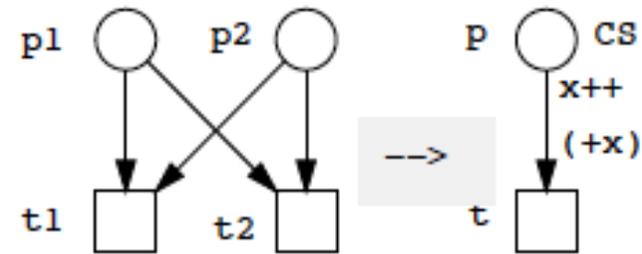
# Coloured Petri net

- A coloured Petri net is a tuple  $N = [P, T, F, \Sigma, c, g, f, m_0]$ , where:
- $P$  is a finite, non-empty set of places.
- $T$  is a finite, non-empty set of transitions.
- $F$  is a finite, non-empty set of directed arcs.
- $\Sigma$  is a finite, non-empty set of colour sets.
- $c : P \rightarrow \Sigma$  is a colour function that assigns to each place  $p \in P$  a colourset  $c(p) \in \Sigma$ .
- $g : T \rightarrow \text{EXP}$  is a guard function that assigns to each transition  $t \in T$  a guard expression of Boolean type.
- $f : F \rightarrow \text{EXP}$  is an arc function that assigns to each arc  $a \in F$  an arc expression of a multiset type  $c(p)_{MS}$ , where  $p$  is the place connected to the arc  $a$ .
- $m_0 : P \rightarrow \text{EXP}$  is an initialisation function that assigns to each place  $p \in P$  an initialisation expression of a multiset type  $c(p)_{MS}$ .

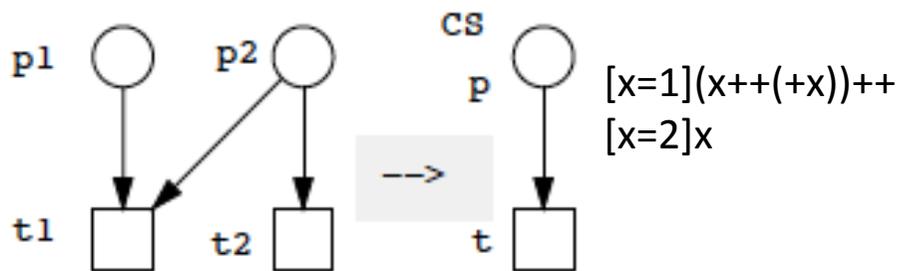
# Coloured Petri net folding



(a)



(b)



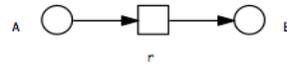
(c)

Declarations:  
 colorset CS = int with 1,2;  
 variable x : CS ;

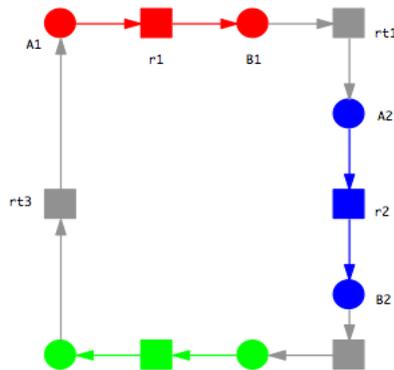
(d)

++: multiset addition  
 (+x): successor  
 [x=2]: guard

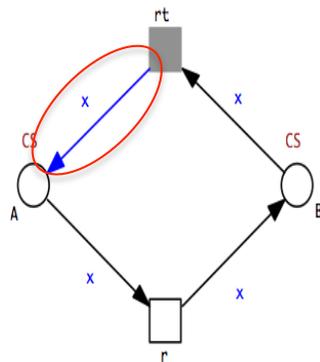
# Simple CPN examples



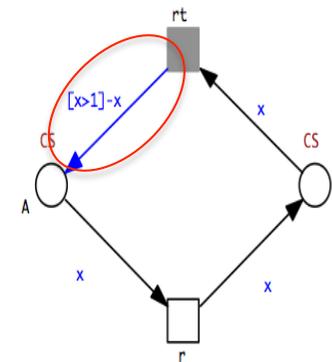
A circuit of cells, each consists of a simple reaction



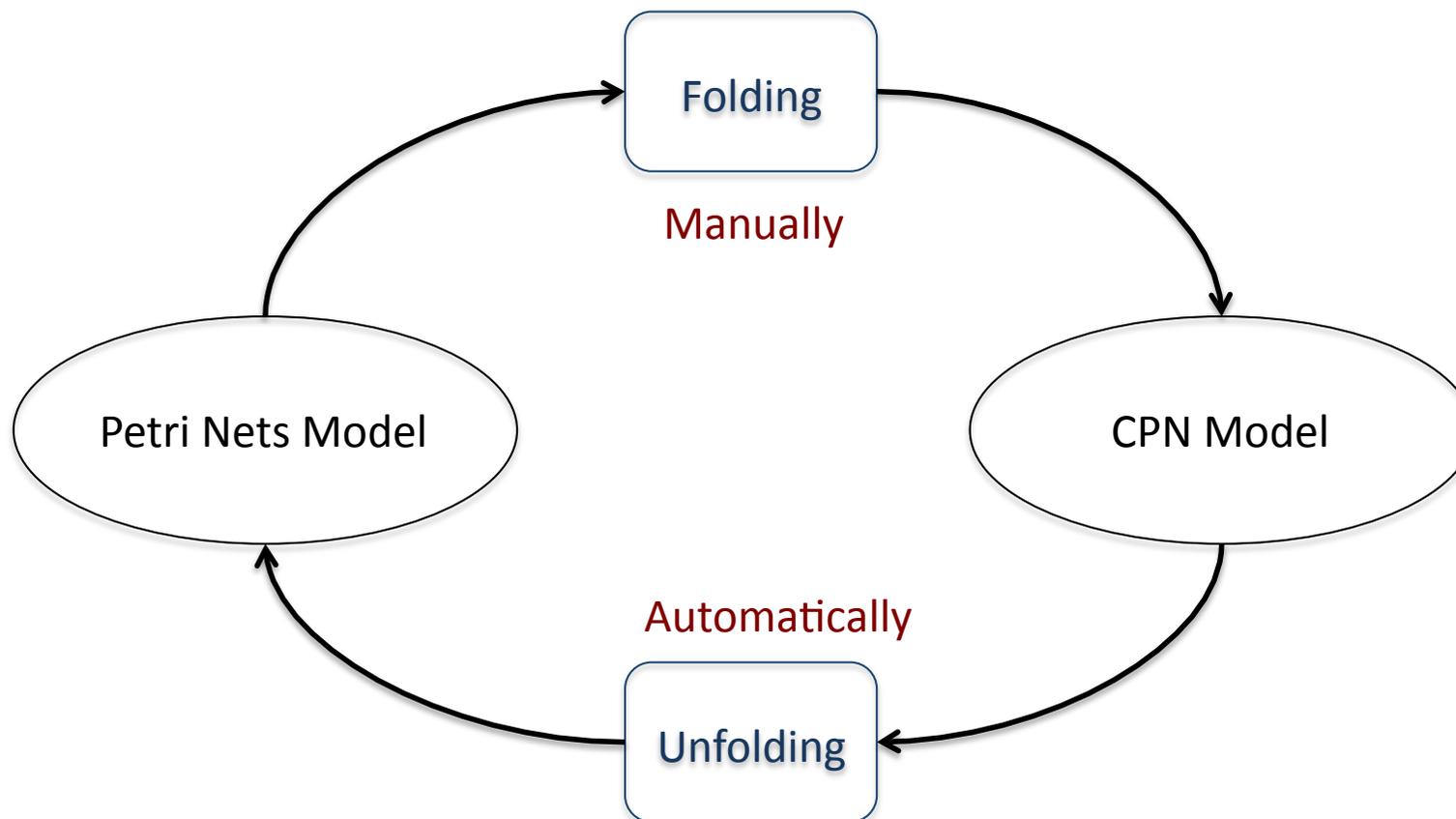
A pipeline of cells, each consists of a simple reaction

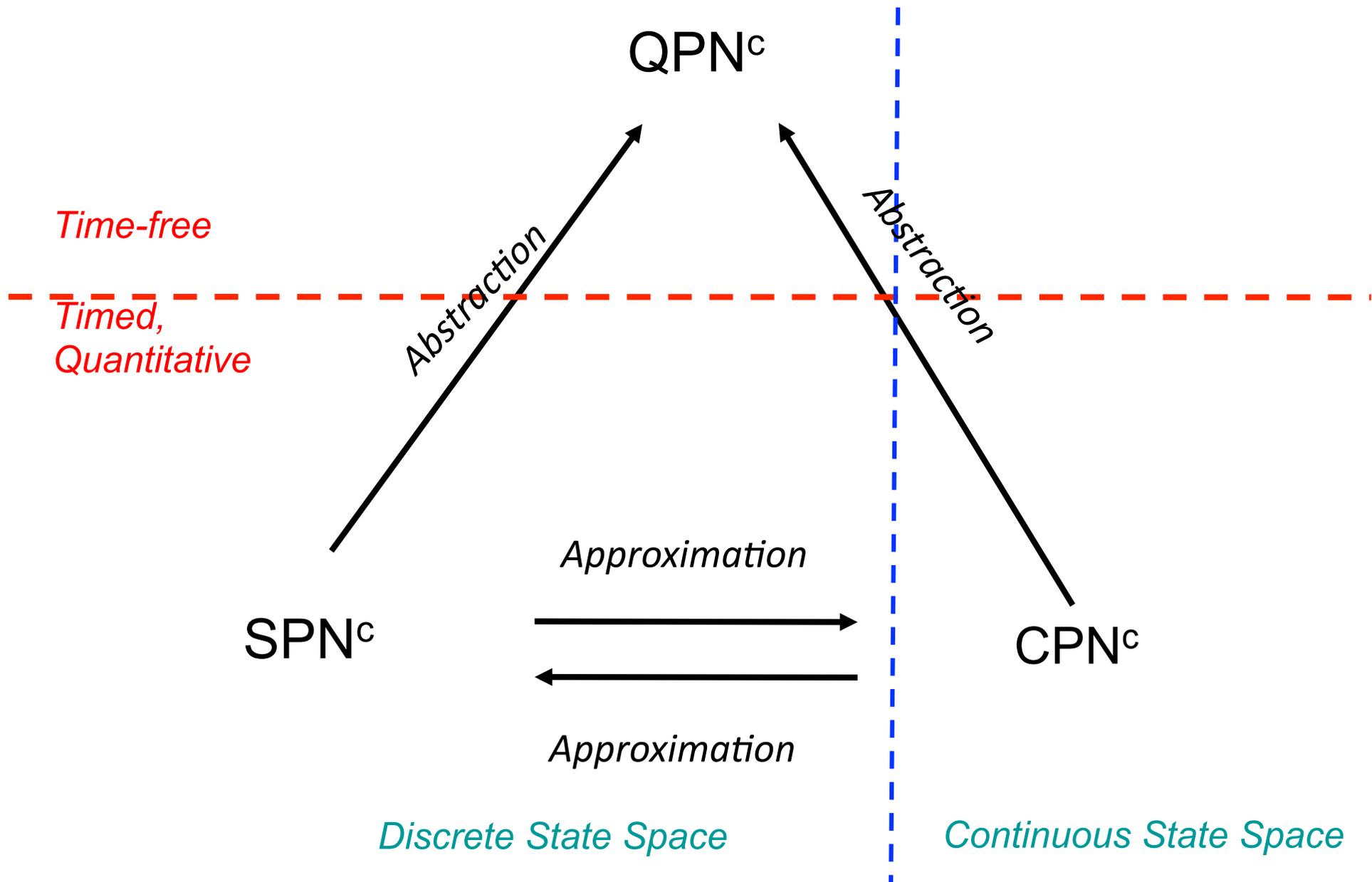


x: arc expression  
 [x>1]: guard  
 -x: predecessor



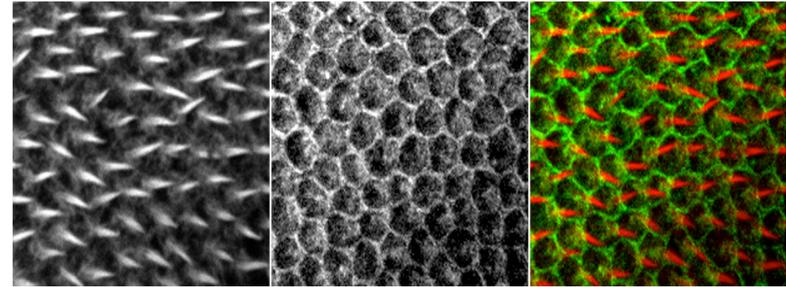
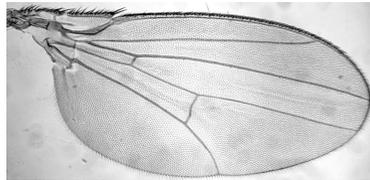
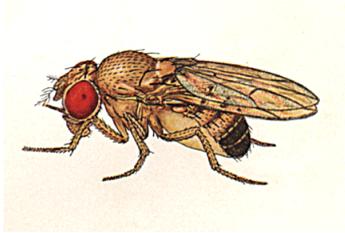
# Coloured Petri Nets in Snoopy



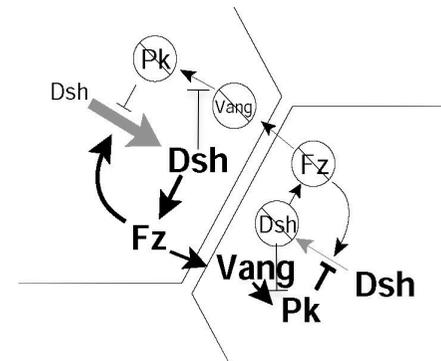
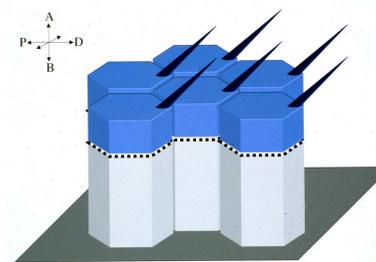


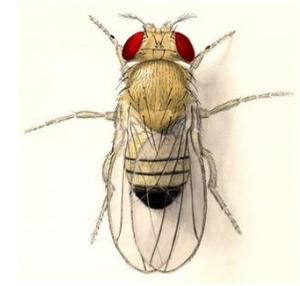
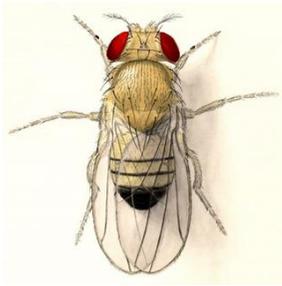
- Liu and Heiner. "Colored Petri nets to model and simulate biological systems". BioPPN 2010.
- Gilbert, Heiner and Lehrack. "A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets." Proc CMSB 2007.

# Multiscale from signalling to organs

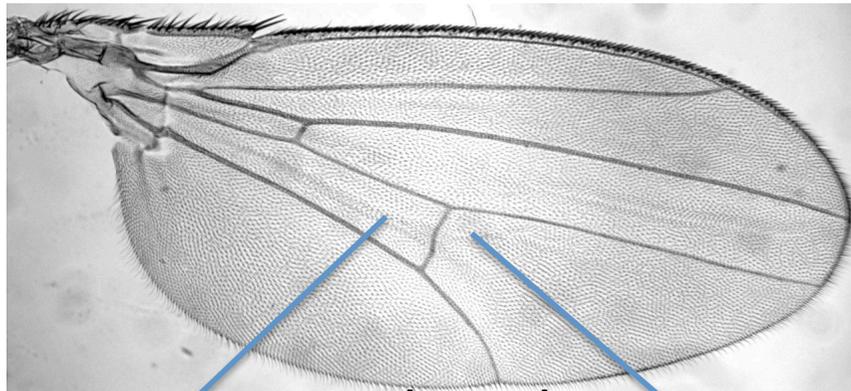


Planar Cell  
Polarity

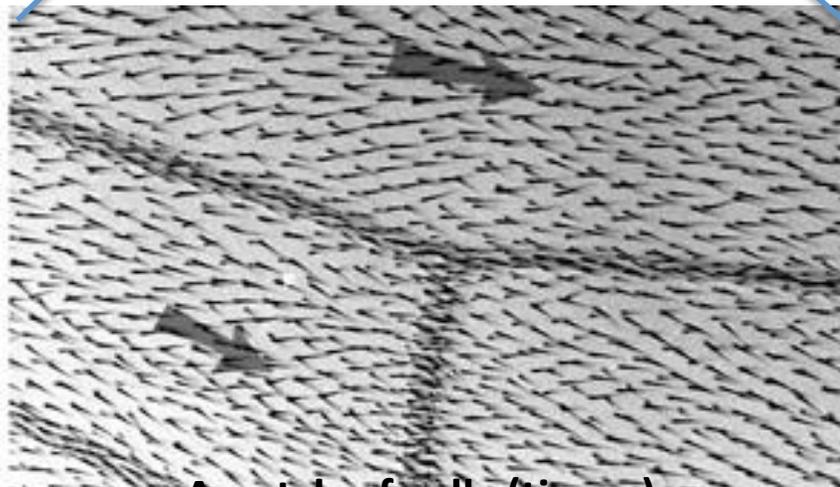




# Planar Cell Polarity



**Wing (Organ)**



**A patch of cells (tissue)**

- PCP: the polarization of a field of cells within the plane of a cell sheet.

- Human pathology:

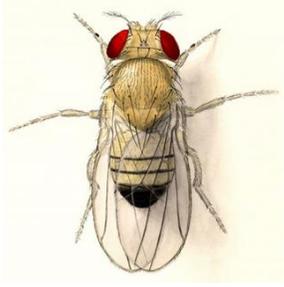
- ✓ Cochlear hair cells

- ✓ Spina bifida

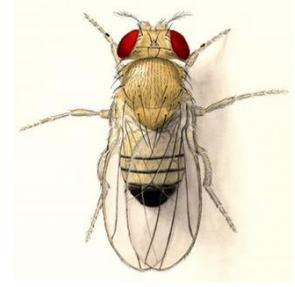
- ✓ Oncogenic Wnt pathway

- Drosophila wing cells, hexagonally packed, planar (300,000)

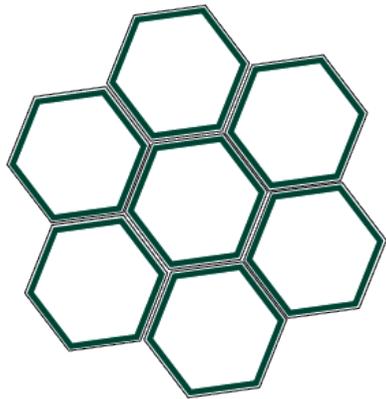
- Hairs point in an invariant distal direction



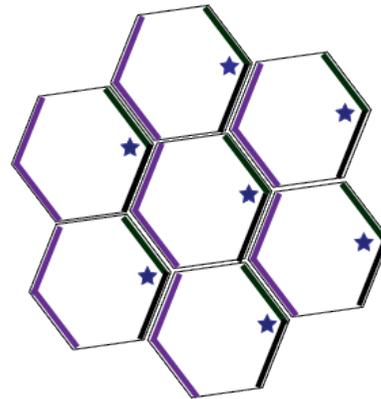
# Biological Model



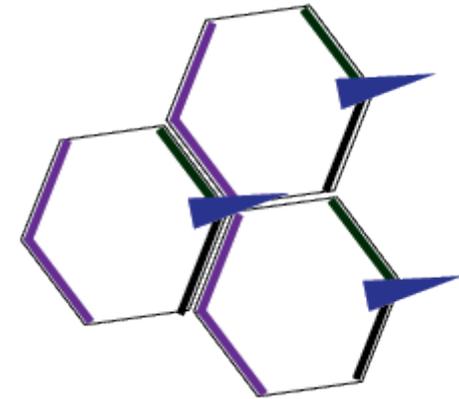
- A core machinery mediates a competition between the **proximal** and **distal** proteins: **Frizzled (Fz)**, **Dishevelled (Dsh)**, **Prickle (Pk)** and **Van-Gogh (Vang)**. **Flamingo (Fmi)** localises at both distal and proximal edges.
- Fmi, Fz and Dsh accumulates on the distal side of the cell, designating it as the future *site for prehair formation*, while Fmi, Vang and Pk accumulates on the proximal side of the neighbouring cell.
- Feedback loops: cells tend to align cell polarity as asymmetric distribution.



Symmetric distribution of protein complexes

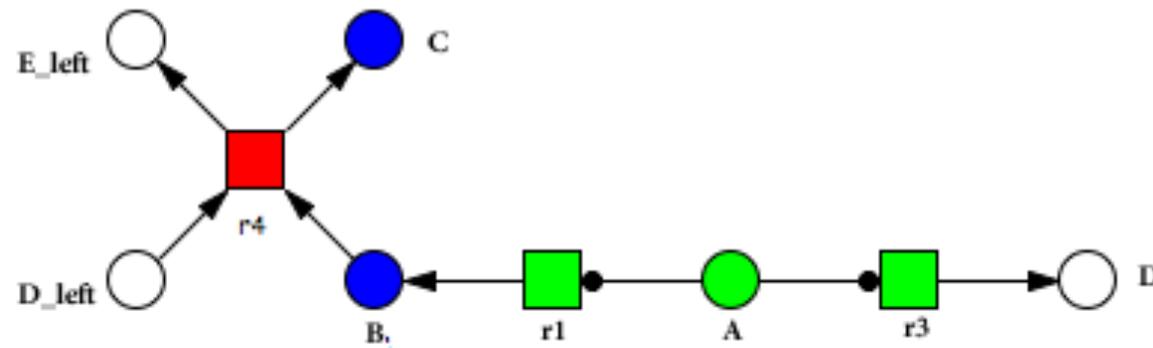


Asymmetric distribution of protein complexes



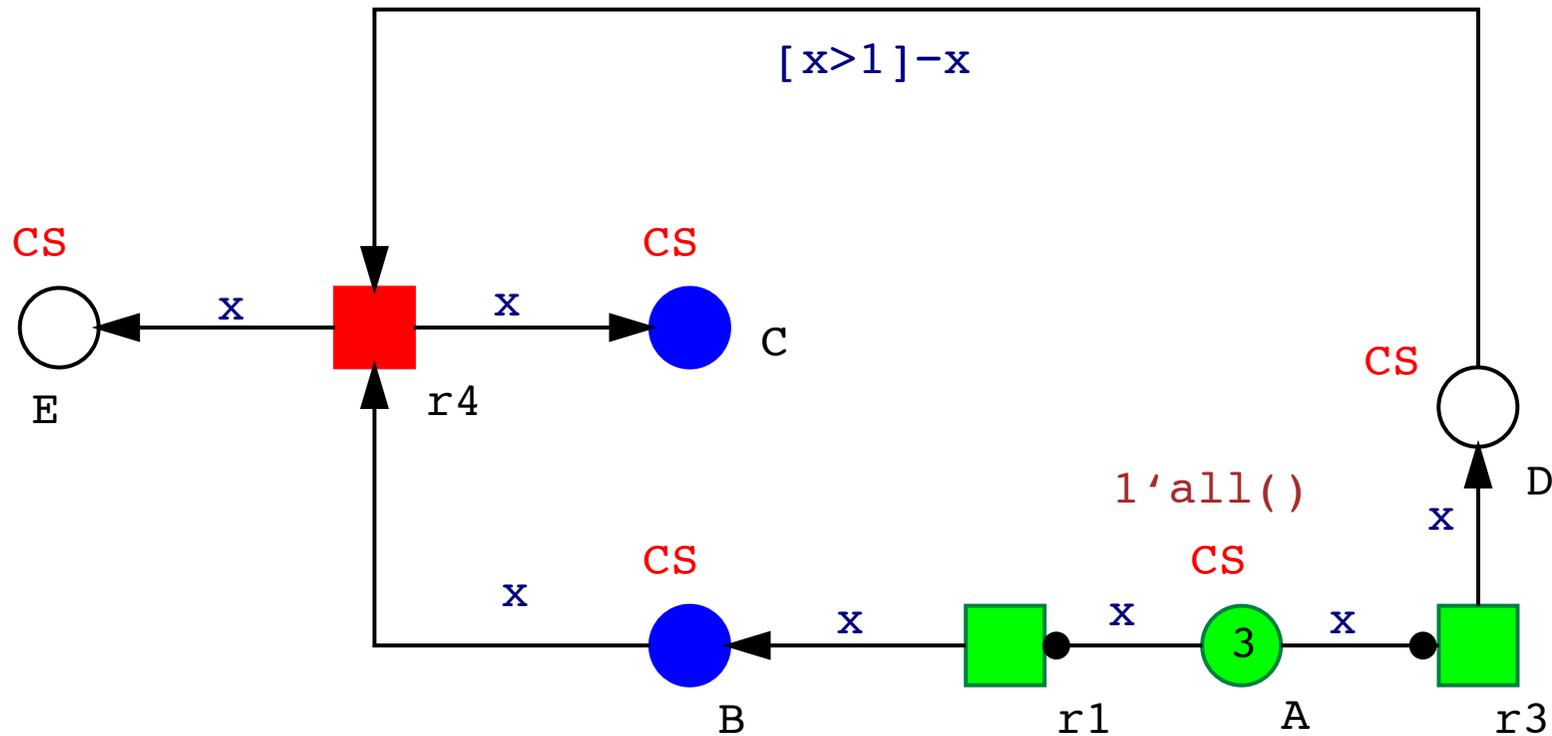
Prehair formation

# Single cell Abstract level



- Four spatial regions as labelled (*Labelled colours are **not** CPN colour sets*)
- D\_left & E\_left: two molecular species (places) from the left-hand side neighbouring cell(s)

# CPN model for cells linked in a pipeline.



colourset CS = int with 1-N ( $N = \text{number of cells}$ );

variable x: CS;

$[x > 1] - x$ : the first cell does not have a left-hand neighbour.

# Spatial organisation & colours

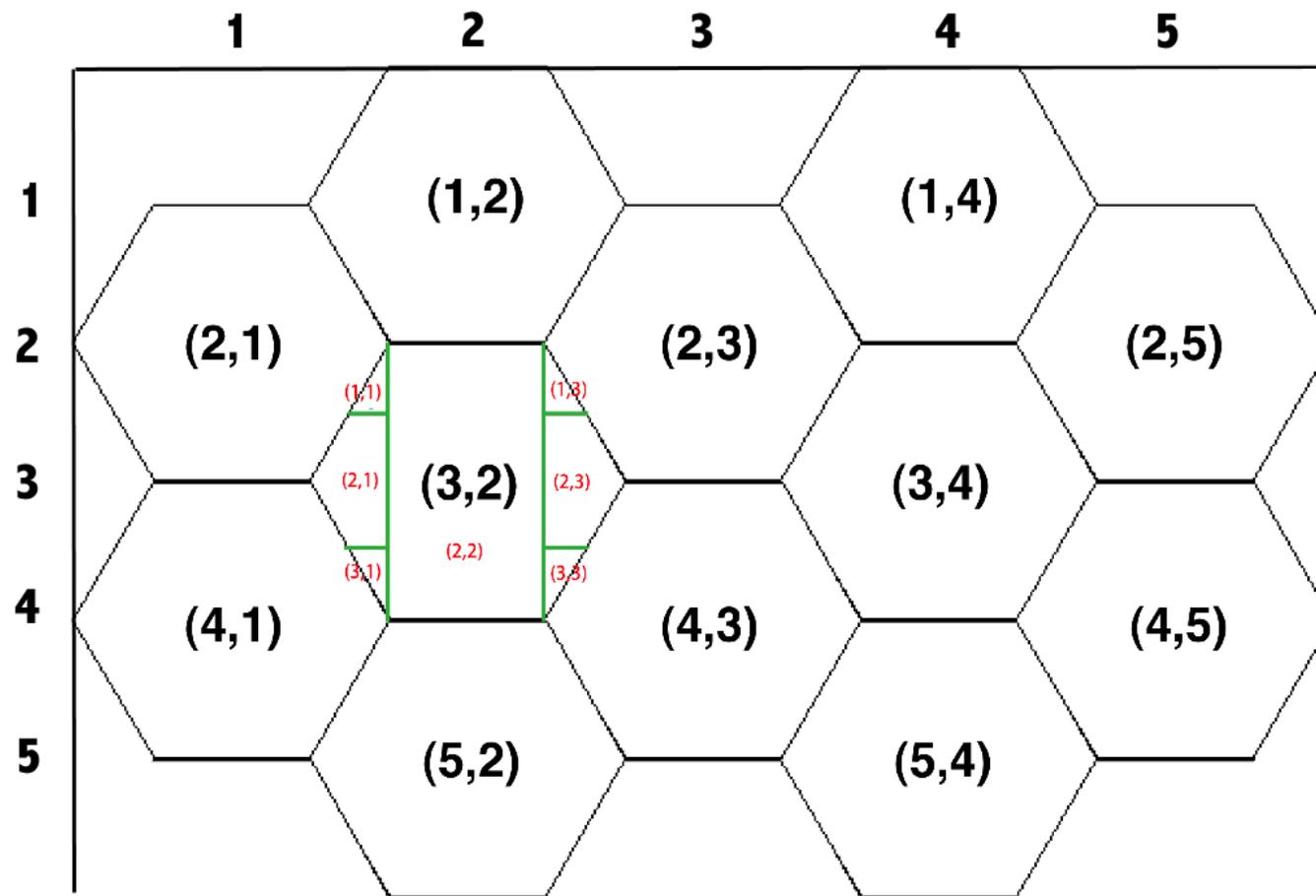
- Reflect organisation by colour structure

(1,1)	(1,2)	(1,3)	(1,4)
(2,1)	(2,2)	(2,3)	(2,4)
(3,1)	(3,2)	(3,3)	(3,4)
(4,1)	(4,2)	(4,3)	(4,4)

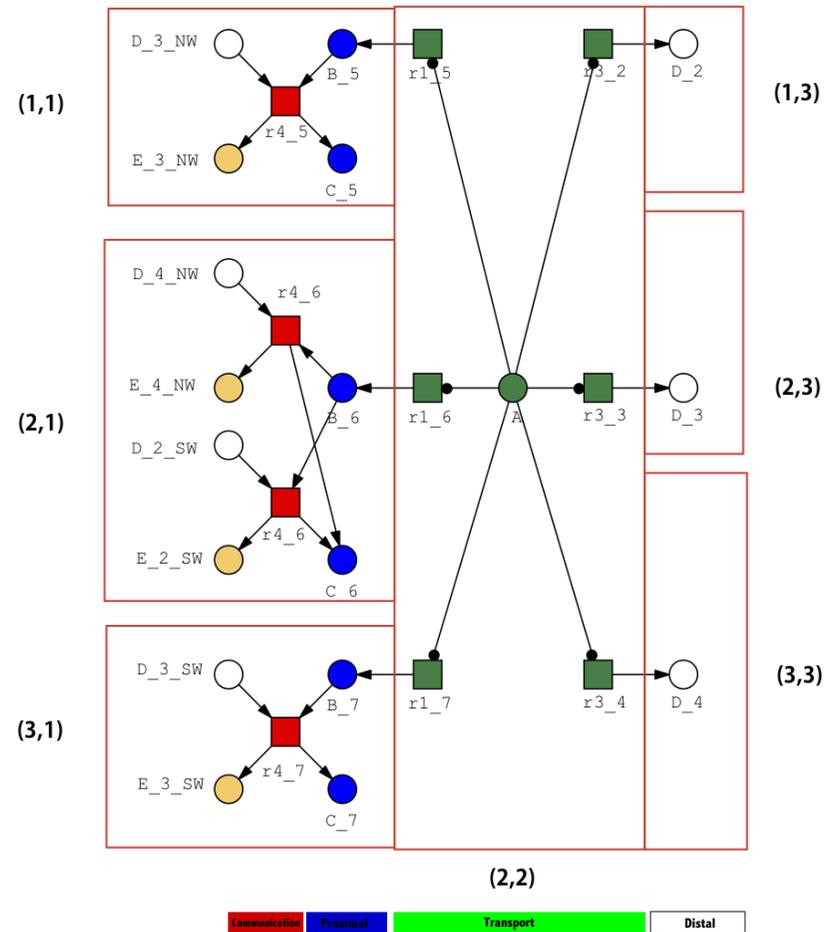
Colourset =  $\{(1,1), (1,2), (1,3), (1,4), (2,1), (2,2), (2,3), (2,4), (3,1), (3,2), (3,3), (3,4), (4,1), (4,2), (4,3), (4,4)\}$

Neighbouring functions: north, south, west, east

# Wing tissue: Cells with logical compartments

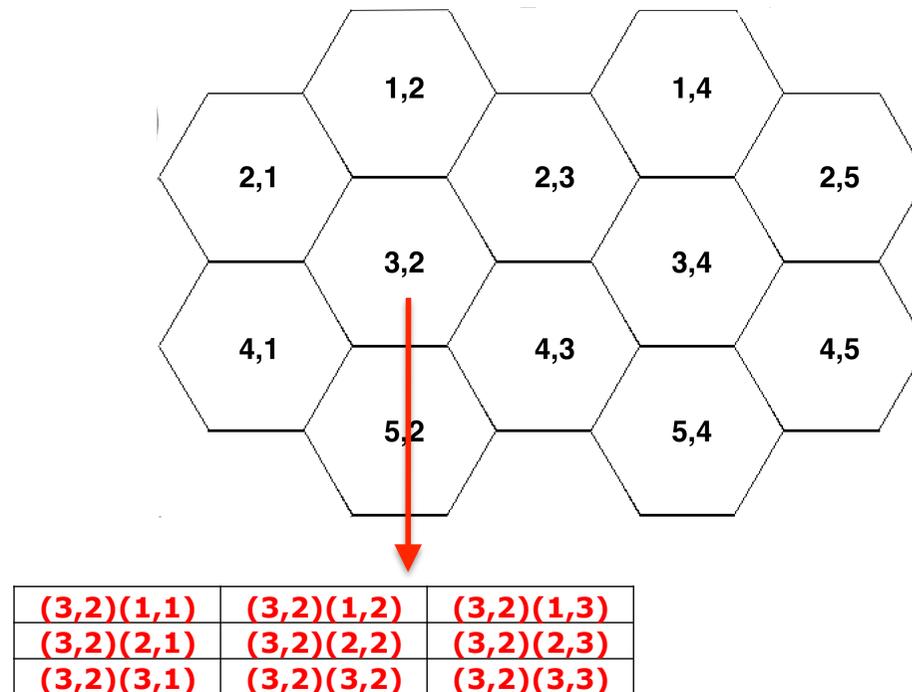


# Petri net model for a single cell



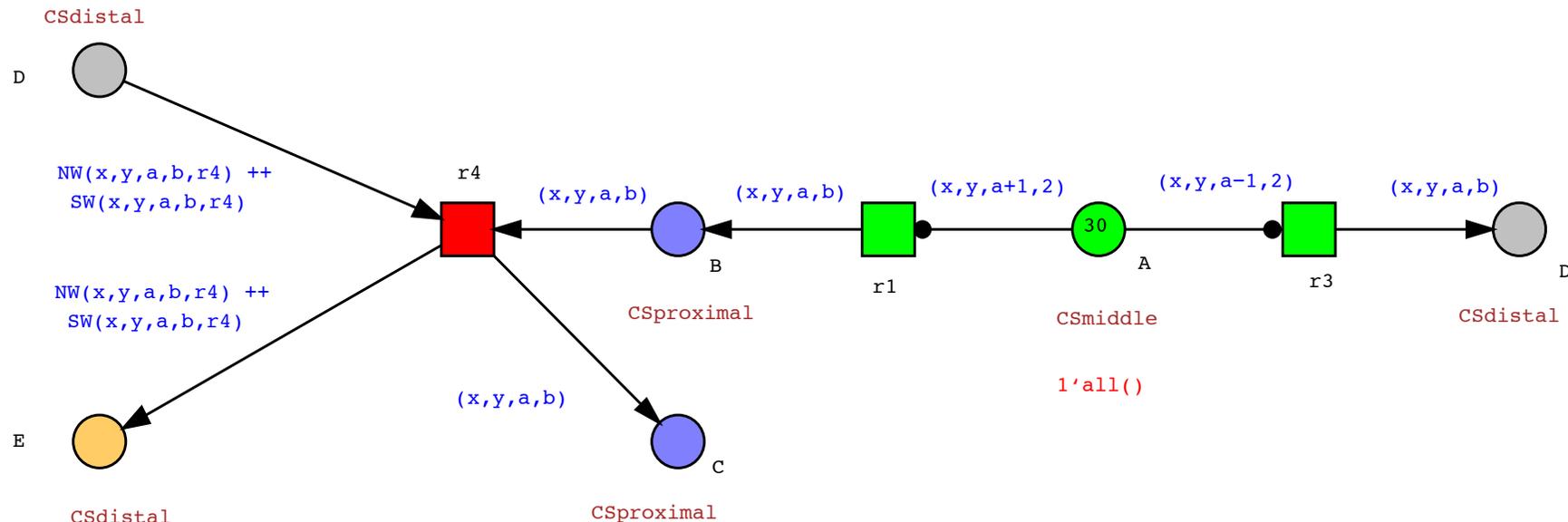
# Hierarchical organisation

- Hierarchically coloured



Colourset =  $\{ \dots, \{ ((3,2)(1,1)), ((3,2)(1,2)), ((3,2)(1,3)), \dots, ((3,2)(3,3)) \}, \dots$

# CPN model of cells with 7 compartments in a 2-D lattice



- 4 spatial regions: communication, proximal, transport and distal.
- Seven virtual compartments ((1, 1), (2, 1), ..., (3,3)).
- Each place or transition belongs to a specific compartment.
- NW and SW denote two left neighbours of the current cell.

## Declarations for CPN model

---

**Declaration**

---

```
Constant  $M = \text{int with } 5$  ;  
Constant  $N = \text{int with } 5$  ;  
Constant  $C = \text{int with } 3$  ;  
Constant  $R = \text{int with } 3$  ;  
colourset  $Row = \text{int with } 1 - M$  ;  
colourset  $Column = \text{int with } 1 - N$  ;  
colourset  $ComR = \text{int with } 1 - R$  ;  
colourset  $ComC = \text{int with } 1 - C$  ;  
colourset  $CSr4 = \text{enum with } c5, c6\_1, c6\_1, c7$  ;  
colourset  $CS1 = \text{product with } Row \times Column$  ;  
colourset  $CS2 = CS1 \text{ with } x\%2 = 1 \& y\%2 = 0 | x\%2 = 0 \& y\%2 = 1$  ;  
colourset  $CS = \text{product with } Row \times Column \times ComR \times ComC$  ;  
colourset  $CS4 = CS3 \text{ with } x\%2 = 1 \& y\%2 = 0 | x\%2 = 0 \& y\%2 = 1$  ;  
colourset  $CSdistal = CS4 \text{ with } b = 3$  ;  
colourset  $CSproximal = CS4 \text{ with } b = 1$  ;  
colourset  $CSmiddle = CS4 \text{ with } b = 2$  ;  
Variable  $x : Row$  ;  
Variable  $y : Column$  ;  
Variable  $a : ComR$  ;  
Variable  $b : ComC$  ;  
Variable  $r4 : CSr4$  ;  
Function  $CSproximal \text{ NW}(Row \ x, Column \ y, ComR \ a, ComC \ b)$  ;  
Function  $CSproximal \text{ SW}(Row \ x, Column \ y, ComR \ a, ComC \ b)$  ;
```

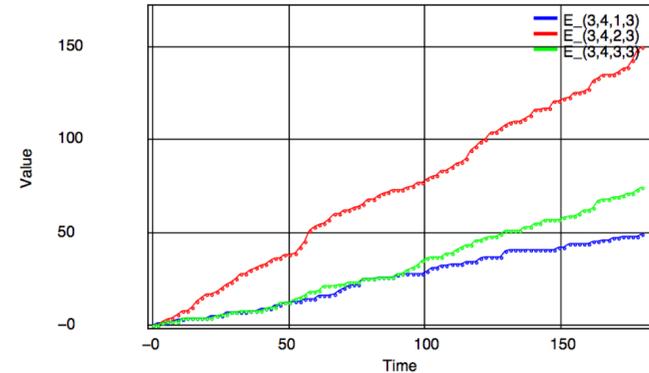
---

# Some statistics

Size			
Grid (M*N)	Cells	Places	Transitions
5*5	12	156	192
10*10	50	650	800
15*15	112	1,456	1,792
20*20	200	2,600	3,200
50*50	1,250	16,250	20,000

# Analysis Results

Stochastic simulation results

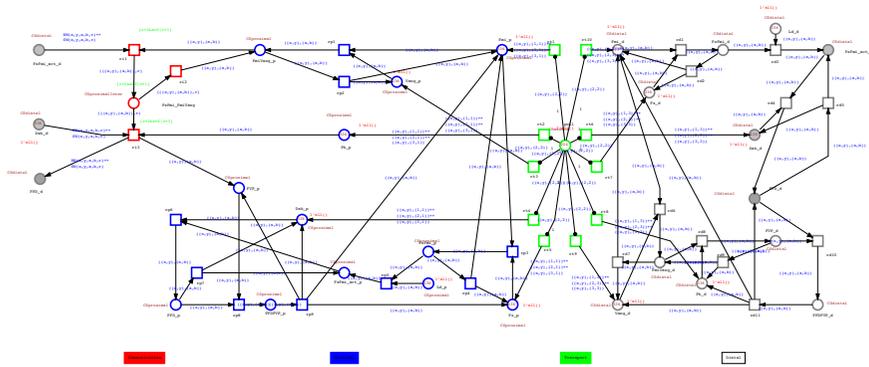


		0			0				
	72	(1,2)	<b>97</b>	69	(1,4)	<b>77</b>	0		
(2,1)	<b>135</b>		49	(2,3)	<b>148</b>	45	(2,5)	0	
	46		58		45		50	0	
		(3,2)	<b>168</b>		(3,4)	<b>170</b>			
	46		48		49		39	0	
(4,1)	<b>167</b>		42	(4,3)	<b>165</b>		43	(4,5)	0
	76	(5,2)	<b>88</b>		68	(5,4)	<b>84</b>	0	
			0				0		

# On-going work

- Refine a more detailed model which includes the cellular machinery of PCP signalling.
- Perform continuous and stochastic simulation analysis.
- Recapitulate the phenotype of wild-type and all known mutant conditions obtained from biological experiments in-silico using our refined model.

# Refined CPN model of PCP signalling



Declarations  
for the CPN  
model

```

Type Declaration
con M = int with 15;
con N = int with 15;
con R = int with 3;
con C = int with 3;

cs Row = int with 1 - M;
cs Column = int with 1 - N;
cs CS1 = product with Row x Column;
cs CS_Cell = CS1 with
  x%2 = 1&y%2 = 0?r%2 = 0&y%2 = 1;
cs ComR = int with 1 - R;
cs ComC = int with 1 - C;
cs CS_CompP = product with ComR x ComC;
cs CS2 = product with CS_Cell x CS_CompP;
cs CSdistal = CS2 with b = 3;
cs CSproximal = CS2 with b = 1;
cs CSmiddle = CS2 with a = 2&b = 2;
cs CSInter = int with 1 - 2;
cs CS3 = product with CSproximal x CSInter;
cs CSproximalInter = CS3 with r = 2&a = 2!r = 1;

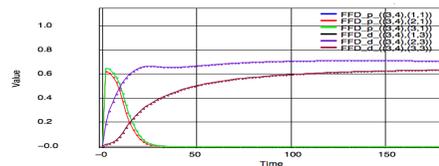
var x : Row;
var y : Column;
var a : ComR;
var b : ComC;
var r : CSInter;

fun CSproximal NW
  (Row x, Column y, ComR a, ComC b, CSInter r)
  {((x=1|y=1)&(r=1&a=1&b=1)|r=2&a=2&b=1)}
  CSproximal SW
  (Row x, Column y, ComR a, ComC b, CSInter r)
  {((x=1|y=1)&(r=2&a=2&b=1)|r=1&a=1&b=1)}
  CSmiddle SW
  (Row x, Column y, ComR a, ComC b, CSInter r)
  {((x=1|y=1)&(a=1|b=2))}
  CSdistal SW
  (Row x, Column y, ComR a, ComC b, CSInter r)
  {((x=1|y=1)&(a=1|b=2))}
  CS3 SW
  (Row x, Column y, ComR a, ComC b, CSInter r)
  {((x=1|y=1)&(a=1|b=2))}
  
```

## Some statistics

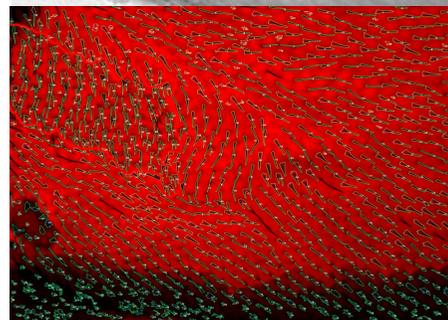
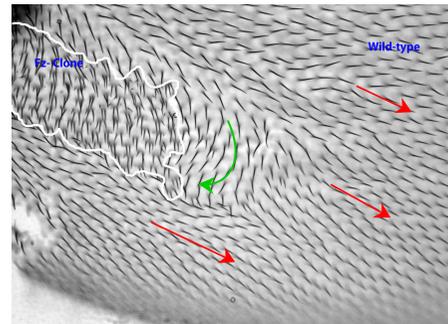
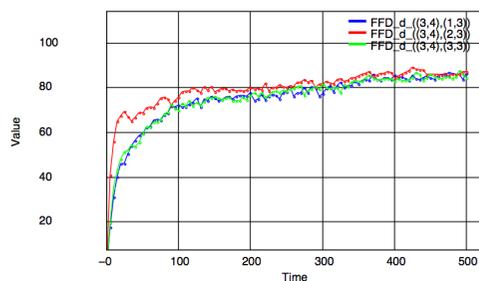
Grid(Mx N)	Size		
	Cells	Places	Transitions
5 x 5	12	924	984
10 x 10	50	3,850	4,100
15 x 15	112	8,624	9,184
20 x 20	200	15,400	16,400
50 x 50	1,250	96,250	102,500

Grid(Mx N)	Time (seconds)			
	Unfolding	Unfolding/Cells	Simulation	Simulation/Cells
5 x 5	0.99	0.0825	13.34	1.1117
10 x 10	3.46	0.0692	235.81	4.7162
15 x 15	8.04	0.0718	1,366.24	12.1986
20 x 20	15.52	0.0776	-	-
50 x 50	161.48	0.1292	-	-

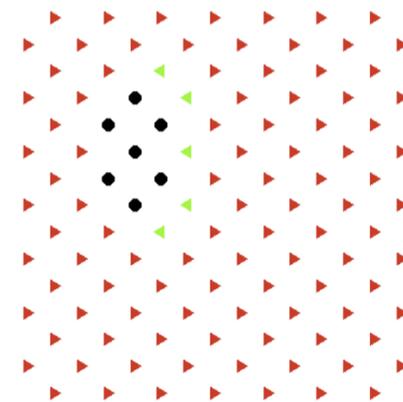


FFD accumulates at the distal edge of the cell rather than the proximal edge at the end of signalling.

Stochastic simulation  
(average of 10 runs)



FFD at distal vs FFD at proximal over Tissue



The paper includes this work has been accepted by CMSB 2011

# Summary

- Coloured Petri nets – a promising approach for multiscale spatial modelling.
- On-going work – refining the model to include more detailed cellular machinery of PCP signalling in order to have some insights into the mechanisms and to describe the phenotype of documented genetic mutations.
- Long term goal – in-silico prediction of effects of mutations in tissues.

# Downloads

- Snoopy for standard PN & CPN:

<http://www-dssz.informatik.tu-cottbus.de/DSSZ/Software/Snoopy>

- CPN models for PCP:

<http://people.brunel.ac.uk/~cspgqgq>

# Acknowledgements

**Brunel:**

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David Tree

