Modelling gradients using Petri nets

LMF Bertens, HCM Kleijn, M Koutny and FJ Verbeek
Imaging and Bioinformatics group, LIACS, Leiden University
School of Computing Science, Newcastle University

Universiteit Leiden
The Netherlands

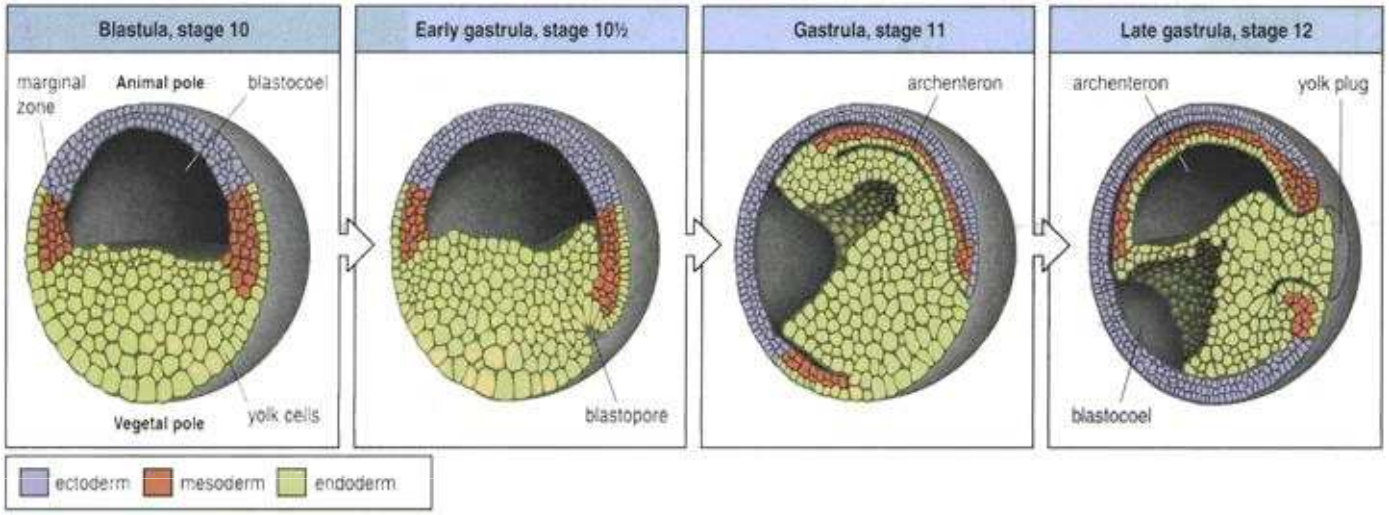
New focus:

using Petri nets for higher level developmental processes, e.g. on tissue and organ level, taking cells as central elements

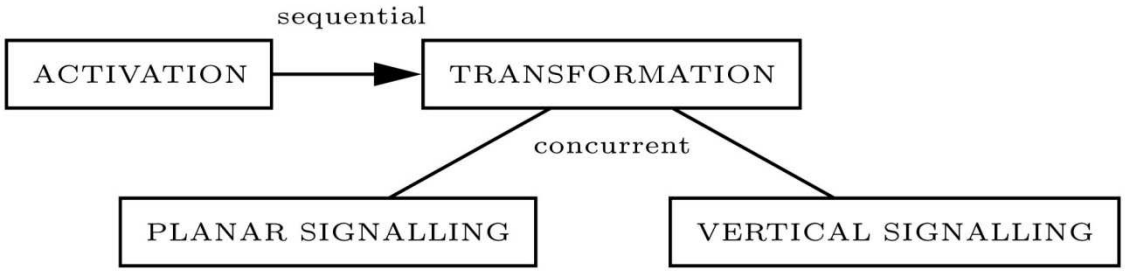
Case study:

embryonic development of the AP-axis formation in *Xenopus laevis*

Anterior posterior axis formation

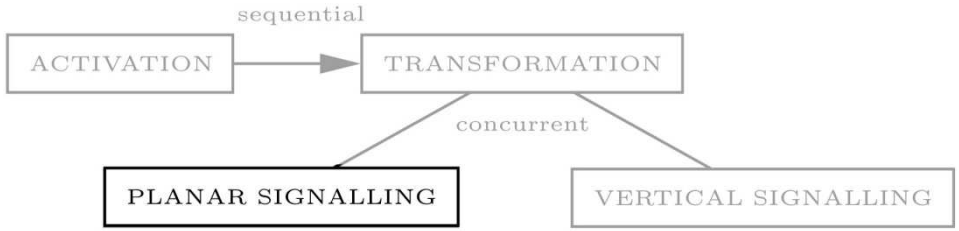


Wolpert, 2002



Modelling the case study

- several sub-processes
- generic use of the building blocks

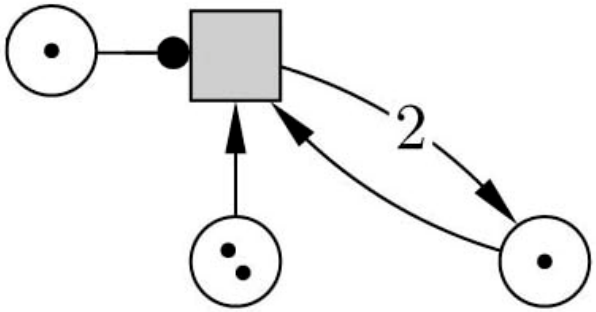


first theoretical model:
gradient formation in planar signalling

- generic for gradients in early development
- main aim: staying close to biological process, both in end result and intermittent steps, thereby making the model generally applicable and robust

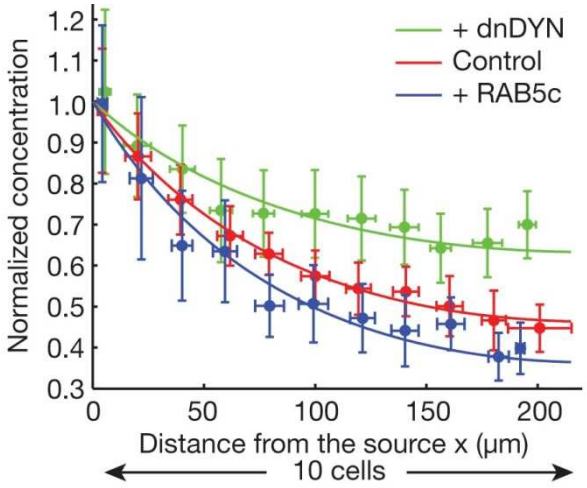
Petri nets with activator arcs and maximal concurrency

- a PN is defined by *places* and *transitions*, connected by *weighted* and *activator arcs*, with token distributions, *markings:*
  PTA-net is tuple $N = (P, T, Act, m_0)$
- activator arcs allow *a priori* testing
- enables auto-concurrency
- maximal concurrency



Biological background

- gradient: gradual and directed change in concentration of a morphogen through a group of cells
- morphogens: signalling molecules that cause cells in different places in the body to adopt different fates and establish embryonic axes
- transient and hard to detect
- slope determined by ρ

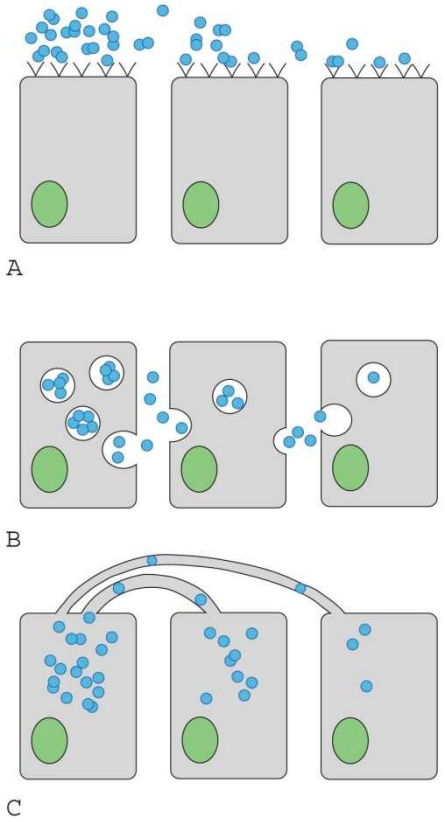


Yu *et al.* 2009

Mechanisms of gradient formation

a) diffusion through extracellular matrix
b) endocytosis: sequential internalisation and re-emission
c) cytonemes

here we focus on diffusion and endocytosis (both concerning neighbouring cells)



Biological modelling decisions

- cells as elementary units
    - advantage as intermediate level between tissue and sub-cellular levels
- tokens as concentration levels: qualitative and quantitative
    - neither on/off nor exact numbers of molecules
    - possibility of quantification (Fgf8, Yu *et al.* 2009)
- realistic modelling of transport between neighbouring cells => diffusion and endocytosis
    - molecular mechanisms possible in sub-nets

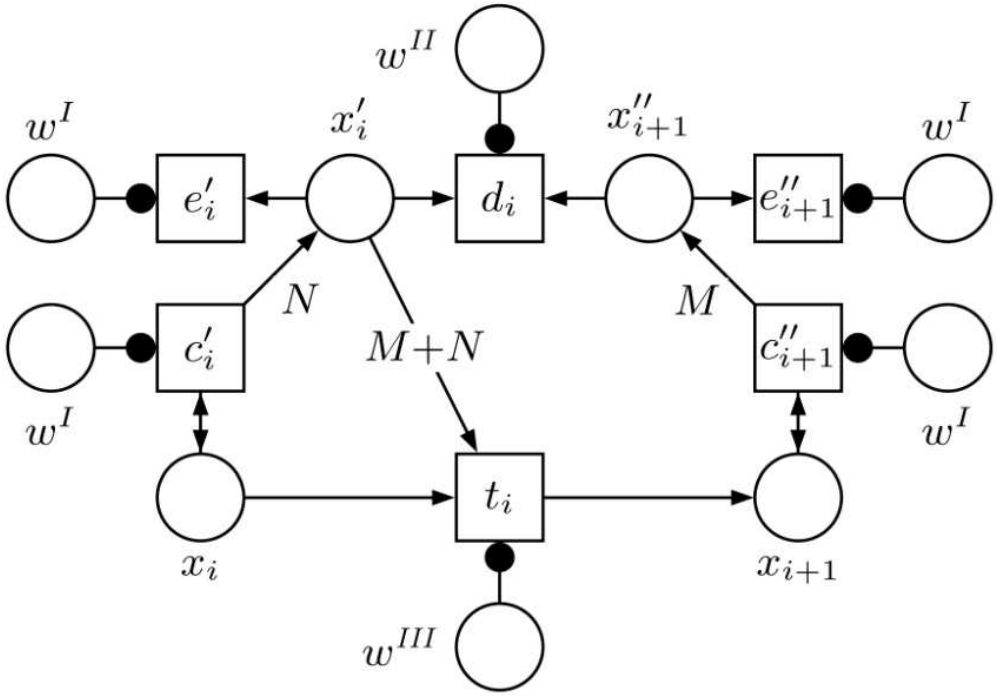
Implementation

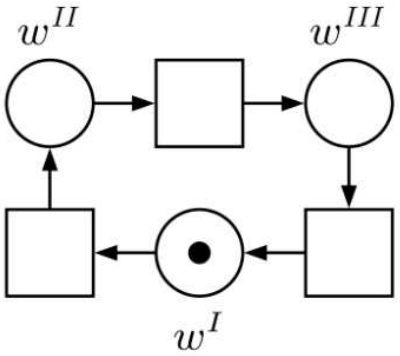
- separation of the biological front (including cells) and the computational background (calculating transport of tokens)
- marking is consistent with biology at all times
- realistic use of maximal concurrency
- ratio $\rho = N/M$, $M > N \geq 1$; ρ is flexible

Implementation

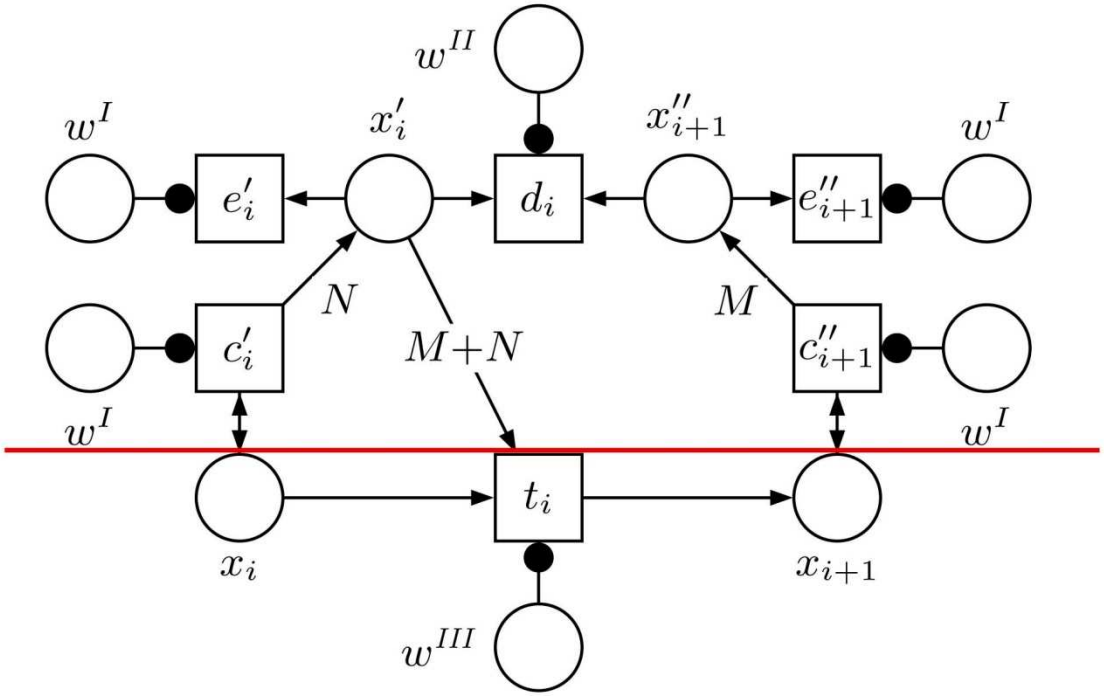
Given are $k \geq 1$ places $x_1, \ldots, x_k$ representing cells. In initial marking x_1 contains K tokens, other places are empty. Tokens get shifted from x_1 to x_k in such a way that:

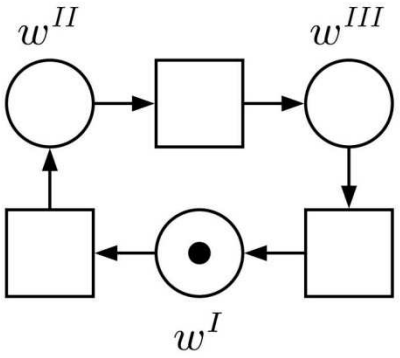
1. The number of tokens in the x_i's remain constant
   $$m(x_1) + \ldots + m(x_k) = K$$ **token preservation**
2. The tokens are distributed monotonically along the sequence of k places, i.e.
   $$m(x_1) \geq \ldots \geq m(x_k)$$ **monotonicity**
3. The ratio of the numbers of tokens in two neighbouring places does not exceed ρ, i.e. for every $1 \leq i < k$ with $m(x_1) \geq 1$:
   $$\frac{m(x_{i+1})}{m(x_i)} \leq \rho$$ **ratio**
4. Shifting continues untill moving even one token violates the above, i.e. for every $1 \leq i < k$ with $m(x_1) > 1$:
   $$\frac{m(x_{i+1}) + 1}{m(x_i) - 1} > \rho$$ **termination**



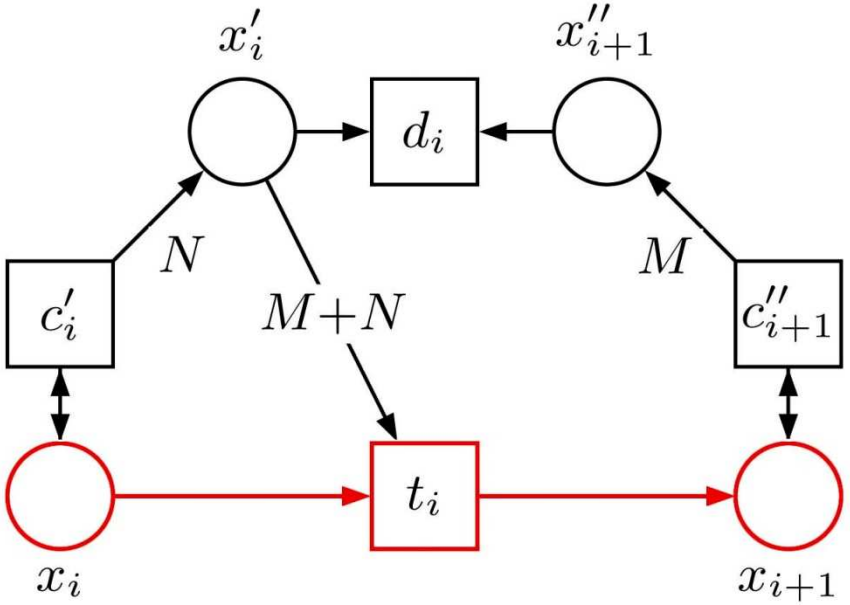


ratio ρ dictates the no. of tokens to be moved: β_i
for each marking m and each $1 \leq i < k$, β_i tokens are moved from x_i to x_{i+1}
tokens keep on been being transferred until $\beta = 0$ for all places => stable marking

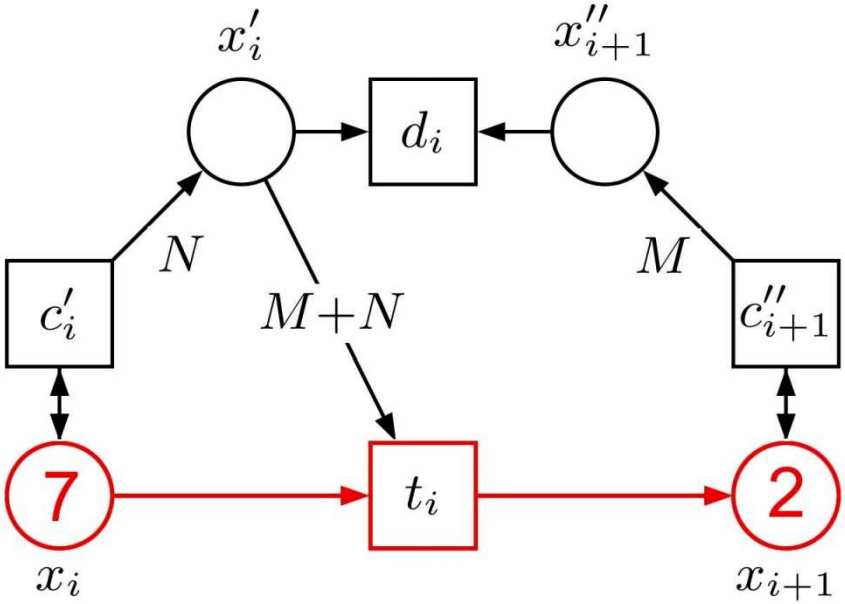




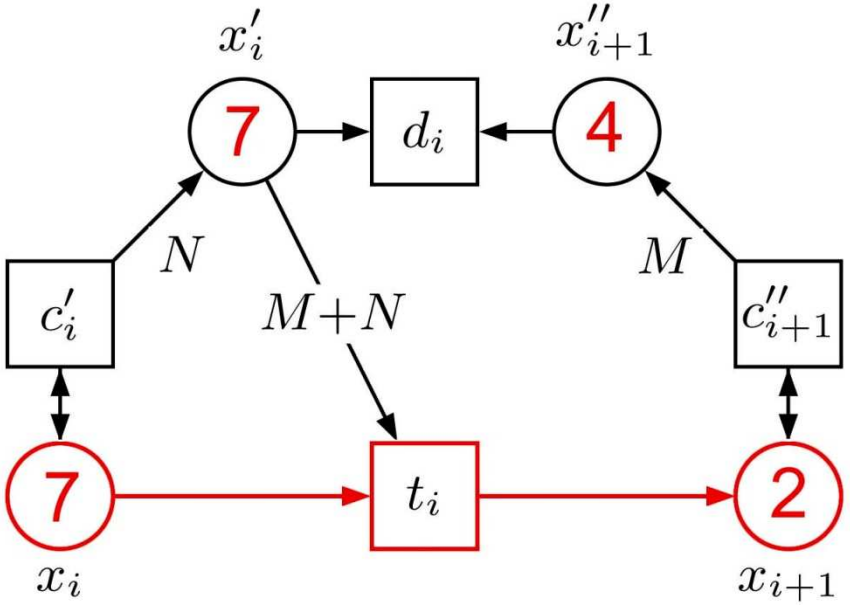
ratio $\rho = N/M$ dictates the no. of tokens to be moved: β_i
for each marking m and each $1 \leq i < k$, β_i tokens are moved from x_i to x_{i+1}
tokens keep on been being transferred until $\beta = 0$ for all places => stable marking


x'_i
x''_{i+1}
d_i
N
M
$M+N$
c'_i
c''_{i+1}
t_i
x_i
x_{i+1}

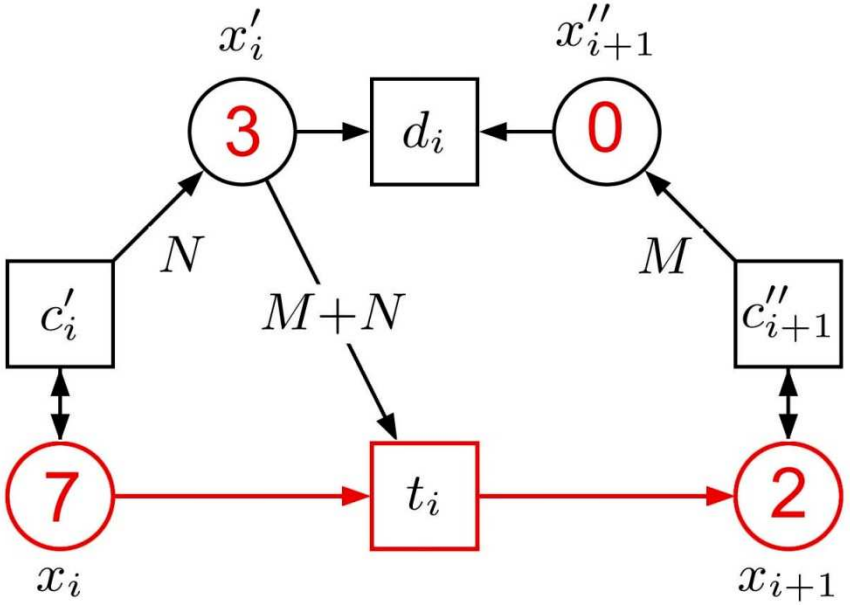
N=1, M=2



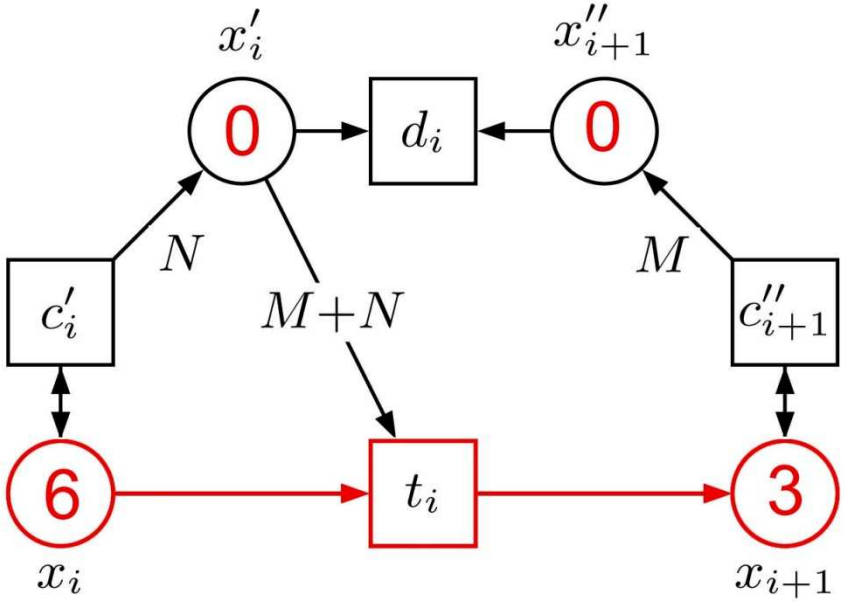
N=1, M=2



N=1, M=2



N=1, M=2



Important biological features

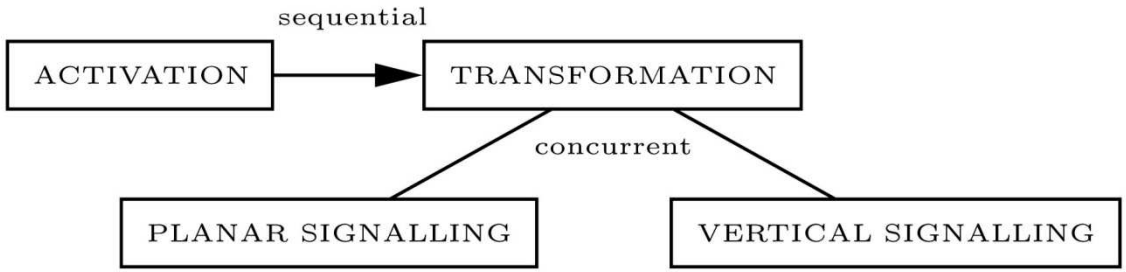
- consistency (through monotonicity and ratio)
- stable markings (through monotonicity and termination)
- focussed on local events; insensitive to specific values of *k* and *K* and therefore scalable
- possibility of local(ly different) use of auxiliary net and local use of ρ
- maximal concurrency, but sequential solution is also possible

Conclusions

- a generally applicable net on higher developmental level
- consistency with biological process, in end result as well as intermittent stages
- possibilities of linking to
    - sub- and supernets
    - other sub-processes in AP-axis formation on same biological level

Future work

- implementation using biological data
- extension to 2- and 3-dimensional gradients
- adding hierarchy through molecular subnets and tissue-level supernets
- linking sub-process to other sub-processes in AP-axis development of *Xenopus laevis,* e.g. vertical signalling



Laura M.F. Bertens
Jetty C.M. Kleijn
Maciej Koutny
Fons J. Verbeek

Hans J. Jansen
Nabila Bardina
Tony J. Durston

lbertens@liacs.nl
www.bio-imaging.liacs.nl

$$\rho = \frac{N}{M} \quad M > N$$

for every $1 \le i < k$:

$$\frac{m(x_{i+1})}{m(x_i)} \le \rho \quad \text{(monotonicity), where } m(x_i) \ge 1$$

$$\rho \cdot m(x_i) \ge m(x_{i+1})$$

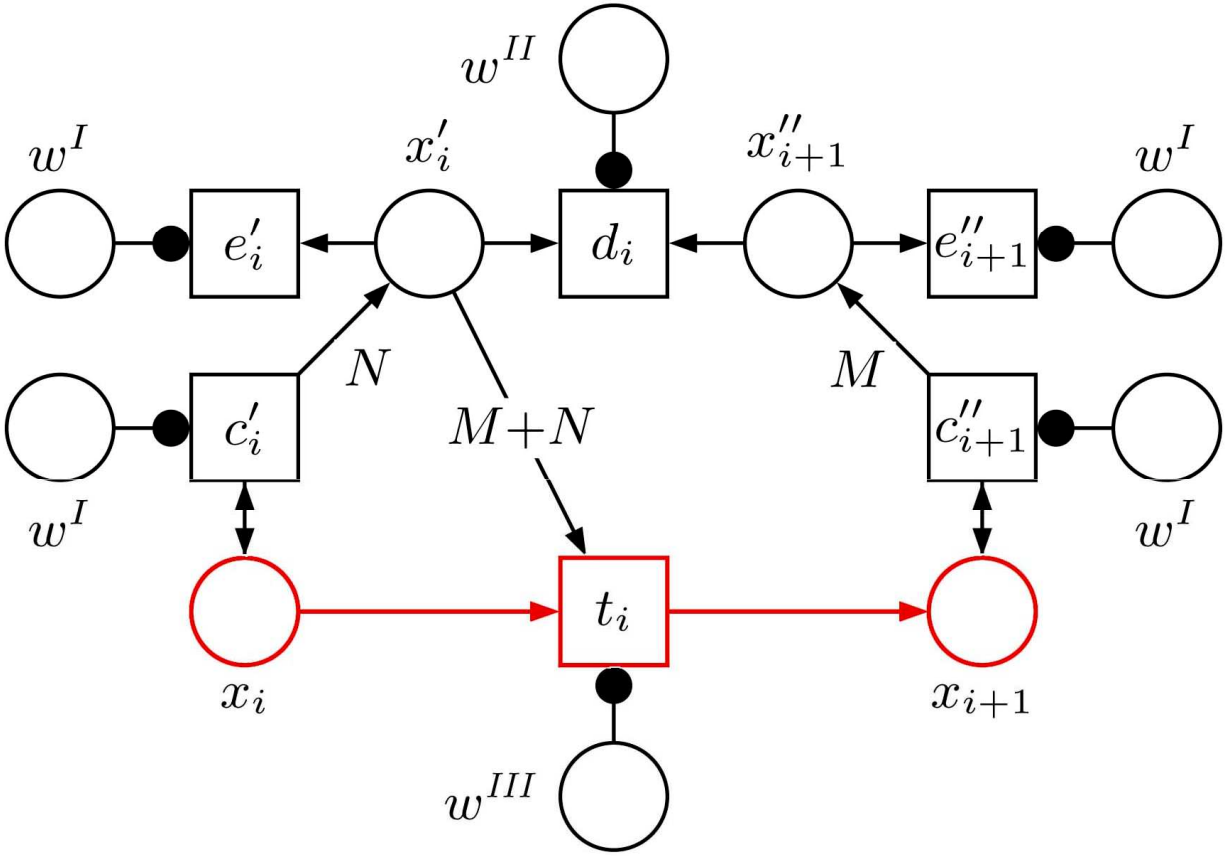
$$\frac{N}{M} \cdot m(x_i) \ge m(x_{i+1})$$

$$N \cdot m(x_i) \ge M \cdot m(x_{i+1})$$

$$N \cdot m(x_i) - M \cdot m(x_{i+1}) \ge 0$$

$$N \cdot m(x_i) - M \cdot m(x_{i+1}) = \alpha_i$$

$$\beta_i \le \left\lfloor \frac{\alpha_i}{M+N} \right\rfloor$$


w^{II}
w^I
x'_i
x''_{i+1}
w^I
e'_i
d_i
e''_{i+1}
N
M
$M+N$
c'_i
c''_{i+1}
w^I
w^I
t_i
x_i
x_{i+1}
w^{III}