Modelling gradients using Petri nets

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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 $\rho$

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 $\rho = N/M$, $M > N \geq 1$; $\rho$ 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 \( \rho \), i.e. for every \( 1 \leq i < k \) with \( m(x_i) \geq 1 \):
   \[ \frac{m(x_{i+1})}{m(x_i)} \leq \rho \]
   **ratio**

4. Shifting continues untill moving even one token violates the above, i.e. for every \( 1 \leq i < k \) with \( m(x_i) > 1 \):
   \[ \frac{m(x_{i+1}) + 1}{m(x_i) - 1} > \rho \]
   **termination**
ratio $\rho$ dictates the no. of tokens to be moved: $\beta_i$
for each marking $m$ and each $1 \leq i < k$, $\beta_i$ tokens are moved from $x_i$ to $x_{i+1}$
tokens keep on been being transferred until $\beta = 0$ for all places => stable marking
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N=1, M=2
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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 $\rho$
- 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
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\[ \rho = \frac{N}{M} \quad M > N \]

for every \( 1 \leq i < k \):

\[ \frac{m(x_{i+1})}{m(x_i)} \leq \rho \quad (\text{monotonicity}), \text{ where } m(x_i) \geq 1 \]

\[ \rho \cdot m(x_i) \geq m(x_{i+1}) \]

\[ \frac{N}{M} \cdot m(x_i) \geq m(x_{i+1}) \]

\[ N \cdot m(x_i) \geq M \cdot m(x_{i+1}) \]

\[ N \cdot m(x_i) - M \cdot m(x_{i+1}) \geq 0 \]

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

\[ \beta_i \leq \left\lfloor \frac{\alpha_i}{M + N} \right\rfloor \]
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