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Modelling Developmental Regulatory Networks

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Reinitz' model

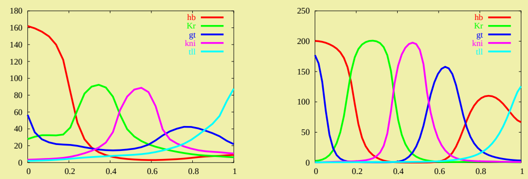
In the 90's Reinitz developed a mathematical model for the simulation of the early developmental stages of *Drosophila* [1]. In the model, gene regulation was isolated, and other processes such as cell-cell interaction and cell movement were ignored. Since in the early stage of *Drosophila* development the level of expression of gene products is a function only of the position along the Anterior-Posterior axis, Reinitz considered a one-dimensional system of ODEs

$$\frac{dg_i^a}{dt} = R_a \Phi\left(\sum_{b=1}^{N_g} W^{ab} g_i^b + m_a g_i^{bcd} + h_a\right) \quad \text{(genetic regulation)}$$

$$-\lambda_a g_i^a \quad \text{(decay)}$$

$$+D_a(g_{i-1}^a - 2g_i^a + g_{i+1}^a) \quad \text{(diffusion)}$$

where a and b denote gene products, i the nucleus number and Φ is a sigmoid function with range [0,1].
The parameters of the model were obtained by inference from experimental data (*circuit approach*). Simulation results of the model, which includes *bcd*, *cad*, *hb*, *Kr*, *kni*, *gt* and *tll*, are plotted below. The simulation covers 30 and 58 nuclei between 35-92% A-P position during cleavage cycles 13 and 14A, respectively. All parameters are taken from [2].



Concentrations of gene products at the end of cleavage cycle 13 (left) and at the end of cleavage cycle 14A (right).

New model

In order to model moving and deformable cells, which is necessary for our real case study, sponges, we split the model into two environments

Intracellular

$$\frac{dg_i^a}{dt} = R_a \Phi\left(\sum_{b=1}^{N_g} W^{ab} g_i^b + m_a g_i^m + h_a\right) - \lambda_a g_i^a$$

$$-S_a(g_i^a, \overline{c}^a(\mathrm{x}_i, t)) \quad \text{(secretion/absorption)}$$

Extracellular

$$\frac{\partial c^a(\mathrm{x}, t)}{\partial t} = \nabla(D_a \nabla c^a) - \lambda'_a c^a$$

$$+\sum_{i=1}^{N_c} \frac{V_i}{V} \frac{\delta(\partial V_i, \mathrm{x})}{|\partial V_i|} S_a(g_i^a, \overline{c}^a(\mathrm{x}_i, t)) \quad \text{(secretion/absorption)}$$

where $\overline{c}^a(\mathrm{x}_i, t) = \int_{\partial V_i} c^a(\mathrm{X}(S), t)dS/|\partial V_i|$, $\mathrm{X}(S) \in \partial V_i$ and the secretion term S_a is used to model the membrane process.
The delta function is defined as

$$\int_{\Re^d} \delta(\Gamma, \mathrm{x}) f(\mathrm{x}) d\mathrm{x} = \int_\Gamma f(\mathrm{X}(S))dS, \quad \mathrm{X}(S) \in \Gamma, \text{ a surface in } \Re^d$$

A classical solution of the PDE does not exist because of the presence of a delta function. Note that the use of $\delta(\Gamma, x)$ implies that a classical solution exists for the integral form of the PDE and so allows to find a numerical solution with the Finite Volume Method. For detailed discussion see [3].

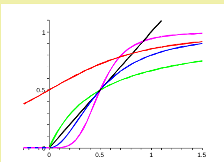
Sigmoid function

Aim: positivity and saturation
Problem when inferring parameters: saturation curves are (computationally) not invertible.
Reinitz: smooth sigmoid function

$$\Phi(x) = \frac{1}{2}\left(\frac{x}{\sqrt{x^2+1}} + 1\right)$$

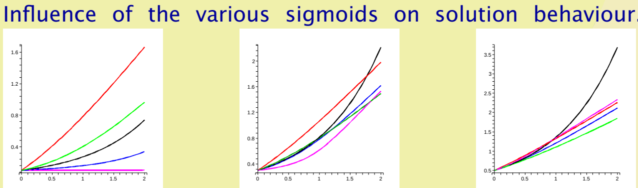
Other option: Hill function

$$H(x) = \frac{x_+^m}{\beta^m + x_+^m}, \quad x_+ = \max(0, x)$$



Black: $y = x$; red: $y = \Phi(x)$; green, blue, magenta: $y = H(x)$, $\beta = 0.5$, $m = 1, 2, 4$

Influence of the various sigmoids on solution behaviour.



$\dot{y} = F_S(y)$ for initial conditions $y_0 = 0.1$, $y_0 = 0.3$, $y_0 = 0.5$
F_S: identity (black), Φ (red), H (green, blue, magenta).

References

[1] Reinitz J and Sharp DH, *Mechanism of eve stripe formation*, Mech Dev 49: 133-158 (1995).

[2] Jaeger J, Surkova S, Blagov M, Janssens H, Kosman D, Kozlov KN, Manu, Myasnikova E, Vanario-Alonso CE, Samsonova M, Sharp DH and Reinitz J, *Dynamic control of positional information in the early Drosophila blastoderm*, Nature 430: 368-371 (2004).

[3] M. Ashyraliyev, J.G. Blom and J.G. Verwer, *On the Numerical Solution of Diffusion-Reaction Equations with Singular Source Terms*, in preparation (2005).

3D-RegNet: Simulation of developmental regulatory networks
In this project we aim to develop a model for simulating regulatory networks that are capable of quantitatively reproducing spatial and temporal expression patterns in developmental processes (case studies: *Drosophila* and sponges). A major issue are correct estimations of the parameter settings in the network model. Therefore the model will be used in combination with an optimization algorithm (simulated annealing) to explore large parameter spaces of regulatory networks and to select specific spatial and temporal expression patterns.
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