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A sensory scientific approach to visual pattern recognition of complex biological systems

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ABSTRACT

A sensory scientific approach for exploring and interpreting image patterns is presented. It is used for analysis of the behaviour of a complex mathematical model — in this case representing two-dimensional pattern-generating protein signalling during cell differentiation. The approach consists of several consecutive research steps, each including statistical planning, image production, image profiling and multivariate data analysis. Initially, a high number of images were produced and profiled by automatic but non-selective computerised image analysis profiling. Then the most interesting images were analysed by descriptive sensory profiling, in two consecutive, increasingly focused experiments. Partial Least Squares Regression models were applied, on one hand, to predict the sensory profile from automatic image analysis, and, on the other hand, to relate the sensory profile to the mathematical model parameters. Previously unknown pattern types for this biological system were thus revealed. Finally, a preliminary sensory morphological wheel was proposed.

1. Introduction

1.1. The human visual system in action

The human visual perception and language capabilities provide an amazingly efficient measuring system for complex samples, as demonstrated by the extensive use of visual terms in descriptive sensory analysis based on trained assessor panels. Scientists in their daily work, both in academia and in the industrial R&D, rely on their own eyes for qualitative and quantitative evaluations, although often informally, subjectively and without recognising it. This paper demonstrates how sensory science can turn human visual sensory perception into relevant and reliable profiling of scientific systems that are too complex for traditional theoretical analysis. It shows how visual information can be acquired, systemised and made operational as efficient tools in scientific projects to model and understand spatially complex biological systems.

Recent knowledge about visual attention from a physiological and psychological point of view is documented in Bundesen and Habekost (2008). What we select to perceive visually is an interaction between the environment and ourselves. The human senses are constantly in action, not just being passive receivers (Gibson, 1979; Harper, 1972; Martens & Tschudi, submitted for publication). A clear interest for sensory methods for visual pattern recognition was evident at the 8th Pangborn Sensory Science Symposium in Italy 2009 (www.pangborn2009.com).

The present study is based on descriptive sensory evaluation of spatial organisation (textures and patterns) of complex samples, from images printed on paper. Previous examples of this are known in food research, e.g., assessing electron microscopy images of whey protein gels (Langton & Hermansson, 1996), and studying structural heterogeneity of potatoes from fMRI-images (Martens et al., 2002). In the present paper, the application comes from systems biology. The word "texture" is currently utilised in the domain of image analysis, as well as deeply inspired by Gibson's use of "texture" in a visual perceptual context (Gibson, 1950, 1979).

The purpose of this paper is to outline a sensory approach for revealing, systemising and interpreting image patterns from biological systems — being reliable and valid in communication across various scientific fields. It describes the sensory part of a study of a complex pattern-generating process (Martens et al., 2009). The challenge was to measure 'what is going on' in biological cells, in a way that can be translated into qualitative understanding and quantitative prediction.

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The choice of reference images, terminology and scale definition in visual assessment will invariably depend on the system to be analysed. But generic reference image collections do exist, for instance Brodatz (1966) published a photographic album for picture textures, for artists and designers. Here we outline, among other things, a preliminary version of a generic way to structure the sensory profile terminology for the analysis of texture and patterns in images of biological structures — a visual sensory vocabulary structured into a sensory '*morphological wheel*'. This addresses other biological research on shape and size and geometrical forms within the science of morphology and will be outlined in Section 3.3.

1.2. The system studied: a mathematical model from systems biology

The sample images of the biological system to be studied here are not from the system itself, but from a *mathematical model* intended to represent a simplified version of current knowledge about the system. This model consists of a large set of coupled non-linear dynamic differential equations describing a certain cell differentiation process in a two-dimensional lattice of cells. This mechanistic model has the capacity to generate spatial patterns of various kinds. Unexpected, complex large-scale patterns are very difficult to reveal and study by traditional mathematical model analysis, if their character were *a priori* unknown. For example, in the present model, Collier, Monk, Maini, and Lewis (1996) primarily described local three-periodic regularities, not the larger-scale patterns emerging when running the two-dimensional multi-cellular model over time till steady state.

How can a butterfly develop its beautiful patterns? How can the organs and limbs of a body become so different, when they all started from the same shared DNA information in the fertilised egg cell? Cell differentiation is still only partly understood in biology. The mathematical model studied here describes how thousands of cells in a two-dimensional lattice of cells develop and change over time. It represents a simple example of how different signalling proteins interact within and between cells, as a step in the fascinating process leading from a single cell in an early embryo to a fully developed adult organism. The model is oversimplified, involving only two signalling proteins and cells in a very regular two-dimensional lattice. But it still has sufficient dimensionality, non-linearity and positive feedback to make theoretical prediction of model behaviour from known modelling conditions very difficult. The sample images to be studied here are not of the biological system itself, but images of spatial patterns generated by the model. Our motivation was to develop sensory science as a generic tool for empirical studies of the behavioural repertoire of overwhelmingly complex mathematical pattern-generating models.

The model is a description of so-called *lateral inhibition* mediated by Delta–Notch signalling (Collier et al., 1996). This system was chosen because it has been explored by both biologists and mathematicians and has relevance to sensory psychophysics (Veflingstad, 2006). Delta (D) and Notch (N) are both trans-membrane proteins that interact only between cells in direct physical contact. D is a ligand that binds to and activates N in neighbouring cells, while N inhibits the activity of D within the same cell. To illustrate how interactions between neighbouring cells cause lateral inhibition, consider a two-cell system (Fig. 1A). When N is activated in cell 1, the production of D is suppressed in the same cell. Then N is suppressed in cell 2, which in turn relieves the inhibition of D, thereby increasing its activity, in this cell. Overall, these results are reflecting an increased activation of N in cell 1, which in turn strengthens the inhibition of D, and vice versa in cell 2. In other words, there is a *positive feedback loop* between pairs of neighbouring cells, driving them towards opposite fates: a cell that produces more ligand forces its neighbours to produce less. In a two-dimensional configuration of square cells, this leads to the well-known, regular checker-board pattern of two-cell states: high D/low N and low D/high N. However, in the more biologically relevant packing of hexagonal cells in, e.g., a 50×50 theoretical cell lattice, these cells lead to patterns that in most cases are highly irregular, with many different protein levels and intricate macroscopic patterns. High N in cell 1 leads to low N in the neighbouring cells 2 and 3, and this causes *frustration* if cell 2 and cell 3 are neighbours.

The mathematical differential equation model for how protein activities of D and N develop over time in each cell is controlled by five model parameters (θ_D, θ_N, p_D, p_N, and μ), see Fig. 1B, through sigmoidal stimulus–response curves (S) as shown in Fig. 1C. The thresholds θ_D and θ_N define the activity levels at which the two stimulus–response functions S_D and S_N reach their half-maximum, or the levels at which the response is most sensitive to changes in the stimulus. The steepnesses p_D, and p_N determine how sensitive the response is near the threshold, or how steep the response curves are. The final parameter μ is simply the ratio between the decay rates for D and N.

However, the initial state of the lattice, i.e., the state from which the pattern evolves, will usually also affect the overall patterning process, and thus needs to be specified. The chosen initial conditions should mimic the initial properties of the biological lattice, in which all cells have almost equal levels, but are most likely (not exactly) identical because of small fluctuations within each cell. By a theoretical analysis it has been shown that the model in Fig. 1B has a homogenous steady state N^* and D^*, i.e., a state in which all cells are equal and in which the activity levels are not changing (Fig. 1D). However, in many cases this state is unstable, implying that any small random changes in the protein activity of the cells will cause the system to move away from the homogenous state, and eventually approach a patterned state, as visualised in Fig. 1A. Thus, a state in which all cells are slightly perturbed from the homogenous steady state in a random fashion seems an appropriate initial state. Here these initial perturbations are represented by two perturbation parameters: general perturbation size (g, the percentage of the homogenous steady-state level) and perturbation direction (s, up (+) or down (−) relative to the homogenous steady-state level), giving a total of seven parameters (Fig. 1D).

In our analysis, the input is the chosen values for the model parameters and random initial conditions, while the output consists of images of the pattern of cell types evident after the simulated differentiation process has reached a steady state. One challenge is to discover, quantify and distinguish patterns that may arise in the output images under different conditions. Another challenge is to predict output patterns resulting from chosen input parameter values.

2. Methods

2.1. Overview of methods

By theoretical analysis of the 'hard' mathematical model, we struggled to describe 'what is going on' during cell differentiation, due to high complexity and a very high number of mathematical equations. Instead, using our senses actively when seeing patterns, we developed an approach to achieve a more informative analysis, in successive steps (carried out in the period 2005–2008). In each step, the data were interpreted by multivariate analysis, using cross-validated PLS regression (Martens & Martens, 2001; Wold, Martens, & Wold, 1983).

First, computer simulation studies of the mathematical model in a theoretical two-dimensional lattice with 50×50 cells were carried out. Initially the parameter values were chosen by trial-