A MODEL FOR SENSING THE HEDGEHOG
CONCENTRATION GRADIENT II:
A CHECK FOR ADEQUACY

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SUMMARY

Motivation: In the present study, our aim was to reveal the molecular machinery
responsible for interpretation of the Hedgehog morphogene gradient.
Results: The model for sensing the gradient of the morphogen Hedgehog
concentration is checked for adequacy using “virtual” gene mutation (Kogai et al., 2006).
A few hypotheses for how the transmembrane proteins Patched, Smoothened and the
morphogen Hedgehog can interact have been tested.

INTRODUCTION

The initial stage of modeling any developmental process is the development of gene
networks (GNs) and their logical analysis, which should identify which blocks are
responsible for the dynamics of the GN functioning. On the basis of the GN blocks thus
identified, mathematical models describing the GN functioning are developed. In this
work, the mathematical model for sensing the concentration gradient of the morphogen
Hedgehog developed on the basis of analysis of the gene network responsible for the
development of the anterior-posterior compartment boundary of the wing imaginal disc in
Drosophila melanogaster is tested for adequacy (Gunbin et al. 2004; Omelyanchuk,
Gunbin, 2004; Kogai et al., 2006).

MODELS

As Lai et al. (2004) put it, “the amount of “freed” Smo can be modeled as the fraction
that is “effectively” not interacting with Ptc.” This fraction is modeled by the Scatchard
relationship in the original system (Model 0) (Lai et al., 2004; Kogai et al., 2006):

\[
\frac{\partial [\text{Smo}]}{\partial t} = \frac{1 + k_{-1} \cdot [\text{Hh}]}{1 + k_{-1} \cdot [\text{Hh}] + k_{-1} \cdot [\text{Ptc}]} \cdot L - k_6 \cdot [\text{Smo}] .
\]

Three more hypotheses for how the proteins Ptc, Smo and the morphogen Hh can
interact (Casali and Struhl, 2004) have been considered:

1) “unliganded Ptc function catalytically to inhibit Smo, and the presence of Hh-
liganded Ptc would titrate the catalytic activity of unliganded Ptc”:
RESULTS AND DISCUSSION

In model 0, the concentrations of all the items that constitute the molecular mechanism of the Hh cascade behave exactly as in the experiment (Kogai et al., 2006, see references herein). The numerical analysis of the model revealed that the number of active receptors of Ptc should be lowest on the anterior-posterior compartment boundary, which is in agreement with the most recent experimental data (Casali, Struhl, 2004; Torroja et al., 2004).

Testing the other hypotheses for interaction between Ptc, Hh and Smo revealed the following: when tested with the same parameters that give a good description of the dynamics of system 0, system 1, which proposes that Ptc exerts a catalytic effect on Smo and gives it a description in terms of an equation of catalytic inhibition, does not stand up to reality (Fig. 1b); system 2, which proposes a stoichiometrical binding for Ptc and Smo (Fig. 1c); system 3, which proposes the presence of Ptc multimers, exerts regulation on the activator form of the protein Ci much more efficiently than the original system (Fig. 1d).

Thus, the processes in the Hh signaling cascade are best described by the original system and the one which proposes the presence of Ptc multimers.

To verify model 0, the system was brought to virtual mutational analysis: we compared the behavior of the system while its certain components were mutant (switched off) and the behavior components (expression of genes or proteins) in the cells within the clones that were mutant for each particular component (gene) (Fig. 2; Kogai et al., 2006).

For example, experimental observations suggest that when the gene ptc is switched-off (k0 = 0), the cells are not responding to Hh signaling, and the activator form of Ci is everywhere in the nuclei, which leads to overexpression of the genes that are regulated through the activator form of Ci (Fig. 2a; Chen and Struhl, 1996). In contrast, when the gene ptc is overexpressed (k0 = 5.0 nM/sec), cells actively absorb Hh (for convenience, shown on a logarithmic scale) and no overexpression of the genes regulated by the protein Ci is observed (Fig. 2b; Casali, Struhl, 2004; Torroja et al., 2004).
When the gene *smo* is mutated, elevated concentrations of the repressor form of Ci in the nucleus are observed both in the experiment and the model \( k_5 \to 0 \) (Fig. 2c; Chen, Struhl, 1996).

When the high-molecular-weight complex CYT is mutated \( J = 0, k_7 = 0 \), the activator form of Ci is accumulated only in the cytoplasm, no repressor form is ever arisen (Fig. 2d; Zhu et al., 2003). When the protein Ci cannot switch from activator to repressor form \( k_8 = 0 \), the activator form of Ci is accumulated both in the cytoplasm and the nucleus, hence a continuous cell response to Hh achieved (Fig. 2e; Chen et al., 1999). When the gene *ci* itself is mutated \( K = 0, k_9 = 0, k_{11} = 0 \), no response to Hh signaling is possible, which is exactly what the model shows (Fig. 2f; Dahmann, Basler, 2000).

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14 At the pictures: Hh – Hh protein; ptc – *ptc* gene mRNA; Ptc - Ptc protein, active form; CYT, - high-molecular-weight complex CYT, form (c); CYT, - high-molecular-weight complex, CYT form (p); Ci(i) – protein Ci inhibitor form; Ci(a) – protein Ci activator form; Ci(n) – protein Ci activator form, nuclear fraction; Ptc(T) – Ptc protein, total forms (Kogai et al., 2006).
Figure 2. The behavior of the system in the anterior compartment of the wing imaginal disc in response to mutation: a – ptc switched off; b – ptc is expressed ectopically; c – smo switched off; d – components missing from the high-molecular-weight protein complex CYT; e – the protein Ci does not switch from activator to repressor form; f – ci switched off.

On the x axis, the relative distance between the anterior-posterior compartment boundary and a location in the anterior compartment; on the y axis, the relative concentration of the system’s components.

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