

Robustness of Hunchback gene pattern formation due to dynamic equilibrium in gap gene system in an early Drosophila embryo

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The expression of genes from gap family in Drosophila embryo is known to be highly variable at the blastoderm stage of development, while the variation is strongly reduced by the start of gastrulation. The establishment of well refined gene expression patterns during the development manifests canalization, the ability of an organism to produce a consistent phenotype despite variations in genotype or environment. This phenomenon is explained by the gap gene cross-regulation and was extensively studied by means of data analysis [1] and mathematical modeling [2,3]. It was speculated that the canalization effect could be understood as arising from the actions of attractors in the gap gene dynamical system.

Following the same line of reasoning we consider the processes of developmental robustness and canalization in the early Drosophila embryo as dynamical effects of varying spatial profiles of Bicoid protein concentration on the formation of the expression border of the gap gene hunchback (hb). The position of Hb border is well established from the nuclear cleavage cycle 13 (NC13) and the concentration gradient gains maximal steepness up to the mid NC14 (Fig. 1).

The dynamics of gap gene expression was modelled [2,3] by a system of differential reaction-diffusion equations for four gap genes hb, Kruppel (Kr), giant (gt) and knirps (kni) in an one-dimensional row of nuclei along the anteroposterior (AP) axis of an embryo. The system non-linearity was described by a sigmoid regulation-expression function of interacting gene products. In the current study we focus on a specific model solution found in [2] and limit the modelling period to NC14, starting from the cycle beginning (time class 1) and till the mid NC14 (time class 6) when Hb pattern is the best refined. The solution at the start and

end of modelling period is presented in Fig. 1.

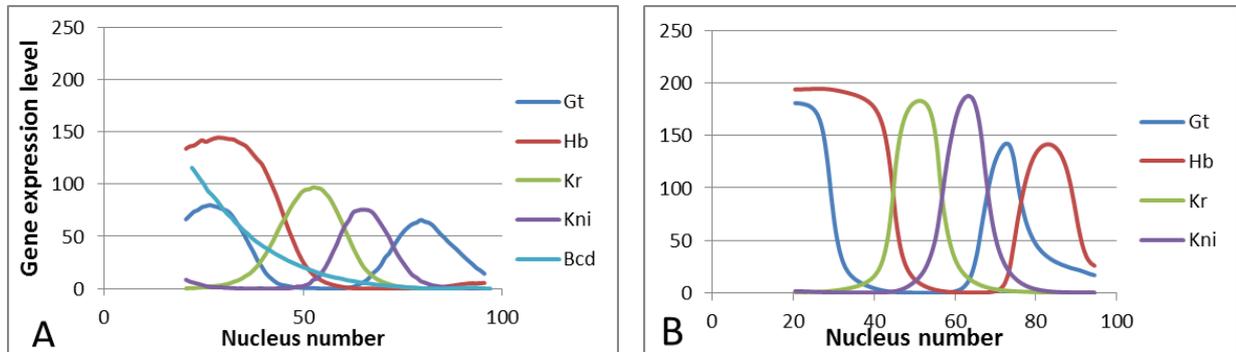


Fig. 1. Model solution presenting spatial expression patterns of four gap genes at (A) beginning of NC14 and (B) mid NC14.

In our previous work [3] the model was studied for its dynamical properties under the assumption of zero diffusion. This assumption was motivated by the fact that in absence of diffusion the model was still capable of reproducing the patterns close to experimental but with sharper domain borders. For the diffusion free model it was shown that Hb border is formed at the boundary of different basins of attraction. However the full reaction-diffusion model though producing the well-established hb pattern did not show such bifurcations with all the nuclei in the vicinity of the border tending to the same attractors. All these shortcomings of the attractor-based approach mean that it makes sense to study the dynamic properties not going beyond the modeling period.

We propose to study a mechanism of border formation associated with the properties of dynamic equilibrium that is observed at the forming Hb border. We show that for the formation of a steep and stationary border by the model it is necessary that there existed a nucleus, that is referred to as a *border nucleus*, in which hb expression level don't change with time and hence is described by a stationary equation. The existence of such a nucleus is also observed in Hb experimental patterns starting from NC13. All the rest genes expressed in this area will be in a dynamic equilibrium and thus the system behavior in the border nucleus is described by three equations thus reducing the system dimensionality by one.

The existence of a steady state nucleus is even true for the model reduced to one equation describing the dynamics of the self-regulating hb gene. In this case the necessity of this

condition can be proved rigorously. In the full four gene system the mechanism of the steep border formation is almost the same, while the position of the border nucleus is defined by the dynamic cross-regulation of all genes.

In the absence of diffusion the steep border don't move with time till the system reaches the attracting state and is still present in the limiting pattern. If the diffusion is non-zero the border position is gradually shifted over time, but if the diffusion rate is small enough the border position remains almost constant till the end of the modeling period (see Fig. 2).

As the dynamic equilibrium is established in the system since the initial moment the position of the border nucleus is defined by the initial conditions and input data and don't change with time. An important advantage of this approach is that the properties of the system in the border nuclei is described by algebraic equations and can be easily handled analytically. Thus we can explicitly formulate the conditions of the system robustness and canalization through the properties of the initial input data.

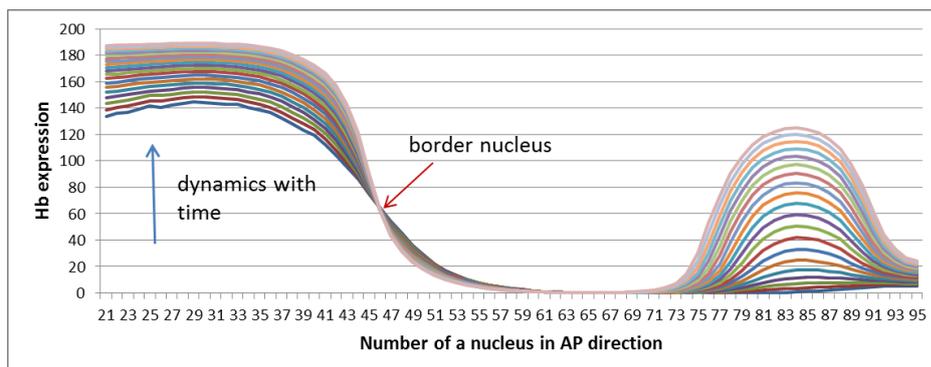


Fig.2. Dynamics of Hb pattern formation during the modelled period in presence of diffusion. The expression level is constant with time in the border nucleus.

For example, the system response to perturbations of initial Bicoid is expressed as a shift of a border nucleus that is established at the initial moment and remains unchangeable during all the modelling period in absence of diffusion, and almost unchangeable otherwise. The robustness in this case means that this shift is smaller than the distance between Bicoid patterns along AP axis. From the equilibrium property it follows that this requirement is met if at the initial moment within the area of Hb border formation the total contribution of all the gap genes (except Bcd) into Hb expression is repressive or, more precisely, does not exceed a

given small threshold value.

In our previous attractor-based study we have come to a conclusion that the hunchback border formation is associated with intersection of the spatial gradient of the maternal Hb protein and a boundary between the attraction basins of two different point attractors. In terms of our approach this means that the border nucleus is located at this intersection, and in spite of the loss due to the diffusion of bifurcation property at the boundary as system reaches the steady state, the (near) dynamic equilibrium of all the genes is observed during the whole modeling period.

Hb gradient is the most steep and well-established in *Drosophila* blastoderm, while the formation of expression domains of the other gap genes is more gradual with a more or less noticeable shift over time. However the mathematical mechanism associated with the dynamic equilibrium is also observed during the whole modeling period or at least its part, for the most part in the end of NC14.

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