Morphogenesis at criticality?

Dmitry Krotov[1,2], Julien O. Dubuis[1,2,3], and William Bialek[1,2]

***Short Abstract* — We study the spatial pattern formed by the gap gene proteins in the early fruit fly embryo, which is anchored by "crossing points" between expression levels of different genes. We explore a broad class of models for such interacting genes and show that the parameters implied by recent quantitative measurements are non-generic, but rather tuned to certain values, so that the entire network operates close to the critical surface in its phase diagram. We derive signatures of critical behavior in the structure of expression noise and time dependence of expression levels. We show that the real experimental data matches these theoretical predictions.**

***Keywords* — embryonic development, gene regulatory networks, gap genes, criticality.**

RESULTS

THE anterior-posterior patterning of the early fruit fly embryo is an experimentally accessible model system which allows many questions about gene regulatory networks to be addressed. Information about positions of nuclei is believed to be transmitted from maternal morphogens to the gap genes, to the pair rule genes and segment polarity genes [1]. In this talk we discuss a subnetwork of the full gene network that is responsible for the patterning of a small region, 0.44-0.51% EL, along the anterior-posterior axis where the expression level of *hunchback* changes from the fully on to the fully off state (gray area in Fig 1). It is plausible that the relevant part of the regulatory network in this small region is given by the diagram in Fig 1: *Bicoid* (Bcd) activates *hunchback* (Hb) and *krüppel* (Kr), while Hb and Kr mutually repress each other. There are a large number of parameters hidden behind this schematic: the number of binding sites for transcription factors, their affinities, etc. Depending on the quantitative choice of these parameters, the behavior of the network can be dominated by the mutual repression between Hb and Kr (as in the bi-stable switch) or the activation from the input. If we imagine a continuous increase in the strength of the mutual repression, the behavior of the network is not continuous: there is a certain critical value and the behavior of the network is qualitatively different on different sides of this sharp transition. On one side, the network is operating in the monostable regime, while on the other side it is in the multistable regime. We discuss a possibility that the real genetic network is operating in the immediate vicinity of this sharp boundary between the two phases. This is what we call criticality.

[1]Joseph Henry Laboratories of Physics, [2]Lewis-Sigler Institute for Integrative Genomics, [3]Howard Hughes Medical Institute, Princeton University, Princeton, New Jersey, 08544, USA.
E-mail: dkrotov@princeton.edu

Such a non-generic design of the network results in highly pronounced signatures in the structure of expression noise

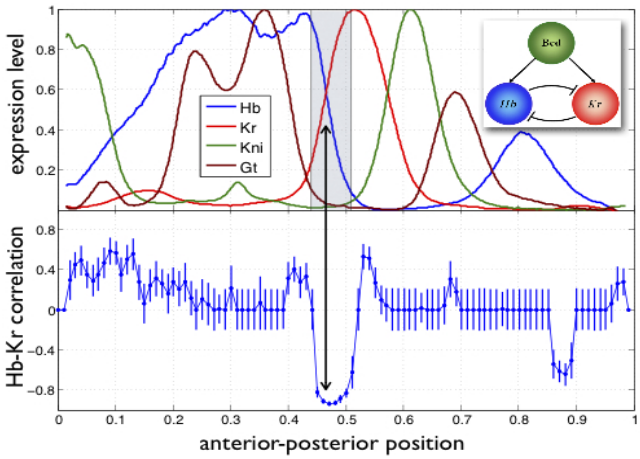

Fig 1. Concentrations of the proteins encoded by the four gap genes (*hunchback, krüppel, knirps and giant*) measured at t=42.7±3.1min after the start of the nuclear cycle 14. The anterior-posterior dependence of the correlation coefficient for the fluctuations of Hb and Kr.

and time dependence of expression levels. More specifically, the fluctuations of expression levels must be strongly correlated or anticorrelated; while the relaxation dynamics toward a steady state must contain multiple time scales that exhibit hierarchy – some of them are fast and some of them are slow. We find a surprisingly high degree of anticorrelation in the real experimental data [2,3,4]. In Fig 1 the anterior-posterior dependence of the correlation coefficient between fluctuations of Hb and Kr is shown. At the crossing point (black arrow), the correlation reaches C = -0.94 ± 0.02. We show that this strong anticorrelation is a separate feature of the data and is not a corollary of the mean expression profiles. We next look at the time dependence of expression profiles measured [2] during nuclear cycle 14, and find two distinct time scales (fast and slow) with a large ratio: $\tau_{slow}/\tau_{fast} \approx 50$. We repeat the above analysis for other crossing points along the anterior-posterior axis and find that most (but not all) of the crossing points exhibit these signatures of critical behavior. These results suggest an interesting possibility that the network of genes responsible for development is operating near criticality.

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