Sir-

We found it disheartening to read in this Journal recently that computational analysis was required to "reveal holes in the current understanding of [Drosophila] segmentation: what represses en [engrailed] anterior to the wg [wingless]-expressing stripe, and what makes Hh [Hedgehog] signaling asymmetric?"[1]. This assertion was reiterated in the accompanying News and Views article[2], which also gave the impression that this problem has not been previously recognized. On the contrary, Phil Ingham and colleagues invoked two competency domains for each segment, one for wg and one for en, precisely to explain the asymmetric response of cells to the Wg and Hh signals[3]. The problem has been covered in at least one review as well[4].

The authors solve half of the riddle by invoking wg-autoregulation to explain why wg is only found anterior of the en/hh domain. While this autoregulation exists[5], there is no evidence to indicate that it can account for the asymmetric response of wg to the Hh signal. The suggestion that the Cubitus-interruptus (Ci) repressor fragment inhibits en expression anterior of the wg-domain is even more speculative. Such handwaving is unneccessary, since we reported several years ago[6] that two forkhead domain transcription factors, Sloppy paired 1 and 2 (Slp) offer the best answer to both halves of the puzzle.

Our data demonstrated that slp activates wg expression and represses that of en. slp is expressed precisely in the "wg competency domain" proposed by Ingham et al.[3], overlapping with wg and adjacent to en/hh. Misexpression of slp on the other side of the en/hh-domain causes wg to be expressed there[6], and ubiquitous expression of wg in slp mutants causes all cells to express en[7]. Thus, slp appears to be sufficient to explain the asymmetric responses to both Wg and Hh.

The most exciting finding made by von Dassow and colleagues is that even when the physical parameters (i.e., half-life, diffusion, binding coefficients) of Hh, Wg, En, Ci and Patched are altered dramatically, many combinations still (roughly) recapitulate the in vivo expression patterns of these genes. We suggest that the frequency of such successful combinations (1 in 200 in their report) would be significantly higher had they included the published data on slp.

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