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Single molecule transcription factor dynamics in the syncytial Drosophila embryo

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During early development in the Drosophila embryo, cell fates are determined over the course of just 2 hours with exquisite spatio-temoral precision. One of the key regulators of this process is the transcription factor Bicoid which forms a concentration gradient across the long axis of the embryo. Although Bicoids' primary role is activation at the anterior, where concentrations are highest, it is also known to play a role in the posterior where there are only 100s of molecules per nucleus. Understanding how Bicoid can find its target at such low concentrations has remained intractable, largely due to the inability to perform single molecule imaging in the context of the developing embryo. Here we use lattice light sheet microscopy to overcome the technical barriers of sample thickness and auto-fluorescence to characterize the single molecule dynamics of Bicoid. We find that off-rates do not vary across the embryo and that instead the on-rates are modulated through the formation of clusters that enrich local concentration. This data is contrary to the current concentration dependent model of Bicoid function since *local* concentration within the nucleus is now a regulated parameter and suggests a previously unknown mechanism for regulation at extremely low concentrations.