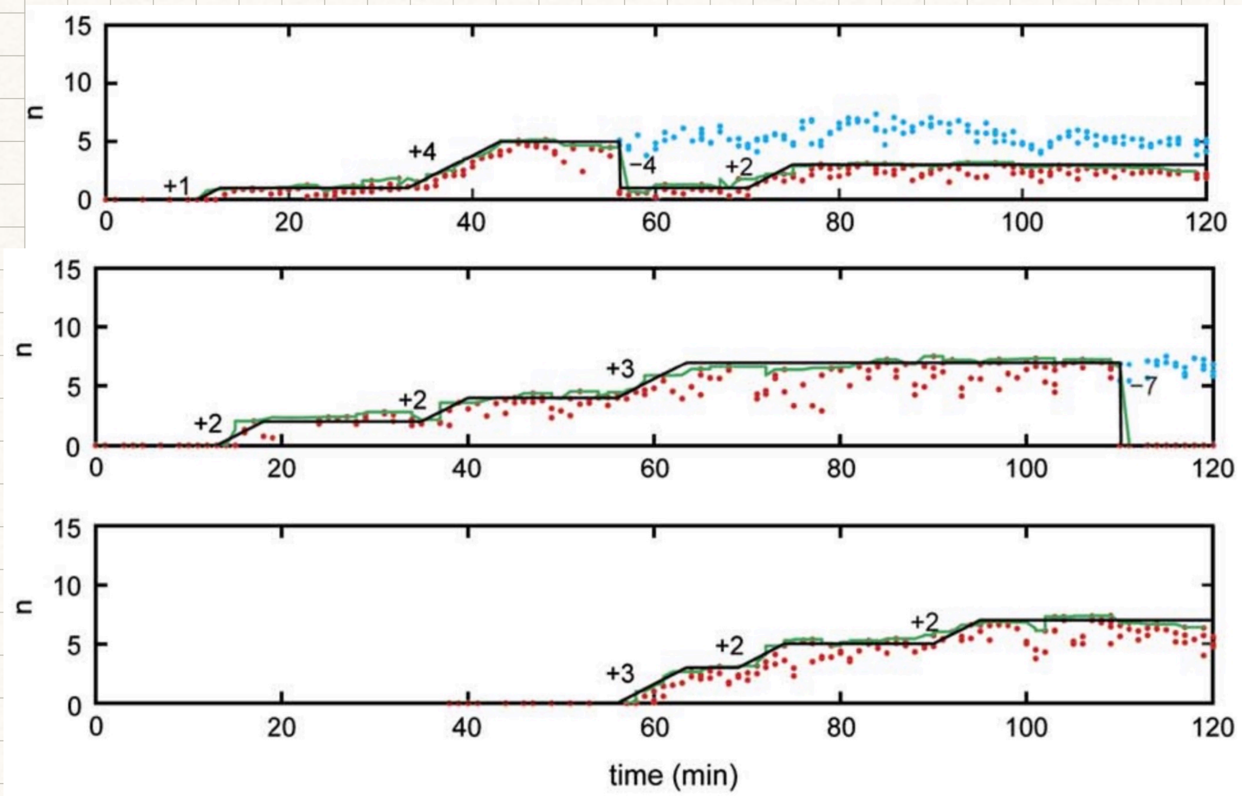
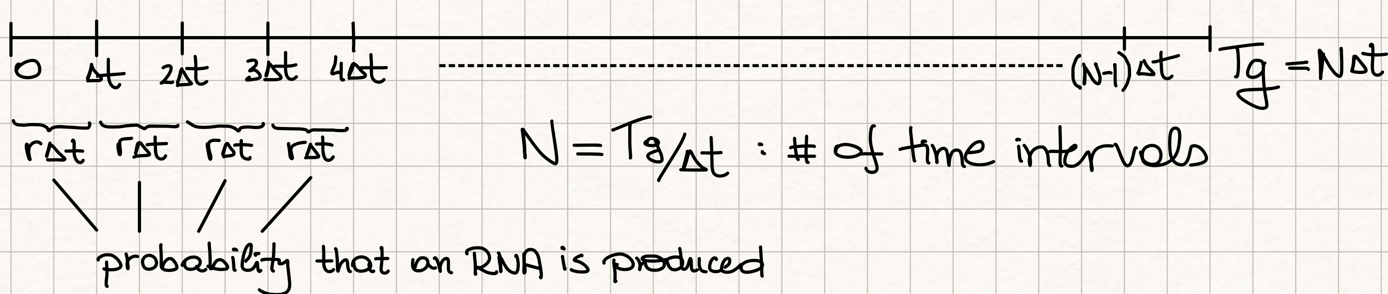
Single-cell transcription dynamics

In experiments on single cells Golding and Co. measured the number of RNAs produced from a single gene:



Are these observations consistent with the simple model of RNA production, where RNA is produced at rate r?

In this experiment RNA is not degraded. Given that the rate of production is r, how many RNAs are produced in a generation time T_g ($T_g \simeq 70$ min in Jdo's experiment)



To produce a single cell trajectory, for every time interval pick a random number between 0 and 1. If this number is less then $r\Delta t$ add one RNA. ⟶ Write Python code and visually compare trajectories...

To compare our model of RNA production to Ido's experiments, we compute the probability distribution of m, the number of RNAs produced in time T_g.

: these are the time intervals in which RNA is produced.

$$p(m) = \underbrace{\frac{N!}{m!\,(N-m)!}}_{\text{multiplicity = \# of ways of choosing } m \text{ intervals from } N} \; \overbrace{(r\Delta t)}^{\text{probability of RNA being produced in time interval } \Delta t}{}^{m} \; \underbrace{(1-r\Delta t)}_{\text{probability of RNA not produced in } \Delta t}{}^{N-m}$$

For $r\Delta t \ll 1$, $N = \frac{t}{\Delta t} \gg m$, since m is of order rT_g (≈ 10 in Ido's experiment)

In these limits the Binomial distribution becomes (it wants to be!!) Poisson.

$$p(m) = \frac{\cancel{N^m}}{m!}\left(rT_g/\cancel{N}\right)^m \left(1 - r\frac{T_g}{N}\right)^N \left(1 - r\frac{T_g}{N}\right)^m \quad \Big\{ \text{I used } \frac{N!}{(N-m)!} \approx N^m \text{ when } m \ll N.$$

$$\underbrace{p(m) = \frac{(rT_g)^m}{m!}\, e^{-rT_g}}_{\text{Poisson distribution}} \quad \Big\{ \text{I used: } \left(1-\frac{x}{N}\right)^N = e^{-x} \text{ for } N \gg 1, \quad \left(1-\frac{x}{N}\right)^m = 1 \text{ for } N \gg m > 1$$

To compare to Ido's data we can compute the mean and variance which he measures. (Could also compare the distributions directly as they do in the Zenklusen et al. paper).

Mean

$$\langle m \rangle = \sum_{m=0}^{\infty} m \frac{\mu^m}{m!} e^{-\mu}, \quad \mu \equiv rT_g$$

$$\langle m \rangle = e^{-\mu} \sum_{m=1}^{\infty} \frac{\mu^m}{(m-1)!} \quad \Big\{ \frac{\cancel{m}}{\cancel{m}(m-1)(m-2)\ldots} = \frac{1}{(m-1)!}; \quad \sum_m \text{ starts at } m=1 \text{ since } m=0 \text{ term is zero}$$

$$\langle m\rangle = e^{-\mu}\sum_{m'=0}^{\infty} \frac{\mu^{m'+1}}{m'!} \quad \Big\}\ m' = m+1;\ \text{change of variables}$$

$$\langle m\rangle = e^{-\mu}\mu \underbrace{\sum_{m'=0}^{\infty} \frac{\mu^{m'}}{m'!}}_{e^{\mu}} = \mu$$

Mean of the Poisson distribution $p(m) = \frac{\mu^m}{m!}e^{-\mu}$ is μ.

<u>Variance</u>

$$\text{var}\, m = \langle m^2\rangle - \langle m\rangle^2$$

$$\langle m^2\rangle = \sum_{m=0}^{\infty} m^2 \frac{\mu^m}{m!} e^{-\mu} \quad \Big\{\ \text{m=0 term in the sum is zero so start it from m=1}$$

$$= \sum_{m'=0}^{\infty} (m'+1)^2 \frac{\mu^{m'+1}}{(m'+1)!} e^{-\mu} \quad \Big\{\ \text{change of variables } m'=m+1$$

$$= \sum_{m'=0}^{\infty} (m'+1) \frac{\mu^{m'+1}}{m'!} e^{-\mu} \quad \rightarrow \text{pull this out}$$

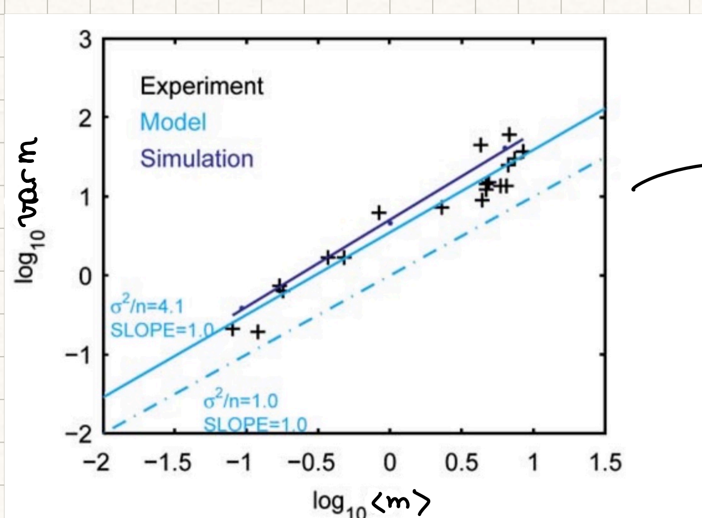
$$= \mu \Bigg(\underbrace{\sum_{m'=0}^{\infty} m' \frac{\mu^{m'}}{m'!} e^{-\mu}}_{\mu \text{ (from the mean calculation)}} + \underbrace{\sum_{m'=0}^{\infty} \frac{\mu^{m'}}{m'!} e^{-\mu}}_{1} \Bigg)$$

$$\langle m^2\rangle = \mu(\mu+1)$$

With this result in hand we compute the variance:

$$\text{var}\, m = \langle m^2\rangle - \langle m\rangle^2 = \mu(\mu+1) - \mu^2 = \mu\ !$$

Variance is equal to the mean! This is a key feature of the Poisson distribution.



→ Ido varies the mean by using different levels of induction and finds $\text{var}\, m \approx 4.1 \langle m\rangle$ which disagrees with the prediction of the model. Therefore, transcription is not described as production of RNA at a constant rate. It is bursty!