DO GENES **WAIT** IN A QUEUE?

Enzymes diffuse around the cell to find genes. But how long does a gene wait?

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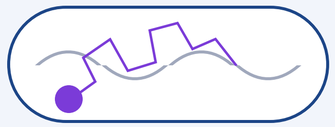
1. The problem

Shop: the server waits at the counter

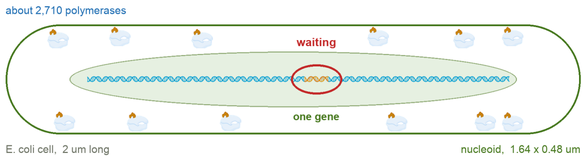


Cell: the server must find the gene

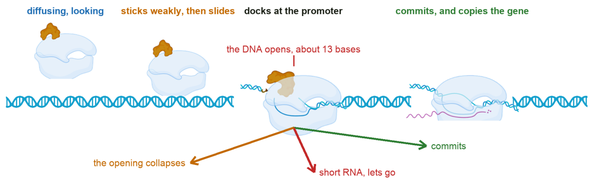
- Inside a cell, the server has to move to find its customer. A gene cannot move, so RNA polymerase, the enzyme that reads it, wanders at random until it meets that gene.
- Classical queueing theory typically assumes the server is already where the job is.
- How long a gene waits is a difficult measurement to take in a living cell. Microscopes can track the polymerase, but not the waiting of the gene.

So, we built a physics simulation of a single *E. coli* cell and used it to estimate how long genes wait for RNA polymerase and what controls that waiting time.

2. The simulation



Transcription as a queue



Genes are the **customers**. Polymerases are the **servers**.

- 3D Brownian simulation of one cell grown in M9 + 0.2% glucose at 37 °C[1]
- Other parameters are taken from measurements at this growth condition. The cell dimension at this condition is assumed
- Recognition rate **calibrated** so the search time falls in the measured 30–120 s range[1]
- Polymerase count swept from about 200 to 3,500 at saturating gene demand (Fig. 1)
- Alternative sigma-factor demand raised up to 32× in a healthy (2,800) and a depleted (700) pool (Fig. 3)

3. The shift in times

Inside our simulated cell, there exists some delay, either for the customer or the server and it depends on the count.

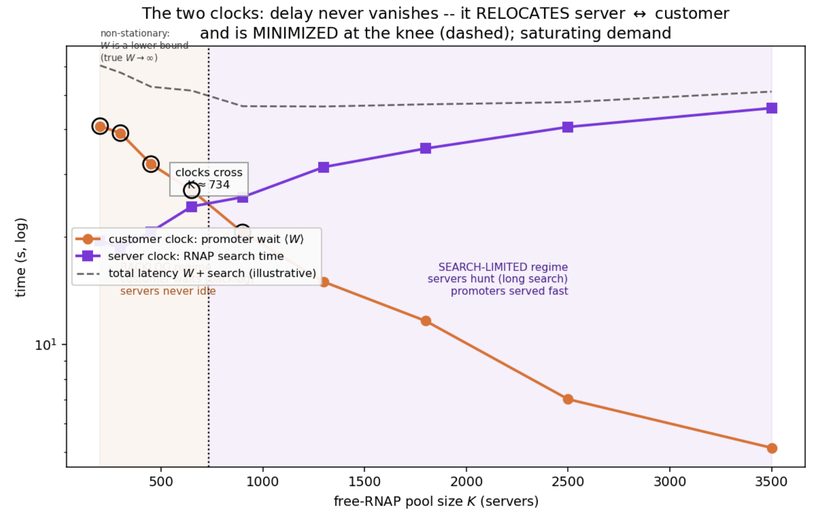


Fig. 1: Gene waiting time **(orange)** and polymerase search time **(purple)** as the polymerase count is varied at saturating gene demand. The two cross near 734 polymerases. Circled points did not reach steady state, so their waits are lower bounds.

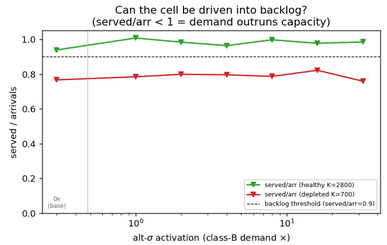
FEW POLYMERASES: THE GENE WAITS

Below 500–750 polymerases, waiting time shoots up and polymerases are never idle.

MANY POLYMERASES: THE ENZYME SEARCHES

Genes are served fast. Each polymerase hunts longer. At its measured count (2,710), only 10–30% of polymerases are busy.

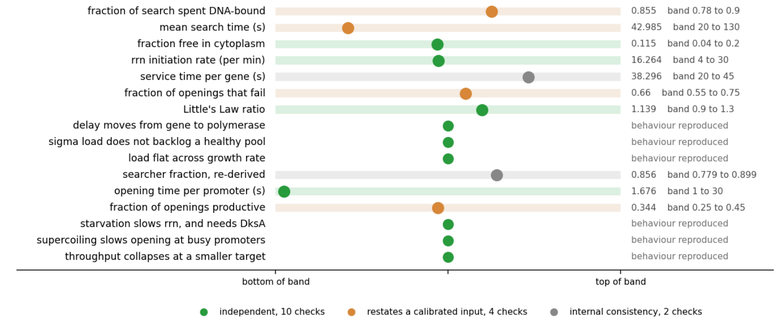
In the model, a traffic jam comes from the shortage of polymerases



- Up to 32× extra sigma-factor demand doesn't stress a healthy pool of polymerases (2,800).
- A depleted pool (700) falls behind at the loads tested.
- The traffic jam comes from a shortage of polymerase. Genes are not competing with each other for it.

Fig. 3: Fraction of gene requests served as demand from an alternative sigma-factor program rises up to 32×. A depleted pool (700) is below the backlog threshold.

4. Can we validate the model?



The independent model measurements[1,3,4] mostly fall within range.

Fig. 2: Sixteen model outputs against published in vivo ranges.
Green: no tuned rate behind the check. **Orange:** restates a calibrated input. **Gray:** internal consistency.

5. The significance

- RNA polymerase is the target of front-line antibiotics such as rifampicin.
- The model predicts a threshold where the partial inhibition of transcription changes gene waiting times a little until the free pool falls below the 500-750 polymerase count, then the waiting time increases sharply.

Limitations

- Promoter recognition rate is calibrated and not measured
- The polymerase count threshold was located at saturating demand, above a real cell's load
- Circled points in Fig. 1 are lower bounds (queue not at steady state)

Next steps

- Test the model against real single-particle tracking data of RNA polymerase
- Track a polymerase and one gene locus together, to measure the recognition rate directly
- Deplete polymerase or starve cells while tracking. The model predicts that search time falls while gene waiting rises

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References

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