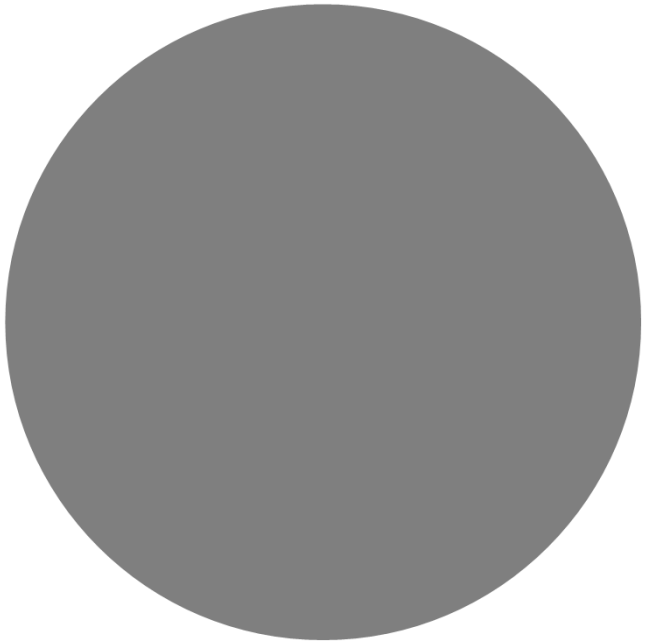
Resource aware translation model incorporating slow codons



Joaquin incorporated one slow codon case into translation model

He did a very elegant report giving results based on certain assumptions

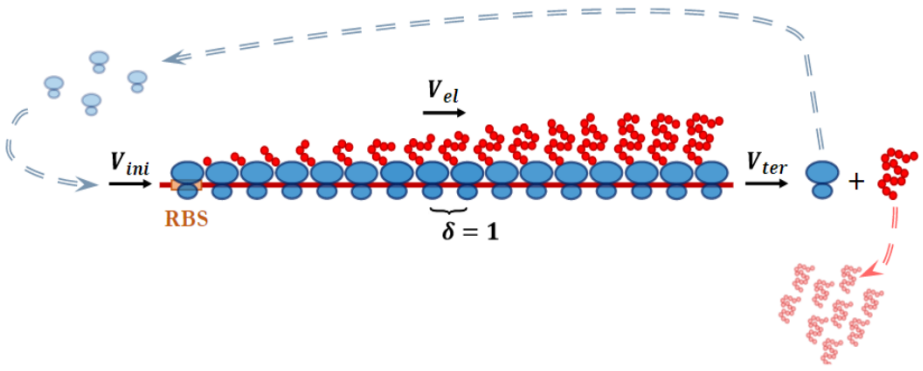
3 of his assumptions are addressed here

A 4th assumption that we do not address is that the binding of the ribosome is not reversible

Assumption I

- Distance is non-zero, the mRNA is not fully covered by ribosomes
- It will be less than 1 though because of the formula
- So result is an average value: sometimes 1 sometimes zero places between ribosome

$$\overbrace{\delta = V_{el} \cdot \frac{1}{V_{ini}}}$$



(b) *High translation initiation rate:* $V_{ini} \geq \nu_{el}$

We thus define the translation termination rate as

$$V_{ter}(R_T) = 2\,M\,\nu^*_{RBS}\,\frac{R_T}{R_{T_{ss}} + R_T}, \tag{2.6}$$

which fulfills the previously stated conditions, since

$$V_{ter}(R_T = R_{T_{ss}}) = 2\,M\,\nu^*_{RBS} \cdot \frac{1}{2} = M\,\nu^*_{RBS} = V_{ini} \tag{2.7}$$

and

$$V_{ter}(R_T < R_{T_{ss}}) < M\,\nu^*_{RBS} = V_{ini}, \tag{2.8}$$
$$V_{ter}(R_T > R_{T_{ss}}) > M\,\nu^*_{RBS} = V_{ini}. \tag{2.9}$$

Having found expressions for the translation initiation and termination rates, we now write down the ordinary differential equations (ODEs) that govern the time evolution of the system.

$$\frac{dR_T}{dt} = V_{ini} - V_{ter} \tag{2.10}$$
$$\frac{dR_{Free}}{dt} = -\frac{dR_T}{dt} = V_{ter} - V_{ini}, \tag{2.11}$$

- Transient dynamics is calculated by assuming a Hill function with coefficient of one
- Maximal rate is two times Vrbs and half maximal rate is achieved at steady-state by definition
- Unphysical when ribosome pool depletes, as pointed out in the report
- Could we understand ribosome concentration dynamics without this assumption?

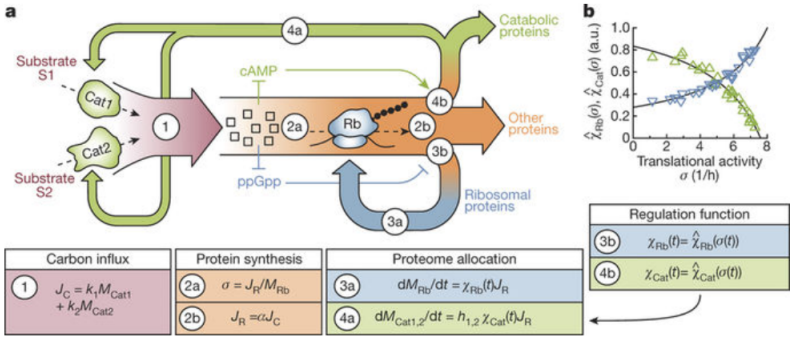
Assumption 2

Literature proposed solutions

- Weiße et al. does not consider polyribosomes
- Erickson et al. top down approach:

- Algar et al. Ribosome flow model, probabilistic approach, then they take expectations, assumes fixed number of total ribosomes, incorporates slow codons

Figure 2: Model of FCR.



the synthesis of catabolic and ribosomal proteins, we observe that while ppGpp-mediated regulation is set by the charging of tRNA by amino acids [21,24,25] cAMP-CRP regulation is set by α-ketoacids [13], which are connected to the amino acids by rapidly reversible trans-amination reactions [29]. We note that these metabolites, which are the drivers of ppGpp and cAMP signaling, are the same "pool of central precursors" discussed in Note 3.2b that molecularly set the magnitude of the translational activity $\sigma(t)$ in Eq. (S25). This leads us to our central approximation that the (time-dependent) effects that these central precursors exert on the regulatory functions $\chi_{Rb}(t)$ and $\chi_{Cat}(t)$ during growth transitions can be mimicked through their effect on the translational activity $\sigma(t)$. As we will show in the next

Literature Proposed solutions II

- Extensive modelling and analysis:
- Chen et al. complex model, capturing most things but not slow codons
- Qian et al. calculating resource demand coefficients in a complex way, no slow codons

Simulation method

Count time and if Tini is reached put a ribosome on mRNA

Zero counter for that ribosome

if Tel is reached move ribosome to next ribosome place if it is not occupied

Benefits

- Fast, scalable method, can set Tini and Tel at any given time to account for change in amino acids, energy or free ribosomes in pool
- Gives intuitive approximation of what we should expect to happen

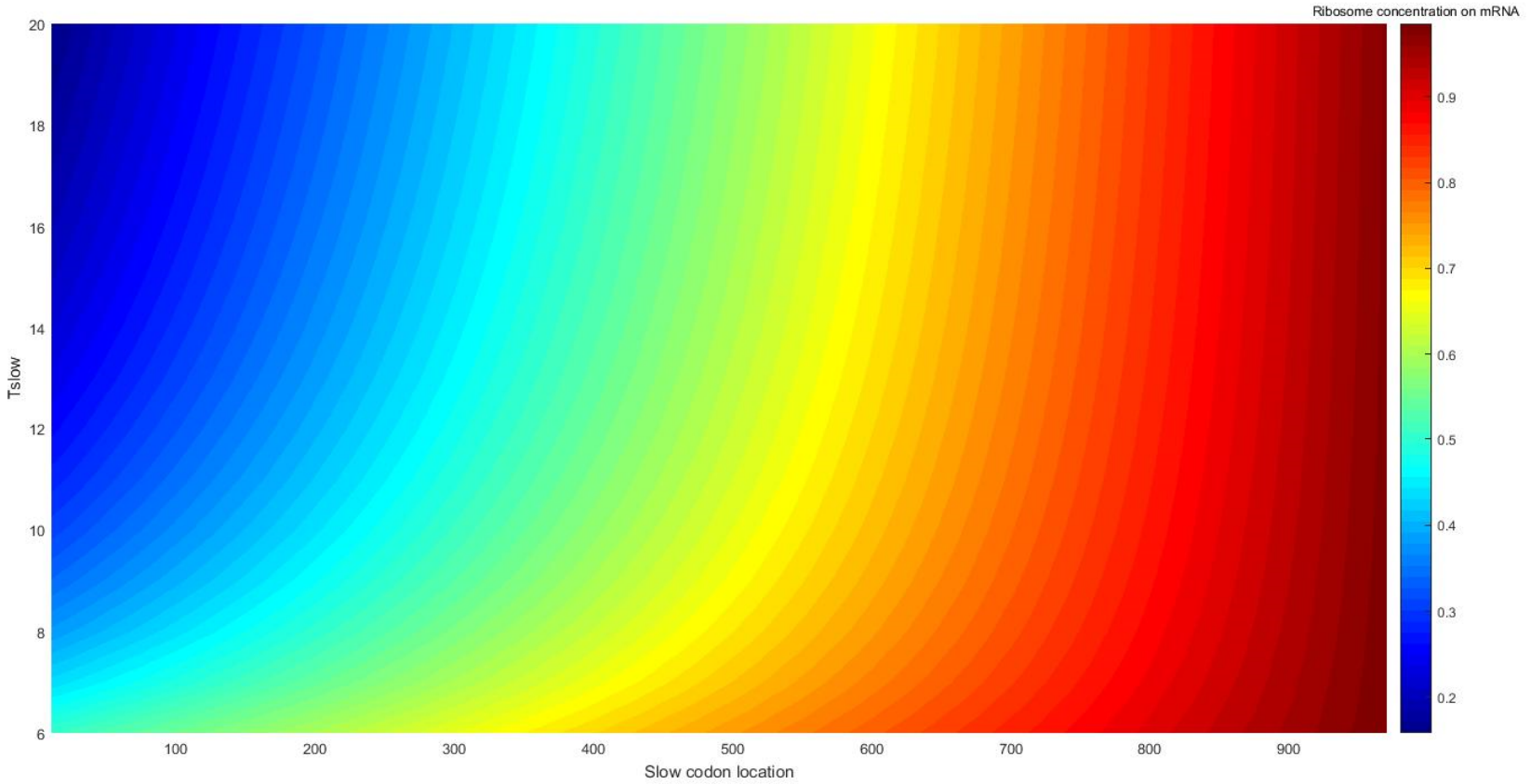
Drawbacks

- No stochastic nature
- Tini, Tel can only take discrete values (so how to increase when no. of free ribosomes decreases?)
- What to do with counter when the above parameters change?

Equations derived from simulation results

- No slow codon
  - Steady-state number: $\frac{T_{el}}{T_{ini}+T_{el}}$ (1)
  - $\frac{dn}{dt} = \left(R_{ss,new} - \frac{T_{el}}{T_{ini}(t-length_{mRNA}*T_{el})+T_{el}}\right) * v_{el}$
- Slow codon
  - Steady-state concentration: $l + (N - l) * \frac{T_{el}}{T_{slow}}$ (2)
    (same as in Joaquin's report)
  - Derived transient concentration analytically
  - So slow codon dynamics known, but how to incorporate finite resources? (only matters in transient because by definition in steady-state "nothing changes")

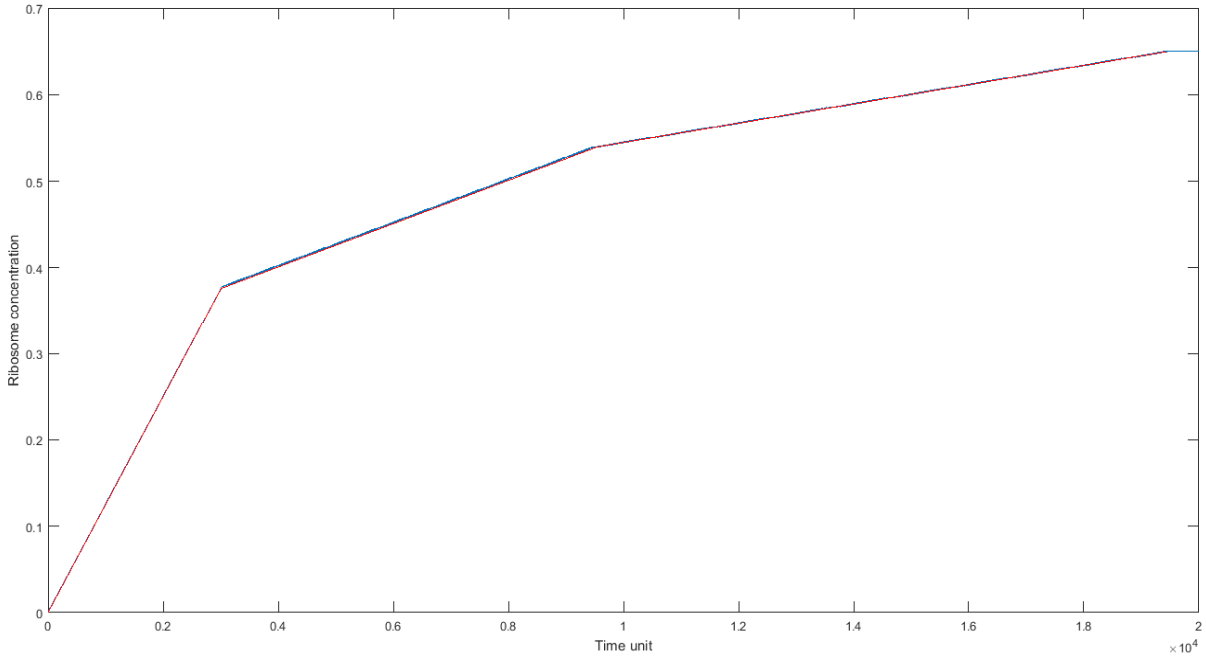
Ribosome concentration on mRNA, steady-state



Assumption 3

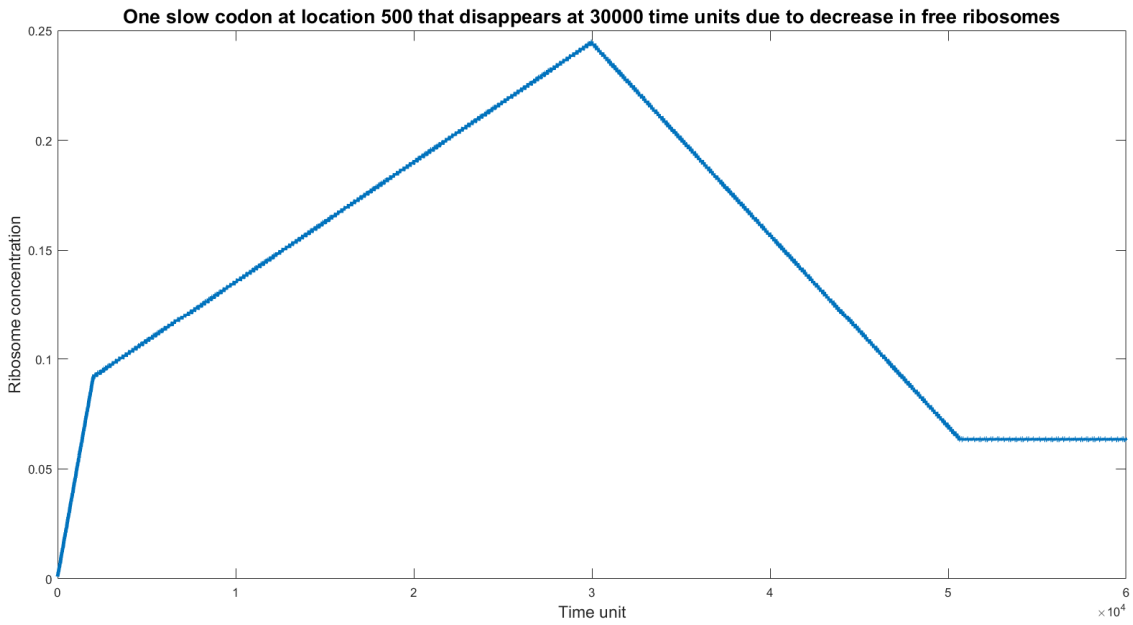
$$R_{T_{ss}}(\nu_{RBS} \leq \nu_{slow}) = \Gamma \cdot \frac{N\nu_{RBS}}{\nu_{fast}}. \qquad (2.14)$$

- In this case, slow codon is not “sufficiently slow”, simulation suggests that steady-state is not affected and the formula is
- $\frac{T_{el}}{T_{ini}+T_{el}}$
- This is because the ribosome cannot reach (and hence be hindered in its movement) the one in front of it, because Tini+Tel>Tslow
- Since initiation rate changes, slow codons will “appear” and “disappear”



- distances = [50 150 200 500 700];
- Tslow = [6 7 9 10 8];
- Tel = 3;
- Tini = 5;

Analytical solution for infinite resources with slow codon (or assuming no burden and steady-state for non-heterologous transcripts)

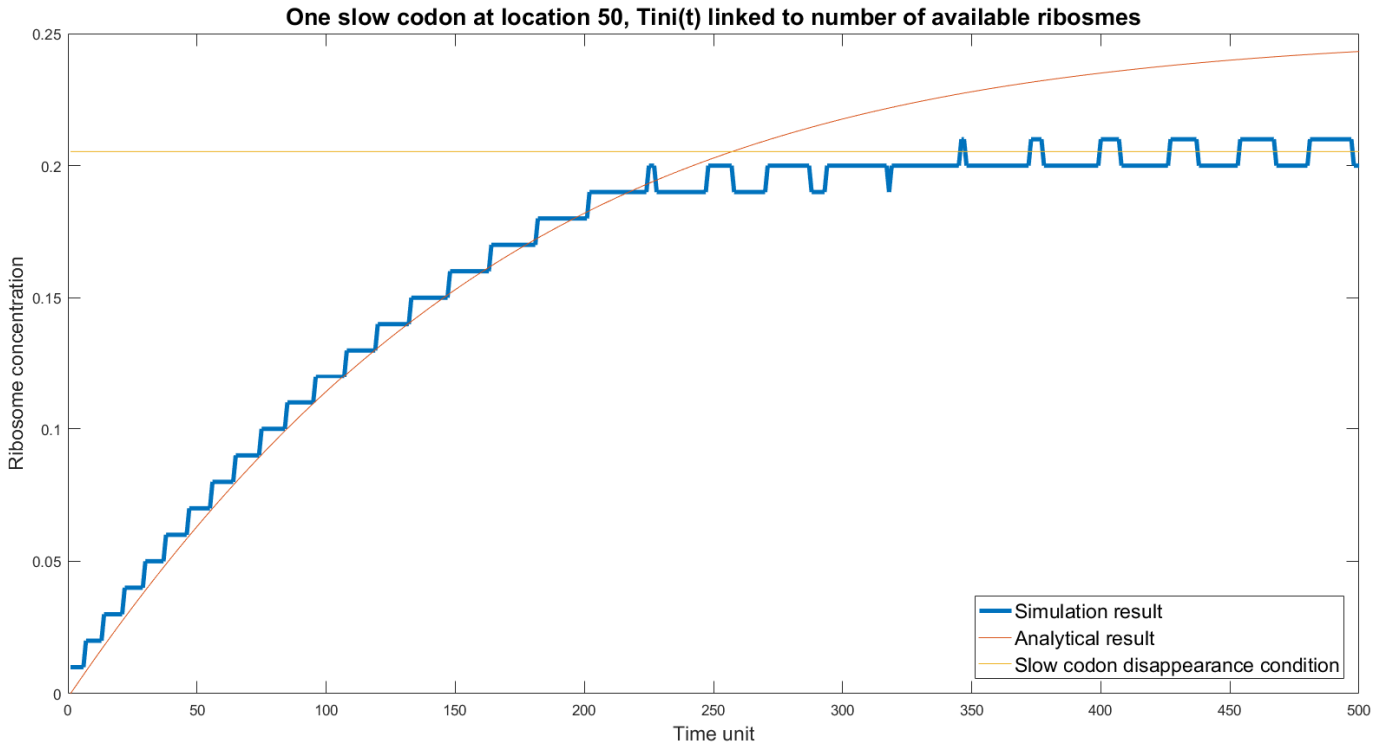


- If ribosomes are sequestered on mRNA, it implies that burden is not big, since sequestration itself did not reduce the free ribosome pool significantly
- Otherwise, slow codon disappears and no more ribosome sequestration -> internal negative feedback when burden is huge
- Oscillations of incomplete queue formations and temporary slow codon disappearance?

Is ribosome queuing on mRNA a problem?

Results

- No. of available ribosomes: 10000
- No. of heterologous transcripts: 400
- Reciprocal slow codon elongation rate: 30 and location: 50
- mRNA length: 100
- Normal codon reciprocal elongation rate: 2
- Initial reciprocal initiation rate: 5



Analytical result derivation

- Assumptions (for more info see slow codon analytical derivation)
  - The numbers are chosen such that no backward congestion processes finish and first ribosome does not reach the end of the mRNA (this is to make sure that slope is initial and does not change, except for the effect of changing Tini)
- Differential equation for the number of ribosomes on mRNA
  - Initial slope (number vs. time): $\frac{1}{T_{el}+T_{ini}(t)}$
  - Assumption on negative feedback of n on Tini: $Tini(t) = \frac{Tini(0)*R_{free,max}}{R_{free,max}-m*n(t)}$, m is the number of transcripts
  - $\frac{dn}{dt} = \frac{1}{T_{el}+\frac{Tini(0)*R_{free,max}}{R_{free,max}-m*n(t)}}$