Supplementary Materials for the paper: Dynamical modeling of microRNA action on the protein translation process

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1 Analytical analysis of the case of very inefficient cap structure

We analyze the system of equations

$$\begin{cases} \dfrac{d\,[40S]}{dt} = -k_1[40S]\ [eIF4F] + k_4[80S] \\ \dfrac{d\,[eIF4F]}{dt} = -k_1[40S]\ [eIF4F] + k_2[mRNA:40S] \\ \dfrac{d\,[mRNA:40S]}{dt} = k_1[40S]\ [eIF4F] - k_2[mRNA:40S] \\ \dfrac{d\,[AUG]}{dt} = k_2[mRNA:40S] - k_3[AUG]\ [60S] \\ \dfrac{d\,[60S]}{dt} = -k_3[AUG]\ [60S] + k_4[80S] \\ \dfrac{d\,[80S]}{dt} = k_3[AUG]\ [60S] - k_4[80S] \\ Prsynth(t) = k_3[AUG]\ [60S] \end{cases} \tag{1}$$

with the following assumptions on the model parameters:

$$k_1 \ll k_4 \ll k_2 \ll k_3; [eIF4F]_0 \ll [40S]_0; [eIF4F]_0 < [60S]_0 < [40S]_0 \tag{2}$$

First of all, notice that, generally speaking, it is not eligible to compare the some parameters k_i: k_1 and k_3 has $\frac{1}{sec\_moles}$ dimensionality while k_2 and k_4 are $\frac{1}{sec}$. So instead of comparing k_1 and k_4, for example, one should rather compare, for example, $k_1[eIF4F]_0$ and k_4. To facilitate this task, we explicitly consider that $[eIF4F]_0$ is on the order of 10^0 in our model, $[60S]_0$ is at the order of 10^1 and $[40S]_0$ at 10^2.

1.1 Approximate steady state solution

From the conservation laws

$$[mRNA:40S]+[40S]+[AUG]+[80S]=[40S]_0, \quad (3)$$

$$[mRNA:40S]+[eIF4F]=[eIF4F]_0, \quad (4)$$

$$[60S]+[80S]=[60S]_0, \quad (5)$$

and the steady state condition

$$k_2\cdot[mRNA:40S]_s=k_3\cdot[AUG]_s\cdot[60S]_s=k_4\cdot[80S]_s=k_1\cdot[40S]_s\cdot[eIF4F]_s, \quad (6)$$

we can derive

$$\begin{aligned}
&[mRNA:40S]_s=\frac{k_4}{k_2}[60S]_0(1-x), [AUG]_s=\frac{k_4}{k_3}\left(\frac{1-x}{x}\right),\\
&[eIF4F]_s=[eIF4F]_0-\frac{k_4}{k_2}[60S]_0(1-x),\\
&[60S]_s=[60S]_0x, [80S]_s=[60S]_0(1-x),\\
&[40S]_s=[40S]_0-[60S]_0(1-x)(1+\frac{k_4}{k_2})-\frac{k_4}{k_3}\left(\frac{1-x}{x}\right)
\end{aligned} \quad (7)$$

where $x=\frac{[60S]_s}{[60S]_0}$ is the fraction of $60S$ in the free (unbound to mRNA) state.

Using (6) and (7) we obtain an equation on x:

$$\begin{aligned}
&x^3+\\
&+x^2\left(\alpha+(\delta-1)+(\beta-1)+\frac{[eIF4F]_0}{[60S]_0}\right)\frac{1}{1+k_4/k_2}+\\
&+x\left(-\alpha+(\delta-1)(\beta-1)+\frac{[eIF4F]_0}{[60S]_0}(-1-2\frac{k_4}{k_3[eIF4F]_0}+\frac{k_2}{k_3[60S]_0}+\frac{k_4}{k_2[eIF4F]_0})\right)\frac{1}{1+k_4/k_2}+\\
&+\gamma(1-\beta)=0,\\
&\alpha=\frac{k_2}{k_1[60S]_0}, \beta=\frac{[eIF4F]_0k_2}{[60S]_0k_4}, \gamma=\frac{k_4}{k_3[60S]_0}, \delta=\frac{[40S]_0}{[60S]_0}
\end{aligned} \quad (8)$$

Having in mind $k_4 \ll k_2$ and assuming that $[eIF4F]_0/[60S]_0$ is sufficiently small, we simplify it to

$$x^3+x^2\left(\alpha+(\delta-1)+(\beta-1)\right)+x\left(-\alpha+(\delta-1)(\beta-1)\right)+\gamma(1-\beta)=0,. \quad (9)$$

From the inequalities on the parameters of the model, we have $\delta>1$, $\gamma\ll 1$, the constant term $\gamma(1-\beta)$ of the equation (9) should be much smaller than the other polynomial coefficients, and the equation (9) should have one solution close to zero and two others:

$$\begin{aligned}
&x_0\approx\frac{\gamma(\beta-1)}{-\alpha+(\beta-1)(\delta-1)}\\
&x_1=\frac{1}{2}\left(-(\alpha+\beta+\delta)+2+\sqrt{(\alpha+\beta+\delta)^2-4\beta\delta}\right)\\
&x_2=\frac{1}{2}\left(-(\alpha+\beta+\delta)+2-\sqrt{(\alpha+\beta+\delta)^2-4\beta\delta}\right)
\end{aligned} \quad (10)$$

.

If $k_1 \gg k_4/[eIF4F]_0$ then we have a situation already solved in the main body of the paper. Let us consider the opposite situation, when $k_1 \ll k_4/[eIF4F]_0$. In this case $\alpha \gg \beta+\delta$ and

$$
\begin{aligned}
x_0 &\approx \frac{\gamma(\beta-1)}{-\alpha} = \frac{k_1 k_4}{k_3 k_2} - \frac{k_1[eIF4F]_0}{k_3[60S]_0} \\
x_1 &\approx 1 - \frac{\beta\delta}{\alpha} = 1 - \frac{k_1[eIF4F]_0[40S]_0}{k_4[60S]_0} \\
x_2 &\approx -\alpha < 0
\end{aligned}
\tag{11}
$$

.

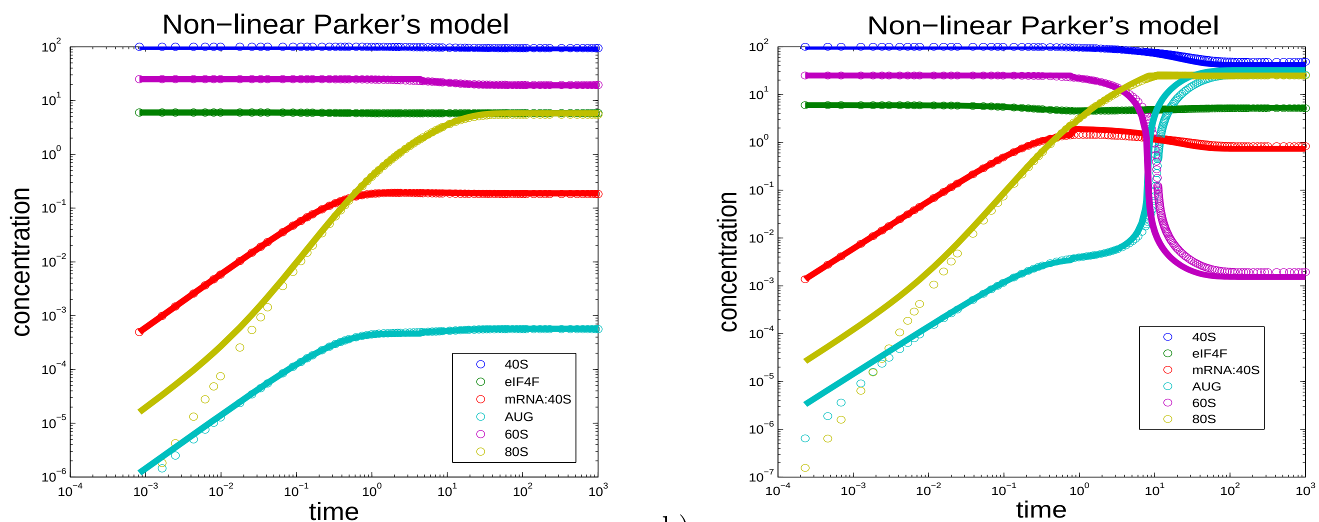
If $\alpha \gg \beta+\delta$ then the solution of the model can be approximated by the dominant system from Fig. 5 of the main body of the paper, Stage 1:

$$
\begin{aligned}
&\begin{bmatrix} [eIF4F](t) \\ [mRNA:40S](t) \\ [AUG](t) \\ [80S] \end{bmatrix} \\
&= \frac{[eIF4F]_0}{\frac{1}{k_1'}+\frac{1}{k_2}} \left(\begin{bmatrix} 1/k_1' \\ 1/k_2 \\ 1/k_3' \\ 1/k_4 \end{bmatrix} + \frac{1}{k_2} \begin{bmatrix} 1 \\ -1 \\ 0 \\ \dfrac{k_2}{k_1'+k_2} \end{bmatrix} e^{-(k_1'+k_2)t} - \left(\frac{1}{k_4} + \frac{1}{k_1'+k_2}\right) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} e^{-k_4 t} \right)
\end{aligned}
\tag{12}
$$

and $[60S]=[60S]_0$, $[40S]=[40S]_0$. This solution is valid on the interval $[0;t']$, $t' = \frac{1}{k_1'+k_2} + \frac{[60S]_0}{10[eIF4F]_0}(\frac{1}{k_1'} + \frac{1}{k_2})$. Following the recipe from the main body of the paper, after this moment it can be prolonged with quasiequilibrium approximation:

$$
\begin{aligned}
&A = \frac{[eIF4F]_0}{k_4\left(\frac{1}{k_1'}+\frac{1}{k_2}\right)} \\
&[80S](t) = \frac{[60S]_0}{10} + A\left(1 - e^{-k_4(t-t')}\right), [40S](t) = \frac{[40S]_0 - [80S](t)}{1+\frac{k_1'}{k_2}[eIF4F]_0}, [60S](t) = [60S]_0 - [80S](t), \\
&[eIF4F](t) = \frac{k_2 \cdot [eIF4F]_0}{k_1[40S](t)}, [mRNA:40S](t) = \frac{k_1[40S](t)[eIF4F]_0}{k_2}, \\
&[AUG](t) = \frac{[eIF4F]_0}{\left(\frac{1}{k_1'}+\frac{1}{k_2}\right) k_3([60S]_0 - [80S](t))}
\end{aligned}
\quad . \tag{13}
$$

Formulas (12-13) completely describes the dynamics of the system in the case $k_1 \ll k_4/[eIF4F]_0$. However, if $\alpha \approx \beta+\delta$ (i.e., when $k_1 \approx k_4/[eIF4F]_0$) then an other dominant system approximates the last stage of relaxation, when $[60S](t)$ becomes much smaller than $[AUG](t)$. Here the same quasi steady-state asymptotic as in the main body of the paper (Stage 2) is valid (see formula (42-44) of the main text). This completes the analysis of the system behaviour in the case when k_1 is relatively small with respect to other parameters. On the Fig. 1 one can see the comparison of these solutions with numerical simulations.



a) b)

Figure 1: a) Simulation of the non-linear protein translation model with parameters $k_1 = 0.001$, $k_2 = 3$, $k_3 = 50$, $k_4 = 0.1$, $[40S]_0 = 100$, $[60S]_0 = 25$, $[eIF4F]_0 = 6$. b) Same as a) but $k_1 = 0.01$. Circles represent the numerical simulation while solid lines gives the analytical solution.