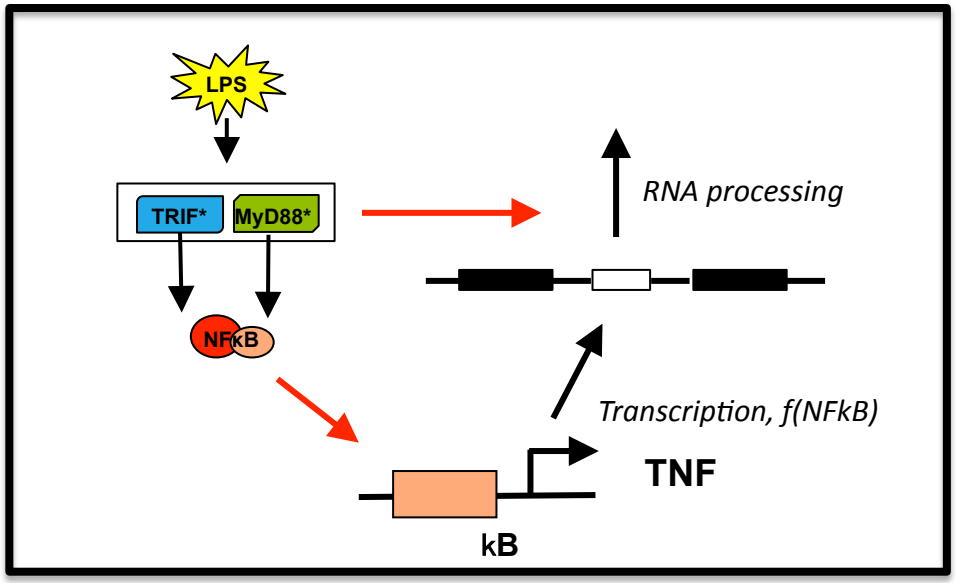
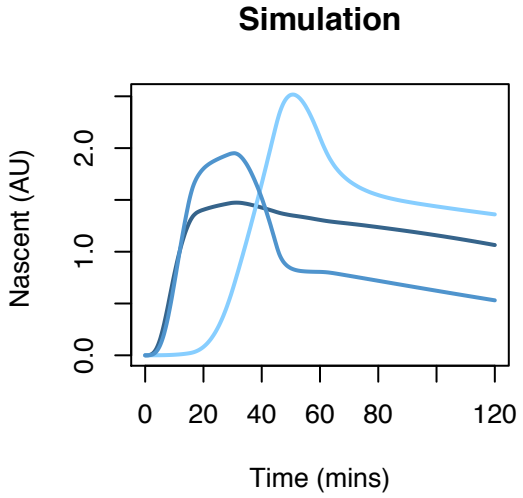
Module1 : Transcription + RNA processing



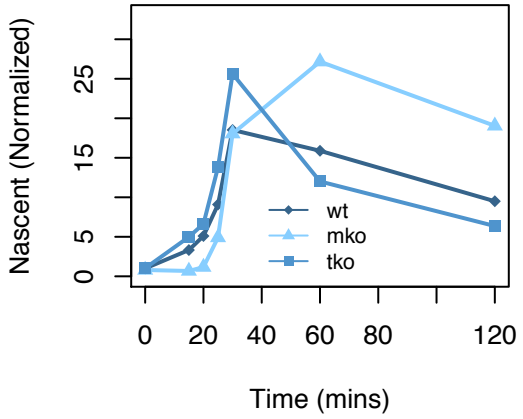


Equation

$$\frac{d[Nascent]}{dt} = V_{tr}\frac{[NF\kappa B_n]^{n_H}}{[NF\kappa B_n]^{n_H} + K_{dtr}^{n_H}} - k_{pr}[Nascent]$$

Initial condition

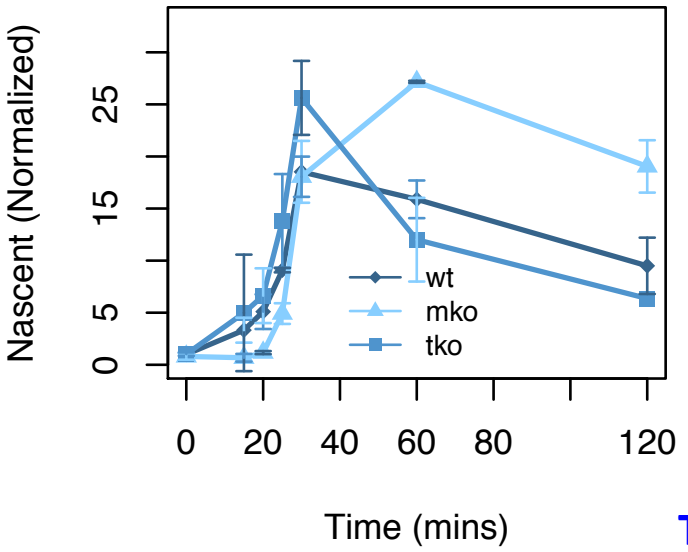
$$[Nascent]_{t=0} = \frac{V_{tr}}{k_{pr}}\frac{[NF\kappa B_n]_{t=0}^{n_H}}{[NF\kappa B_n]_{t=0}^{n_H} + K_{dtr}^{n_H}}$$



Parameters (n_p= 5)

$$V_{tr} = 1(fixed), K_{dTr} = 0.65, n_H = 2, k^{wt}{}_{pr} = 0.4\,\mathrm{min}^{-1}, k^{mko}{}_{pr} = \frac{k^{wt}{}_{pr}}{4.2}, k^{tko}{}_{pr} = \frac{k^{wt}{}_{pr}}{1.5}$$

Experiment



Score function (modified chi square)

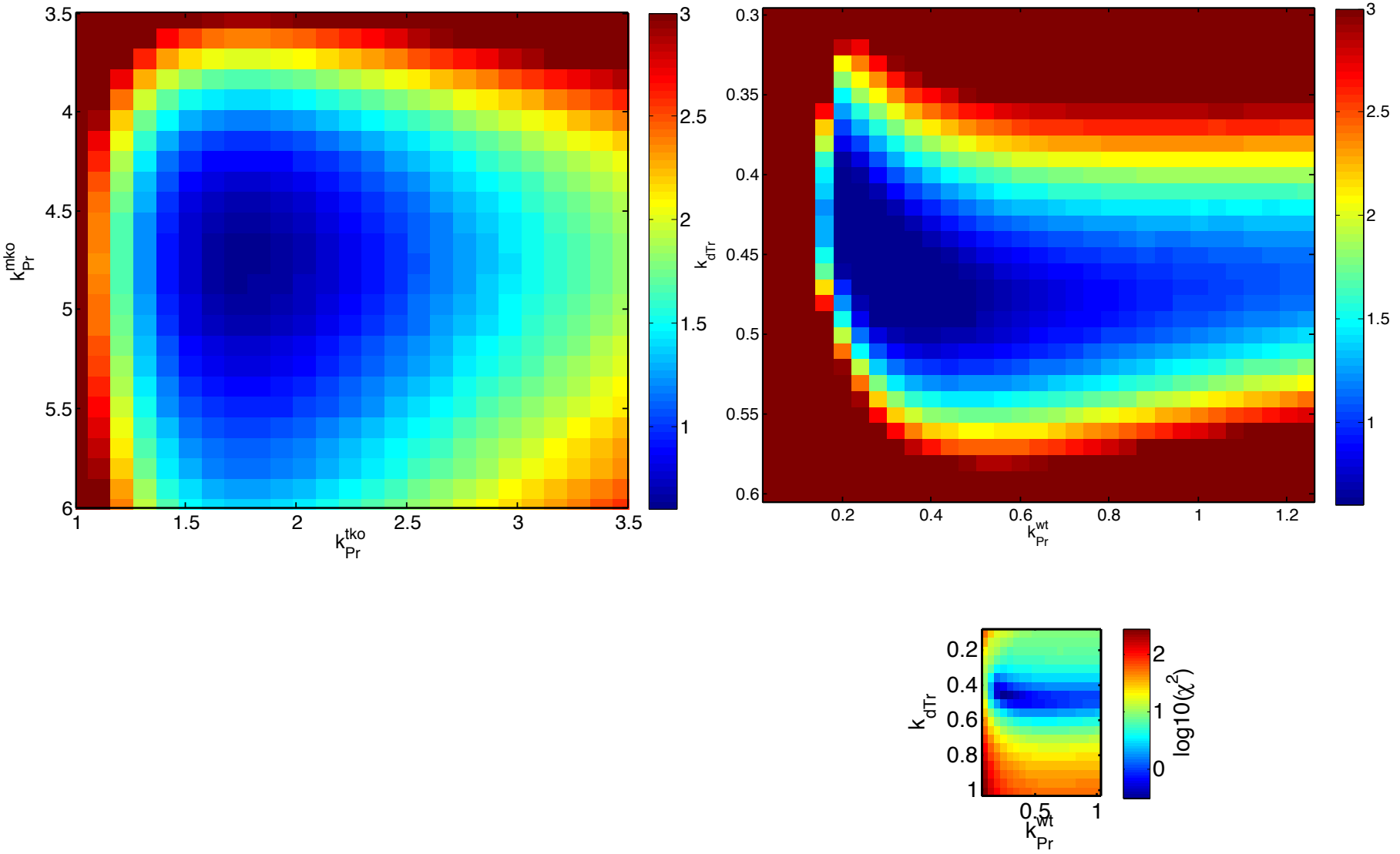
$$\chi^2_{\mathrm{m}} = \frac{1}{n_F - n_p - 1} \sum_{i=1}^{n_F} \frac{(F_i^s - F_i^e)^2}{\sigma_i^2}$$

Table of features (n_F=9)

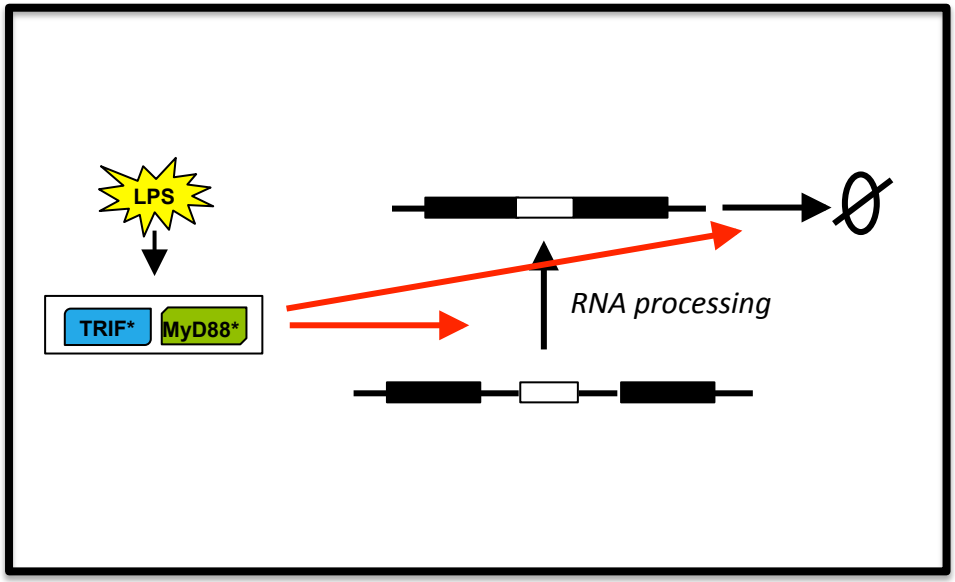
Index(i)	Feature	Value(F^e_i)	Error(σ_i)
1	Peak time (wt)	30 min	5 min
2	Peak time (mko)	60 min	10 min
3	Peak time (tko)	30 min	5 min
4	Peak_wt/Peak_mko	0.68	0.11
5	Peak_wt/peak_tko	0.75	0.22
6	Wt(60)/tko(60)	1.55	0.67
7	Wt(60)/mko(60)	0.59	0.07
8	Wt(120)/mko(120)	0.52	0.21
9	Wt(120)/tko(120)	1.49	0.43

How well the model capture the features.

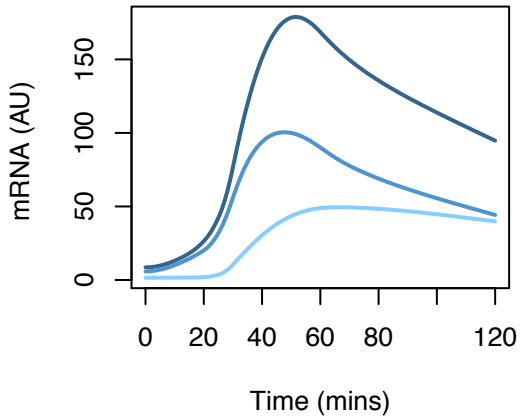
Score heat map for different parameters.



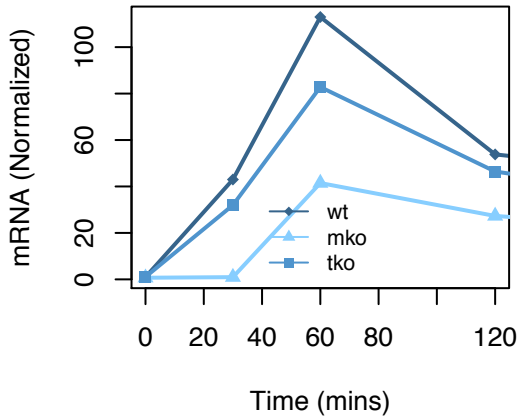
Module 2: RNA processing + stabilization



Simulation



Experiment



Equation

$$\frac{d[mRNA]}{dt} = k_{pr}[Nascent] - k_{\deg mRNA}[mRNA]$$

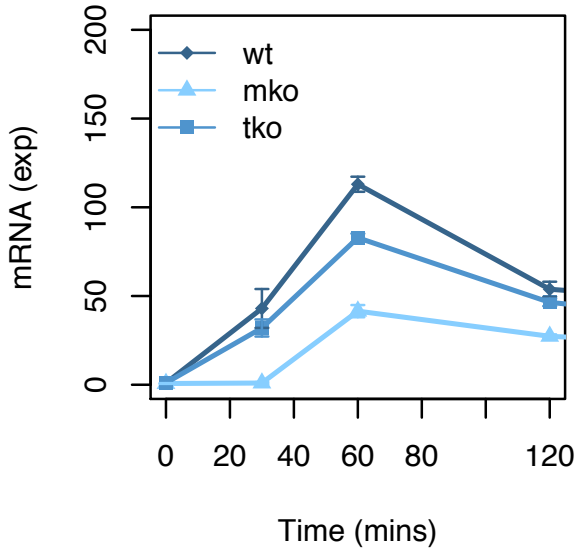
Initial condition

$$[mRNA]_{t=0} = \frac{k_{pr}}{k_{\deg mRNA}}[nascent]_{t=0}$$

Parameters (n_p= 5)

$$k^{wt}{}_{pr} = 0.6\,\min^{-1}, k^{mko}{}_{pr} = \frac{k^{wt}{}_{pr}}{4.5}, k^{tko}{}_{pr} = \frac{k^{wt}{}_{pr}}{1.5}, k^{tko}{}_{\deg mRNA} = 0.07\,\min^{-1}, k^{wt/mko}{}_{\deg mRNA} = \begin{cases} -\frac{0.05}{30}t + 0.07\,\min^{-1} (0 \le t < 30\,\min) \\ \frac{0.05}{30}(t-30) + 0.02\,\min^{-1} (30\,\min \le t < 60\,\min) \\ 0.07\,\min^{-1} (60\,\min \le t) \end{cases}$$

Experimental data



Score function (modified chi square)

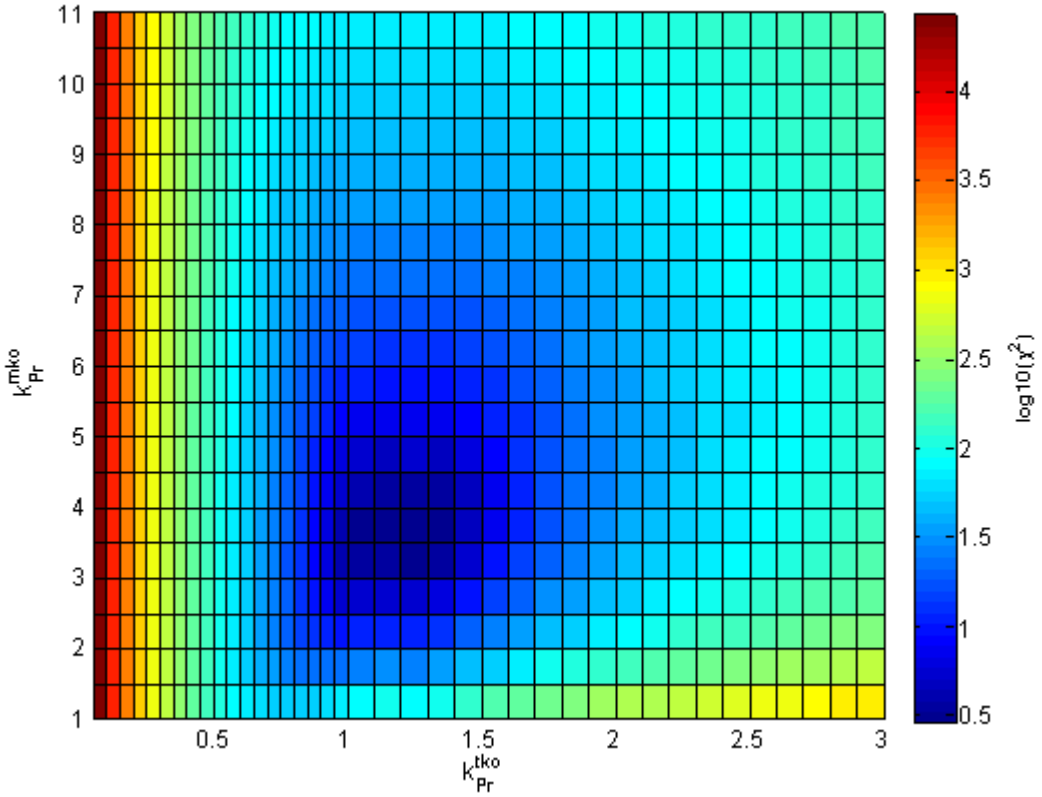
$$\chi^2_{\mathrm{m}} = \frac{1}{n_F - n_p - 1} \sum_{i=1}^{n_F} \frac{(F_i^s - F_i^e)^2}{\sigma_i^2}$$

Table of features (n_F=7)

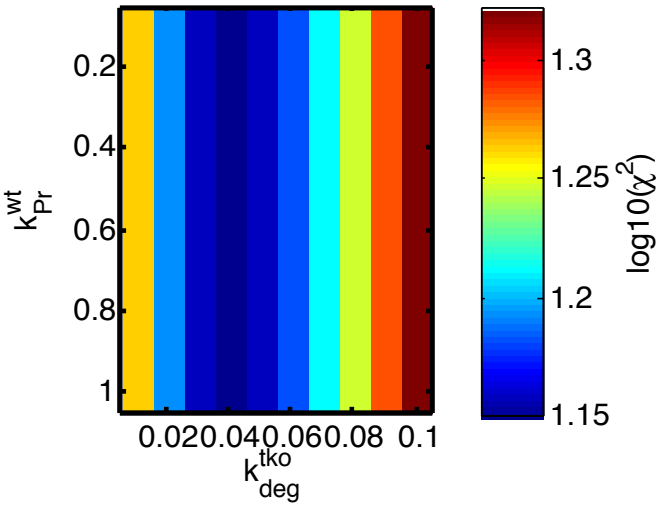
Index(i)	Feature	Value(F^s_i)	Error(σ_i)
1	Peak time (wt)	60 min	10 min
2	Peak time (mko)	60 min	10 min
3	Peak time (tko)	60 min	10 min
4	Peak_tko/Peak_wt	0.73	0.05
5	Peak_mko/peak_tko	0.50	0.06
6	wt_120/mko_120	1.98	0.23
7	Wt_120/tko_120	1.17	0.14

How well the model capture the features.

Score heat map for different parameters.



As long as keep the same ratios of processing rate between wt, mko and tko, the fit doesn't depend on the processing rate.



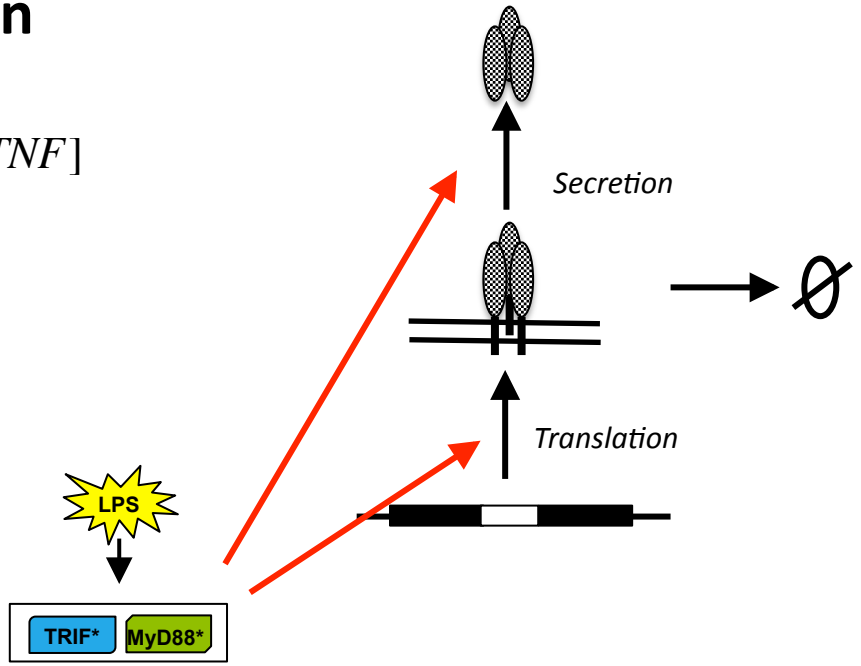
Module 3: Translation + Secretion

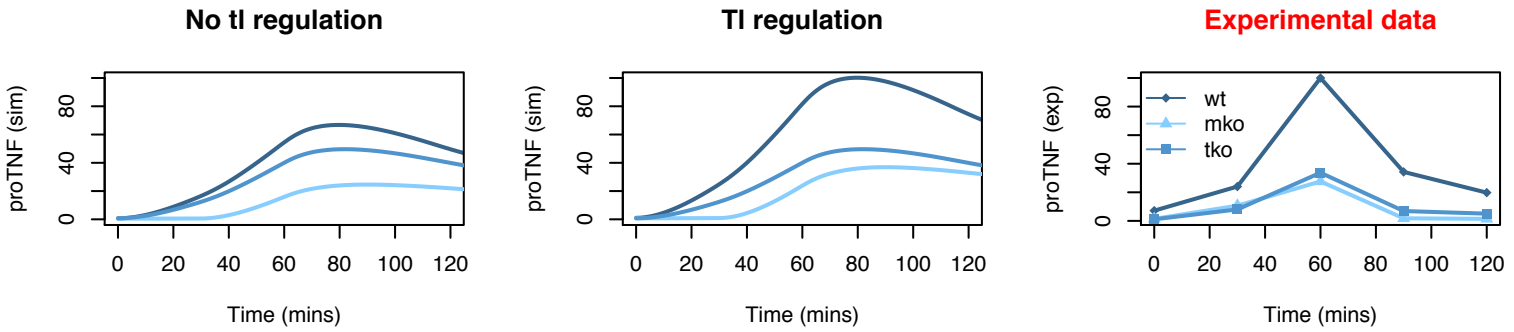
$$\frac{d[proTNF]}{dt} = k_{tl}[mRNA] - k_{\deg P}[proTNF] - k_{\sec}[proTNF]$$

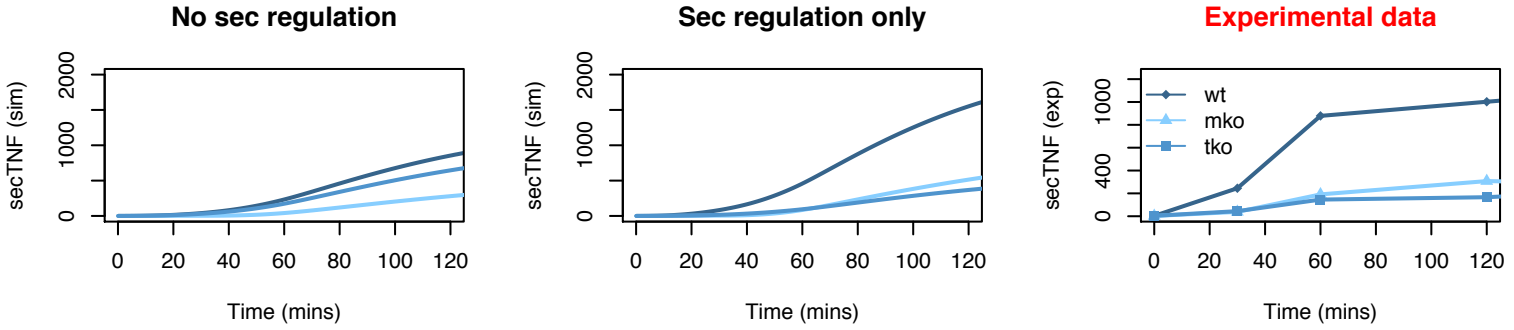
$$[\sec TNF](t) = \int_0^t k_{\sec}[proTNF]dt$$

$$k_{tl}^{\ wt/mko} = 0.05\,\min^{-1}, k_{tl}^{\ tko} = \frac{k_{tl}^{\ wt}}{1.5}, k_{\deg P} = 0.07\,\min^{-1},$$

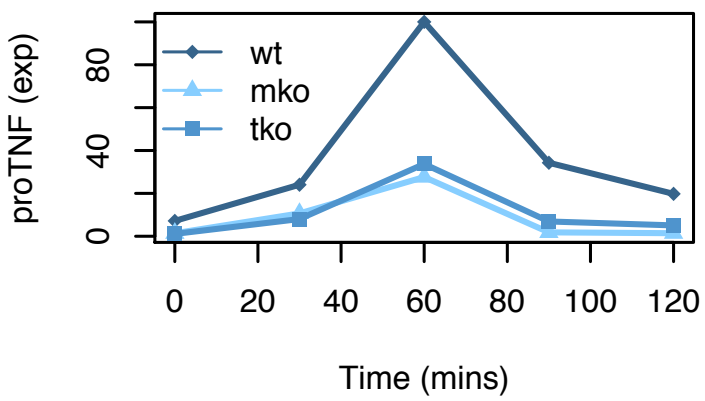
$$k_{\sec}^{\ wt/mko} = 0.07\,\min^{-1}, k_{\sec}^{\ tko} = \frac{k_{tl}^{\ wt}}{5}$$





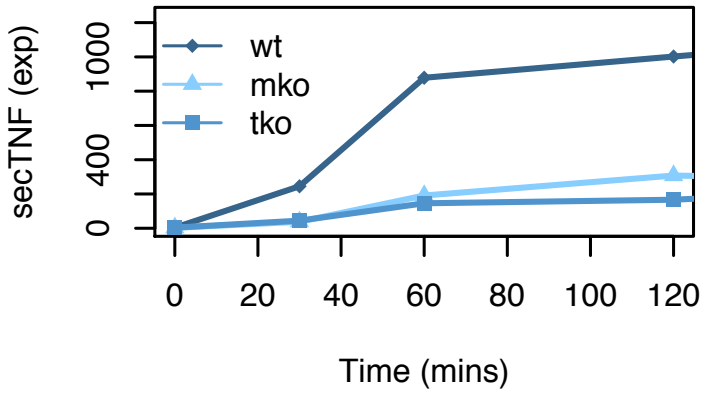


Experimental data



Index(i)	Feature	Value(F^s_i)	Error(σ_i)
1	Peak time (wt)	60 min	10 min
2	Peak time (mko)	60 min	10 min
3	Peak time (tko)	60 min	10 min
4	Peak_tko/Peak_wt	0.34	0.06
5	Peak_mko/peak_tko	0.82	0.14
6	wt_120/Peak_wt	0.20	0.04
7	Wt_120/tko_120	3.9	0.65
8	wt_120/mko_120	14	2.3
9	Tko_30/mko_30	0.75	0.12

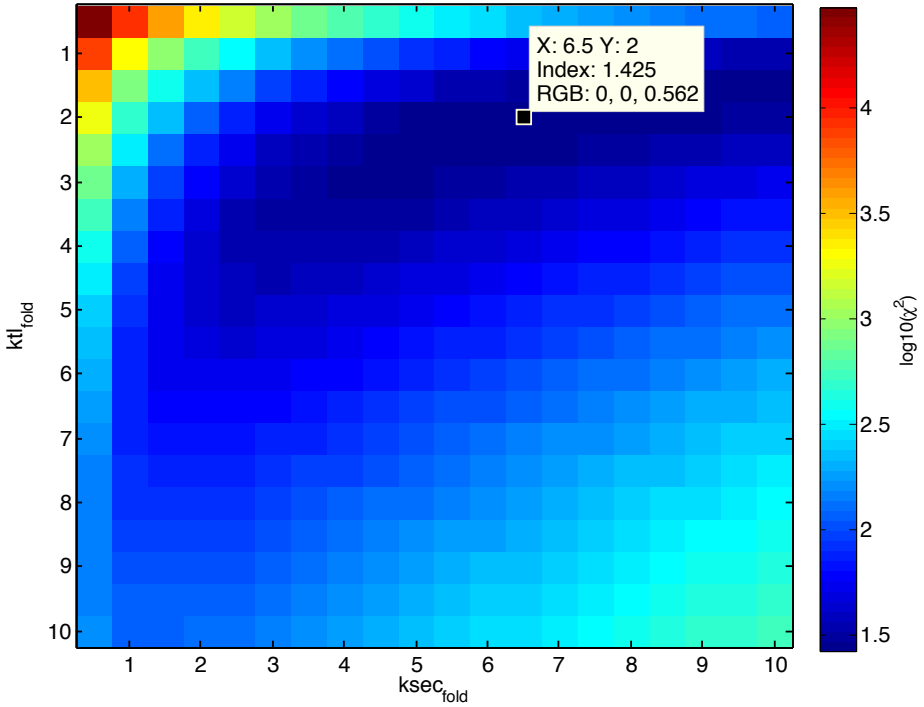
Experimental data

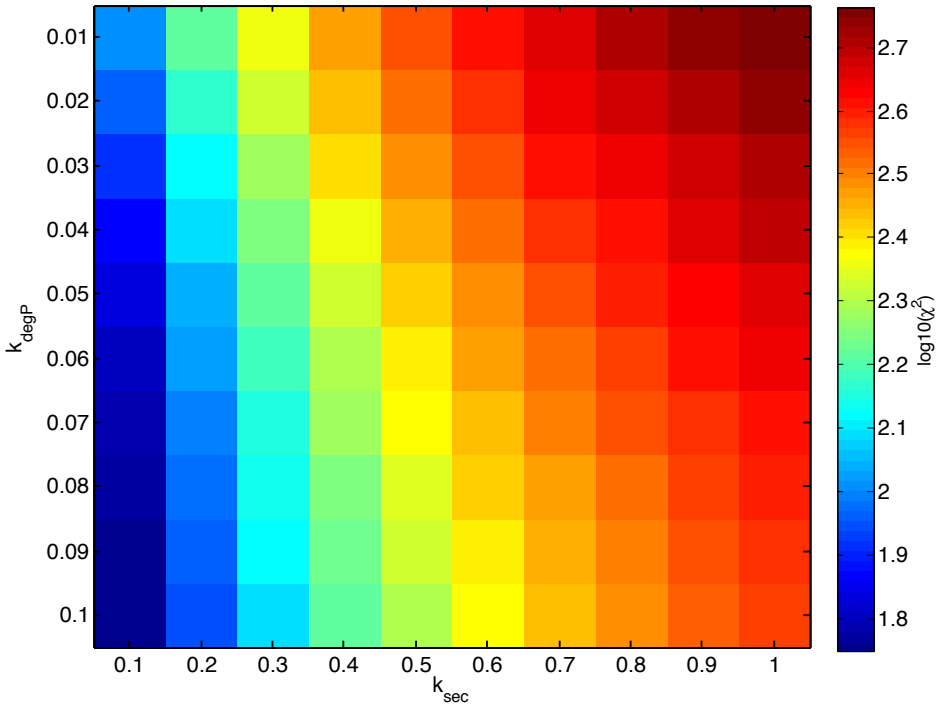


Index(i)	Feature	Value(F^s_i)	Error(σ_i)
1	tko_60/wt_60	0.17	0.03
2	Mko_60/tko_60	1.4	0.54
3	Tko_120/wt_120	0.17	0.03
4	Mko_120/tko_120	1.9	0.76
5	wt_120/wt_60	1.2	0.16

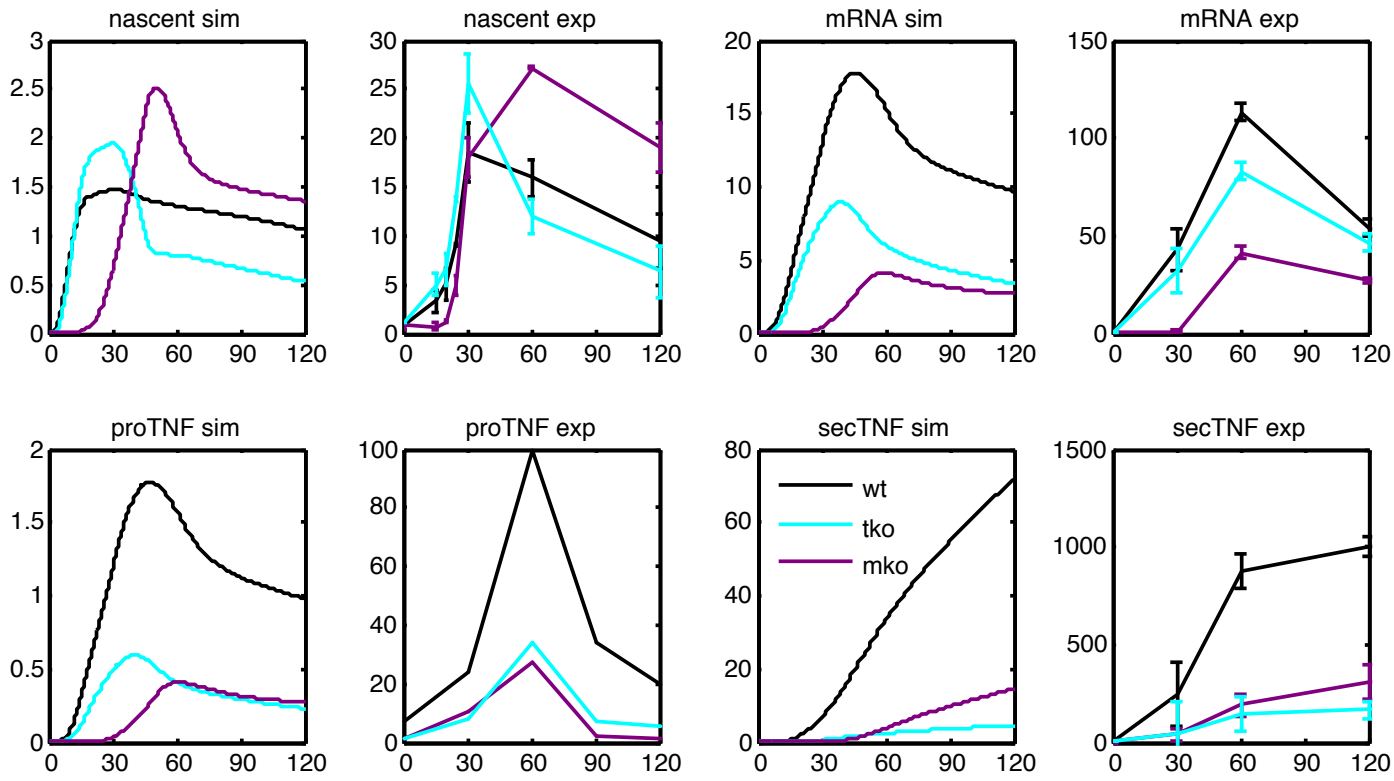
How well the model capture the features.

Score heat map for different parameters.





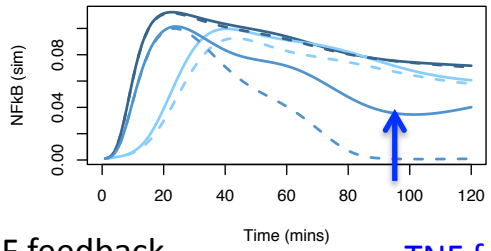
Module 1 to 3, together (NFkB as input)



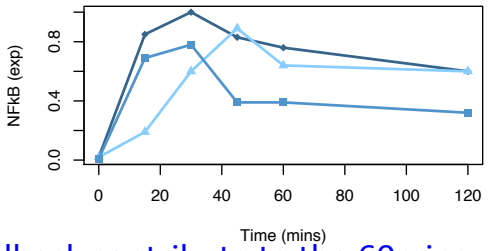
ID	Name	Values
1	Km_tr	0.65
2	Km_tr_fold	2
3	V_tr	1
4	k_pr	0.4
5	k_sec	0.07
6	k_tl	0.05
7	kdeg_m	0.02
8	kdeg_p	0.07
9	n	2
10	pr_fold_mko	4.2
11	pr_fold_tko	1.5
12	sec_fold	5
13	tl_fold	1.5

Linking with TLR4 model

Simulation

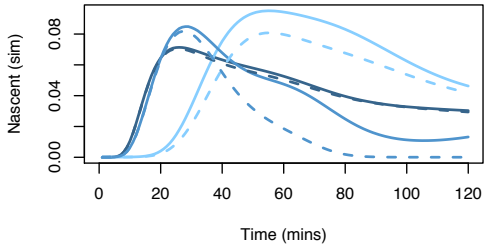


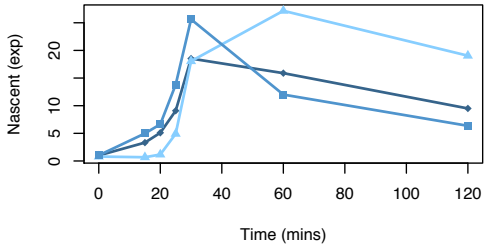
Experimental data

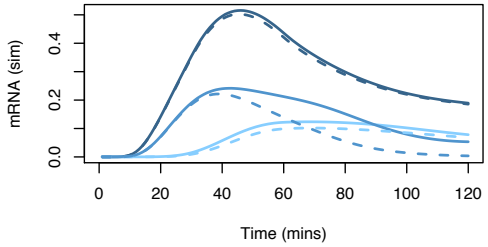


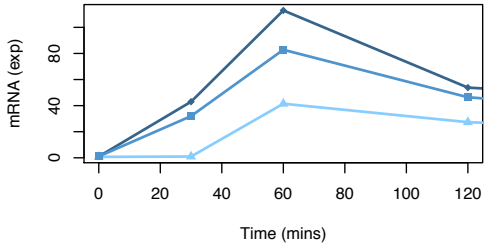
Dashed lines: without TNF feedback
Solid lines: with TNF feedback

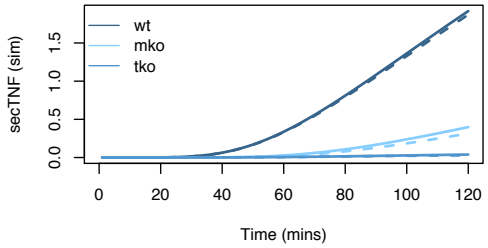
TNF feedback contribute to the 60mins -120mins activity in trif knockout

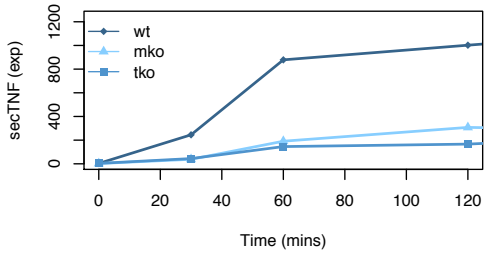






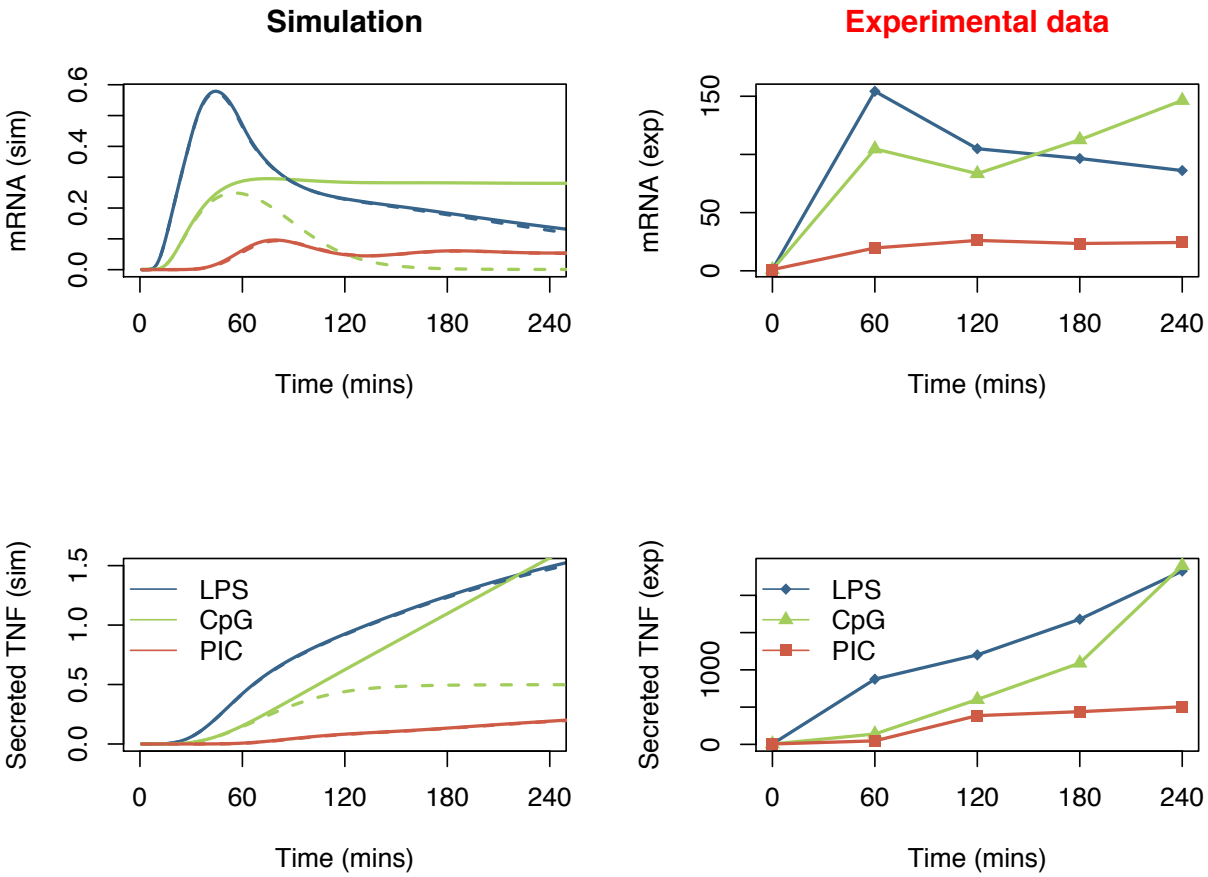






CpG and PIC stimulation (with / without TNF feedback)

Feedback toggled by TNFR synthesis



CpG and PIC stimulation (with / without TNF feedback)