ACS Synthetic Biology

pubs.acs.org/synthbio
Addition/Correction

Correction to "Cell-Free Gene Expression Dynamics in Synthetic Cell Populations"

David T. Gonzales, Naresh Yandrapalli, Tom Robinson, Christoph Zechner,* and T-Y. Dora Tang*

*ACS Synth. Biol.***2022***11*120521510.1021/acssynbio.1c00376

Cite This: *ACS Synth. Biol.* 2024, 13, 3471−3484

Read Online

ACCESS | Metrics & More | Article Recommendations

After publication, we identified an error in the calculation of the likelihood threshold used to determine approximate 95%-confidence intervals from profile likelihoods. The likelihood-based confidence intervals are estimated as the regions with

$$\left\{\theta_i \,\middle|\, PL(\theta_i) + \ln p(D \mid \hat{\theta}) < \frac{\chi^2(\alpha, df)}{2}\right\}$$

where $\chi^2(\alpha,df)$ is the α-quantile of the chi-squared distribution with df degrees of freedom, which is set to the number of model

Original text	Correction (highlighted in yellow)	Location
The parameters K_l and τ_d were weakly identifiable, and b is non-identifiable.	The parameter τ_d is weakly identifiable and b is non-identifiable.	Main text, page 211
Likelihood-based CIs of each parameter were estimated by the regions in $\{\theta_i \vert PL(\theta_i) + \ln p(D\vert\hat{\theta}) < \chi^2(\alpha, df)\}$ (11) where $\chi^2(\alpha, df)$ is the chi-squared distribution with α=0.95 confidence level and df degrees of freedom, which is the number of parameters of the model.	Likelihood-based CIs of each parameter were estimated by the regions in $\{\theta_i \vert PL(\theta_i) + \ln p(D\vert\hat{\theta}) < \chi^2(\alpha, df)/2\}$ (11) where $\chi^2(\alpha, df)$ is the chi-squared distribution with α=0.95 confidence level and df degrees of freedom, which is the number of parameters of the model.	Main text, page 212
Likelihood-based confidence intervals were estimated as the regions with $\{\theta_i \vert PL(\theta_i) + \ln p(D\vert\hat{\theta}) < \chi^2(\alpha, df)\}$ (S34) where $\chi^2(\alpha, df)$ is the chi-squared distribution with α=0.95 confidence level and df degrees of freedom, which here is the number of parameters. Graphically, this means that the confidence intervals are found at the intersections of the profile likelihood and the significance threshold horizontal line at $-\ln p(D\vert\hat{\theta}) + \chi^2(\alpha, df)$.	Likelihood-based confidence intervals were estimated as the regions with $\{\theta_i \vert PL(\theta_i) + \ln p(D\vert\hat{\theta}) < \chi^2(\alpha, df)/2\}$ (S34) where $\chi^2(\alpha, df)$ is the chi-squared distribution with α=0.95 confidence level and df degrees of freedom, which here is the number of parameters. Graphically, this means that the confidence intervals are found at the intersections of the profile likelihood and the significance threshold horizontal line at $-\ln p(D\vert\hat{\theta}) + \chi^2(\alpha, df)/2$.	Supplementary Material, page S25

Published: October 1, 2024

https://doi.org/10.1021/acssynbio.4c00583

Table 1a. (Original) Parameter Estimates and Likelihood-Based 95% CI from the Resource-Limited Gene Expression Model Fitting on Bulk DNA and RNA Titration Experiments ($\hat{\theta}_{\text{bulk}}$) and Synthetic Cell Population DNA Titration Experiments ($\hat{\theta}_{\text{cell}}$)[a]

parameter	description	$\hat{\boldsymbol{\theta}}_{bulk}$	95% CI	$\hat{\boldsymbol{\theta}}_{cell}$	95% CI	units
k_r	RNA transcription rate	2894	2728 - 3674	1899	1631 - 3537	nM/h
K_r	Dissociation constant between RNAP and DNA	3.67	2.89-5.68	8.86	6.97 - 18.66	nM
δ_r	RNA degradation rate	0.0392	0.0361-0.0422	0.0081	0.00239 - 0.0143	1/h
k_p	Protein translation rate	2568	2211-3108	1954	1617 - 2696	nM/h
K_p	Dissociation constant between ribosome and RNA	703	530-1347	1319	819 - 2038	nM
k_{mat}	mCherry maturation rate	2.15	(±0.12)	2.15	(±0.12)	1/h
δ_{TsR}	TsR degradation rate	0.231	0.171-0.298	0.154	0.136 - 0.175	1/h
δ_{TlR}	TlR degradation rate	0.0884	0.0441-0.1187	0.244	0.184 - 0.684	1/h
K_l	Michaelis–Menten constant for TlR degradation	1.21×10^{-6}	$-\infty$ - $+\infty$	0.232	$-\infty$ - 0.713	
A	scaling factor for consumption of TsR with transcription	4.45×10^{-4}	4.18×10^{-4} - 4.57×10^{-4}	6.60×10^{-4}	6.21×10^{-4} - 6.74×10^{-4}	
b	scaling factor for consumption of TlR with translation	1.78×10^{-4}	1.18×10^{-4} - 2.42×10^{-4}	4.46×10^{-13}	$-\infty$ - $+\infty$	
τ_d	time delay for protein translation	0.433	0.254 - 0.560	0.0576	$-\infty$ - 0.279	h
τ_l	time lag between the reaction start and data collection	2.81×10^{-9}	$-\infty$ - $+\infty$	0.457	0.342 - 0.535	h

[a] Parameters with CIs at $-\infty$ and/or $+\infty$ are non/weakly-identifiable within one order of magnitude from $\hat{\theta}$.

Table 1b. (Corrected) Parameter Estimates and Likelihood-Based 95% CI from the Resource-Limited Gene Expression Model Fitting on Bulk DNA and RNA Titration Experiments ($\hat{\theta}_{\text{bulk}}$) and Synthetic Cell Population DNA Titration Experiments ($\hat{\theta}_{\text{cell}}$)[a]

parameter	description	$\hat{\theta}_{bulk}$	95% CI	$\hat{\theta}_{cell}$	95% CI	units
k_r	RNA transcription rate	2894	2811 - 3283	1899	1765 - 2740	nM/h
K_r	Dissociation constant between RNAP and DNA	3.67	3.28 - 4.67	8.86	7.92 - 14.78	nM
δ_r	RNA degradation rate	0.0392	0.0377 - 0.0407	0.0081	0.0045 - 0.0120	1/h
k_p	Protein translation rate	2568	2390 - 2837	1954	1786 - 2325	nM/h
K_p	Dissociation constant between ribosome and RNA	703	615 - 1115	1319	1043 - 1676	nM
k_{mat}	mCherry maturation rate	2.15	(±0.12)	2.15	(±0.12)	1/h
δ_{TsR}	TsR degradation rate	0.231	0.202 - 0.264	0.154	0.145 - 165	1/h
δ_{TlR}	TlR degradation rate	0.0884	0.0550 - 0.1035	0.244	0.214 - 0.503	1/h
K_l	Michaelis–Menten constant for TlR degradation	1.21×10^{-6}	$-\infty$ - $+\infty$	0.232	0.074 - 0.646	
a	scaling factor for consumption of TsR with transcription	4.45×10^{-4}	4.31×10^{-4} - 4.51×10^{-4}	6.60×10^{-4}	6.40×10^{-4} - 6.67×10^{-4}	
b	scaling factor for consumption of TlR with translation	1.78×10^{-4}	1.48×10^{-4} - 2.10×10^{-4}	4.46×10^{-13}	$-\infty$ - $+\infty$	
τ_d	time delay for protein translation	0.433	0.341 - 0.491	0.0576	$-\infty$ - 0.194	h
τ_l	time lag between the reaction start and data collection	2.81×10^{-9}	$-\infty$ - $+\infty$	0.457	0.399 - 0.496	h

[a] Parameters with CIs at $-\infty$ and/or $+\infty$ are non/weakly-identifiable within one order of magnitude from $\hat{\theta}$.

Table S26a. (Original) Parameter Estimates and 95% Likelihood-Based Confidence Intervals of Model 2 Using Synthetic Cell Population Data

Parameter	$\hat{\theta}$	95% CI	
k_r	1899	1631	3537
K_r	8.86	6.98	18.66
δ_r	0.0081	0.00239	0.0143
k_p	1954	1617	2696
K_p	1319	819	2038
k_{mat}	2.15	(±0.12)	
δ_{TsR}	0.154	0.136	0.175
δ_{TlR}	0.244	0.184	0.684
K_l	0.232	$-\infty$	0.713
a	6.60E-04	6.21E-4	6.74E-4
b	4.46E-13	$-\infty$	$+\infty$
τ_d	0.0576	$-\infty$	0.279
σ_r	23.48	21.83	28.25
σ_p	71.58	66.40	86.09
τ_l	0.457	0.342	0.535

Table S26b. (Corrected) Parameter Estimates and 95% Likelihood-Based Confidence Intervals of Model 2 Using Synthetic Cell Population Data

Parameter	$\hat{\theta}$	95% CI	
k_r	1899	1765	2740
K_r	8.86	7.92	14.78
δ_r	0.0081	0.0045	0.0120
k_p	1954	1786	2325
K_p	1319	1043	1676
k_{mat}	2.15	(±0.12)	
δ_{TsR}	0.154	0.145	0.165
δ_{TlR}	0.244	0.214	0.503
K_l	0.232	0.074	0.646
a	6.60E-04	6.40E-04	6.67E-04
b	4.46E-13	$-\infty$	$+\infty$
τ_d	0.0576	$-\infty$	0.1942
σ_r	23.48	22.64	25.90
σ_p	71.58	68.91	79.06
τ_l	0.457	0.399	0.4960

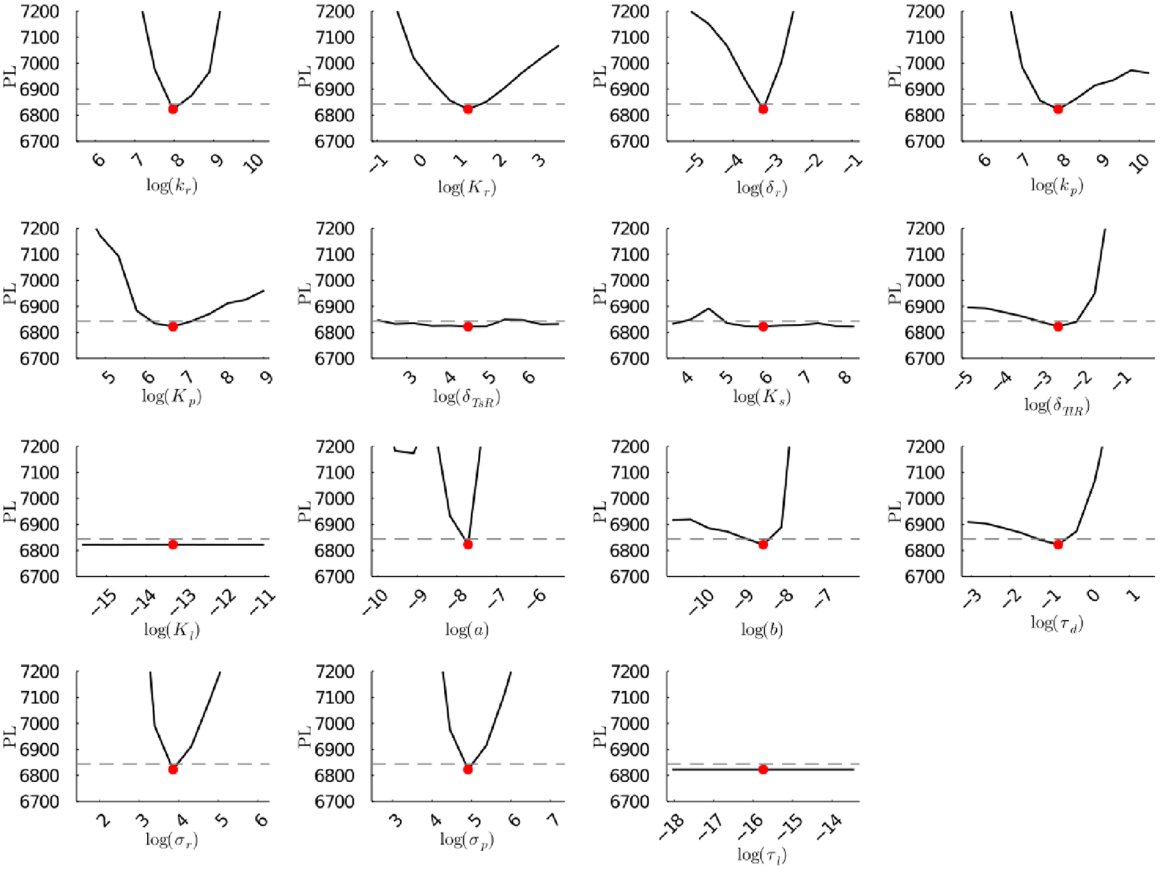

Figure S25a. (Original) Profile likelihoods of parameters from model 1. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The y-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the x-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

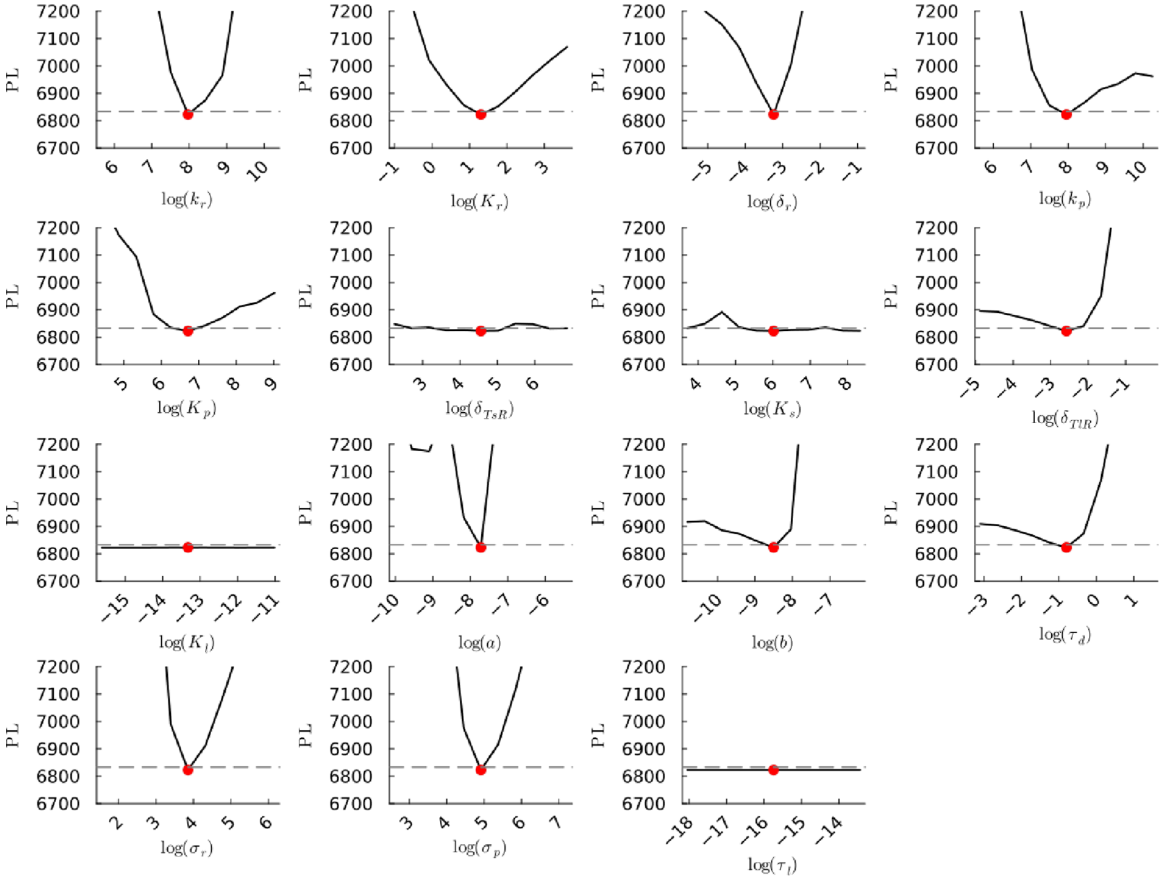

Figure S25b. (Corrected) Profile likelihoods of parameters from model 1. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

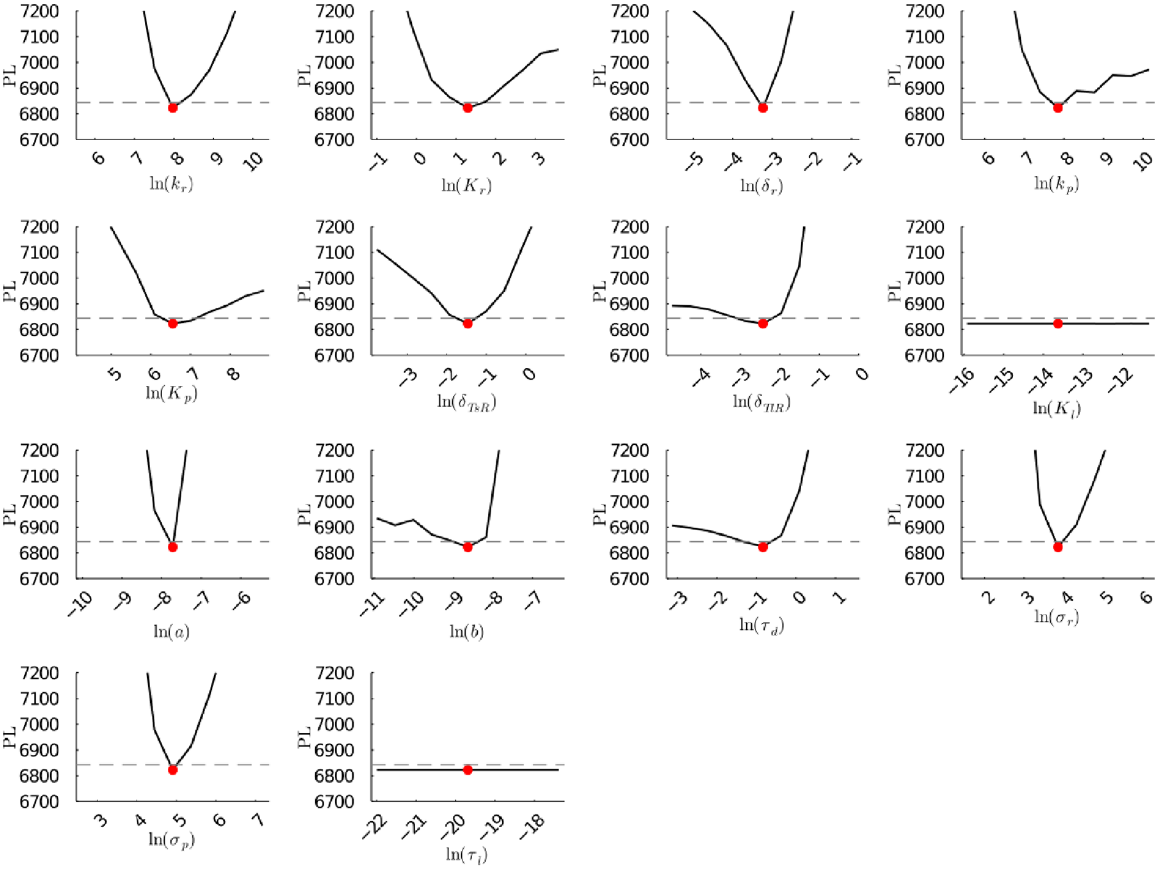

Figure S26a. (Original) Profile likelihoods of parameters from model 2. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

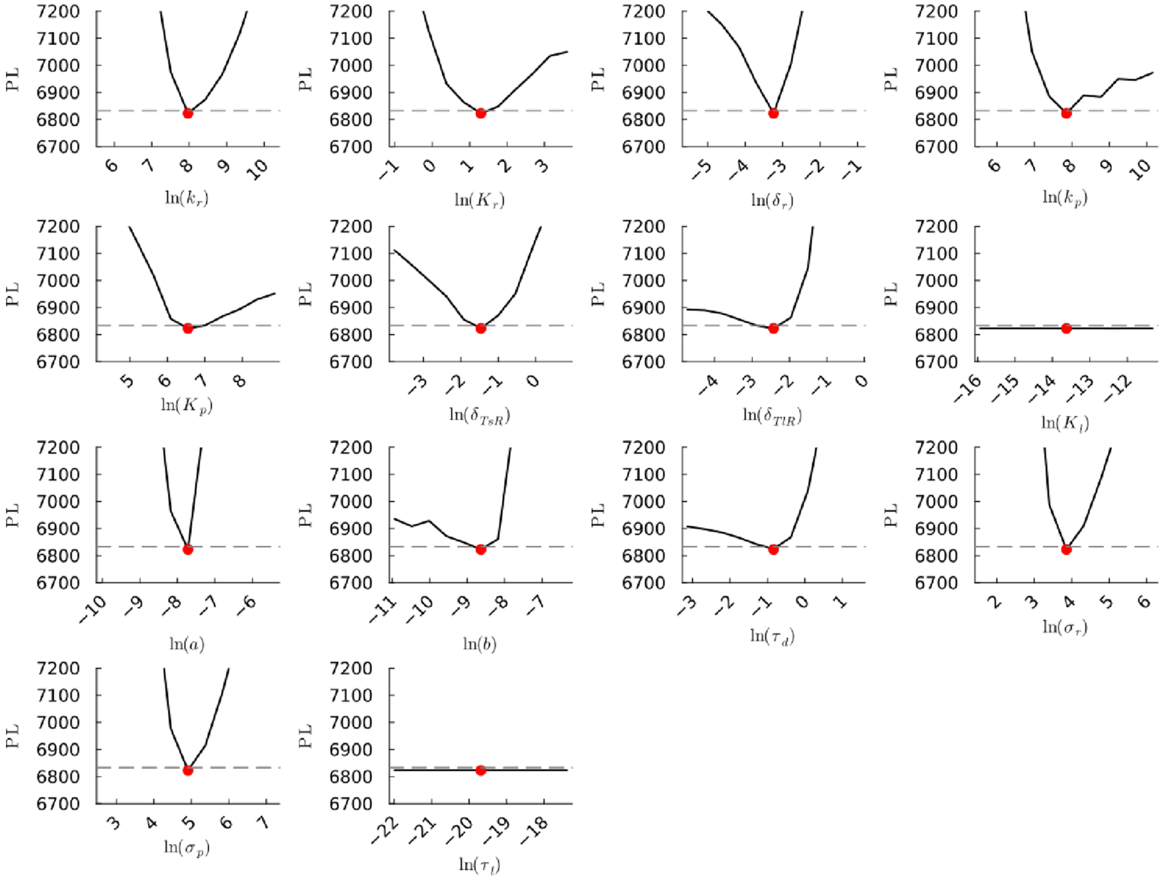

Figure S26b. (Corrected) Profile likelihoods of parameters from model 2. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

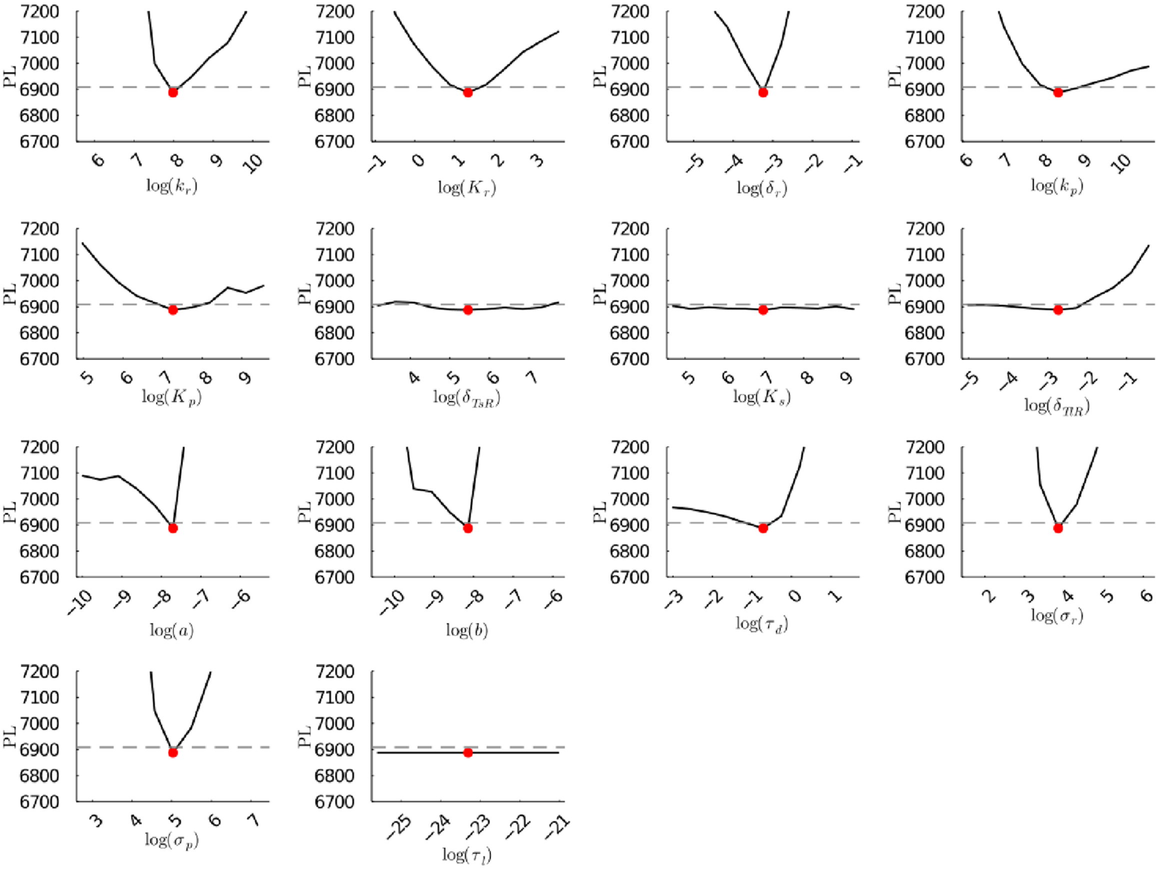

Figure S27a. (Original) Profile likelihoods of parameters from model 3. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

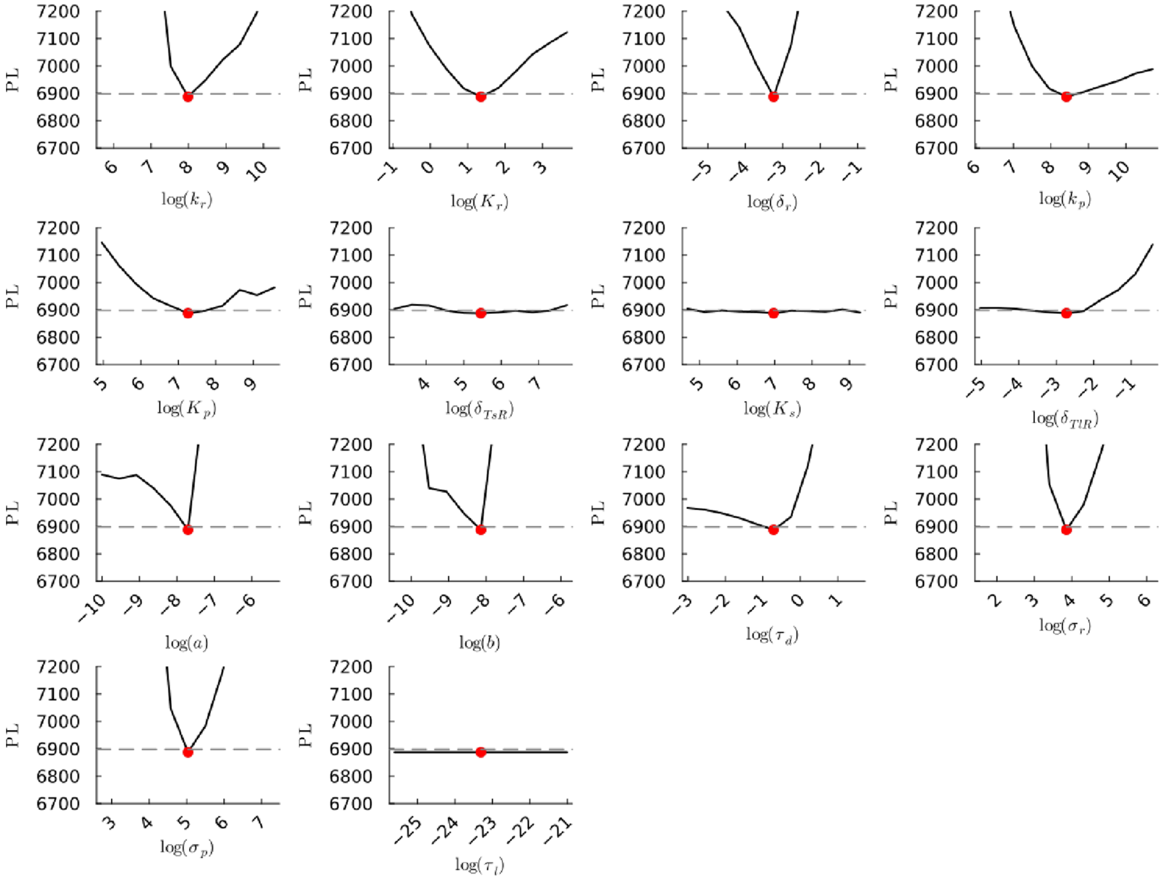

Figure S27b. (Corrected) Profile likelihoods of parameters from model 3. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

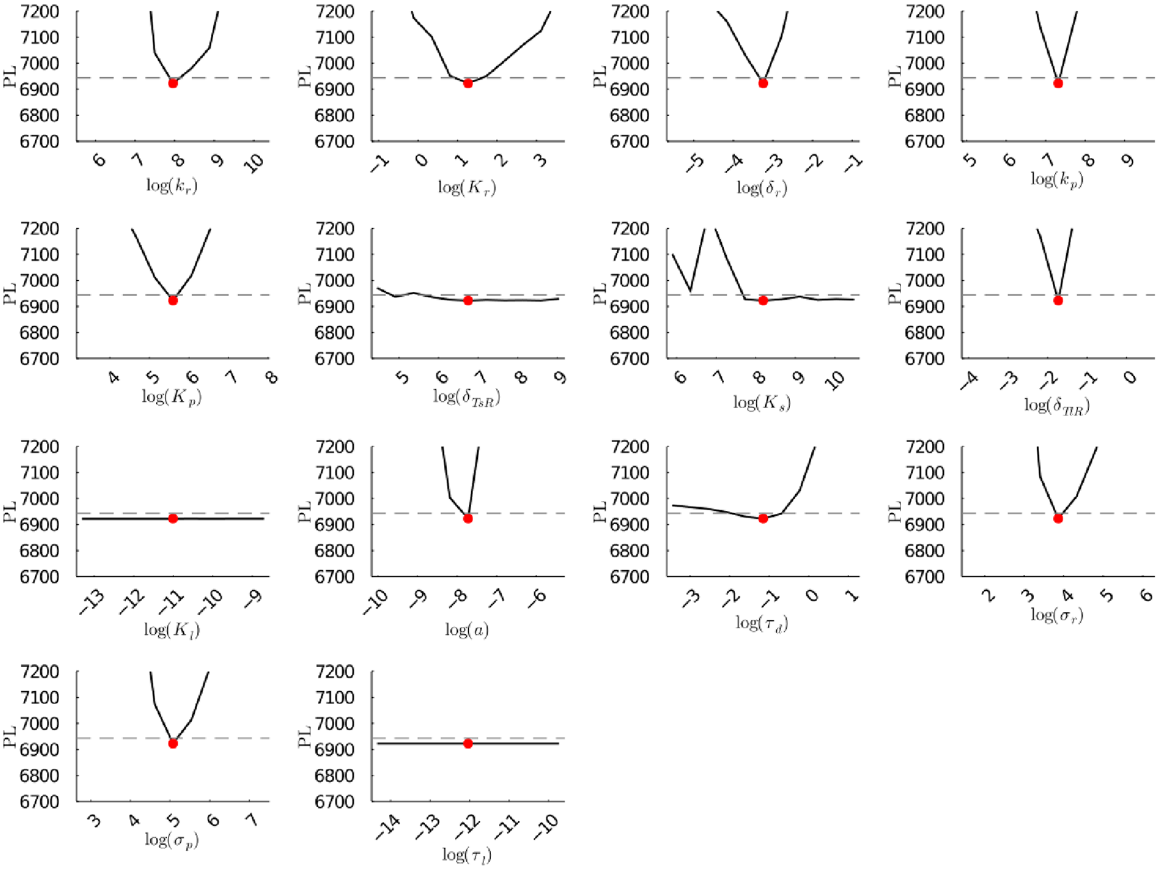

Figure S28a. (Original) Profile likelihoods of parameters from model 4. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

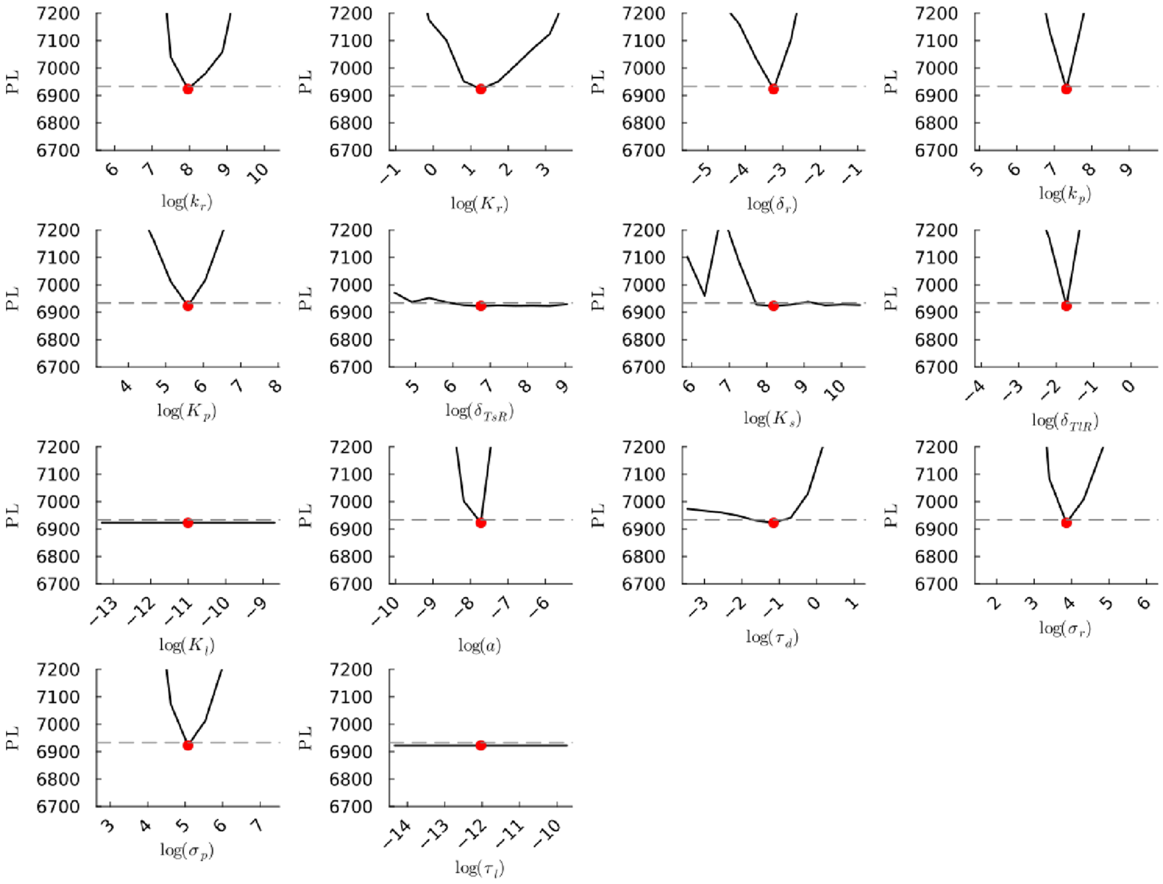

Figure S28b. (Corrected) Profile likelihoods of parameters from model 4. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

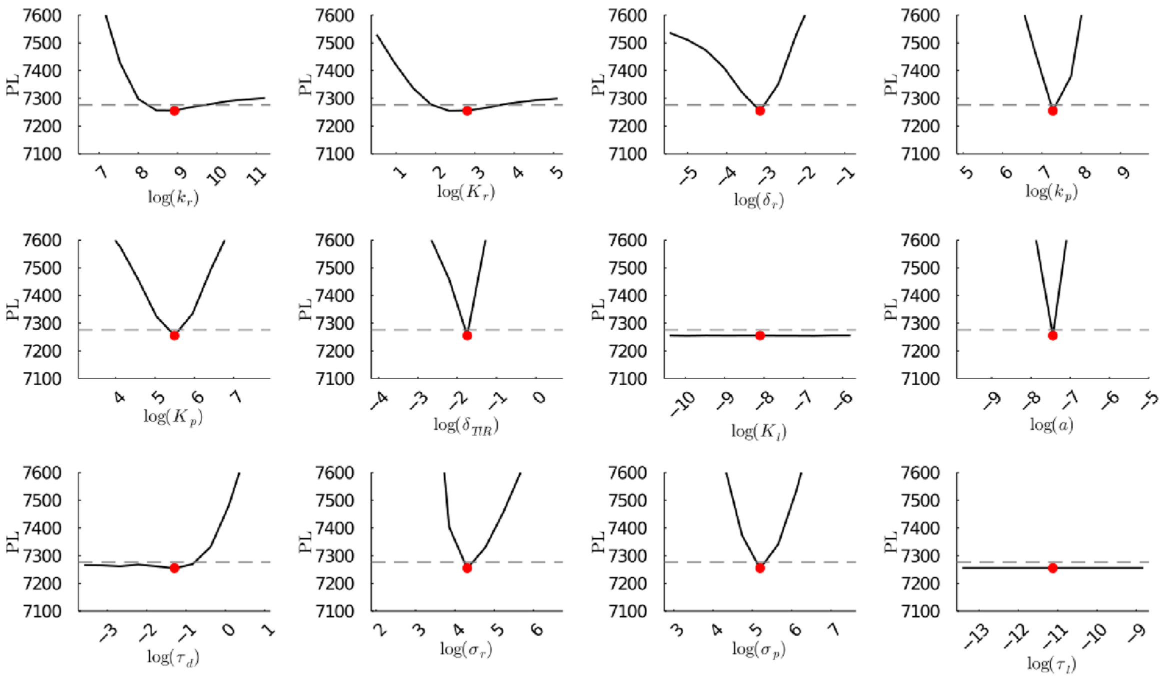

Figure S29a. (Original) Profile likelihoods of parameters from model 5. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

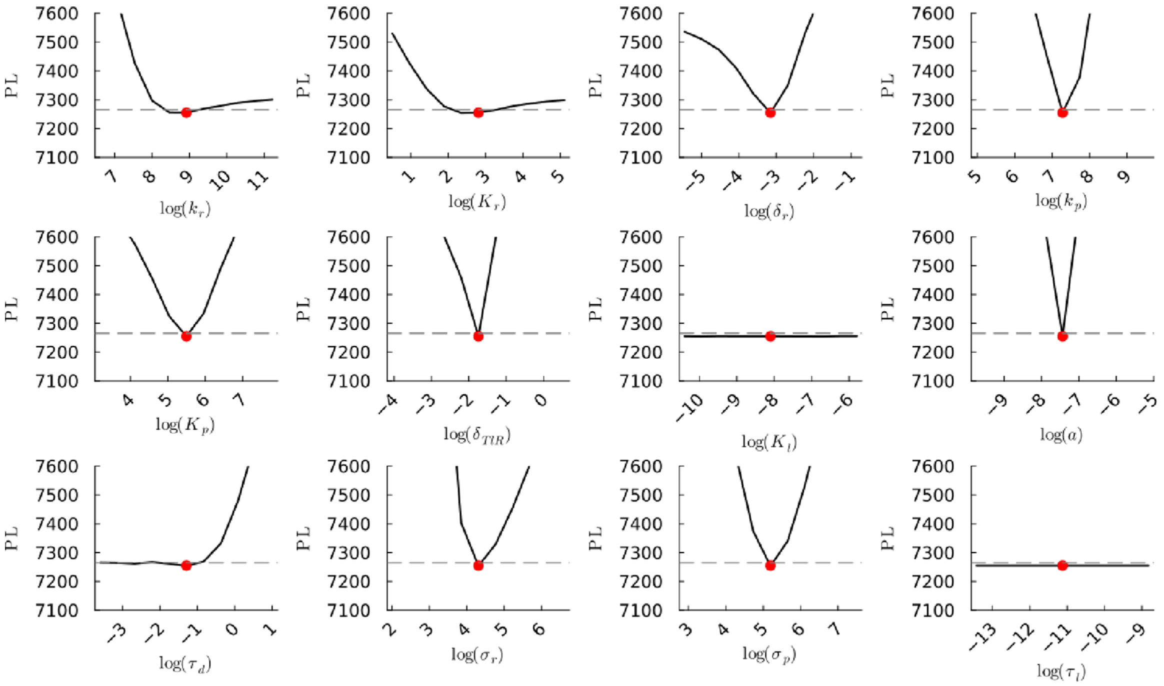

Figure S29b. (Corrected) Profile likelihoods of parameters from model 5. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

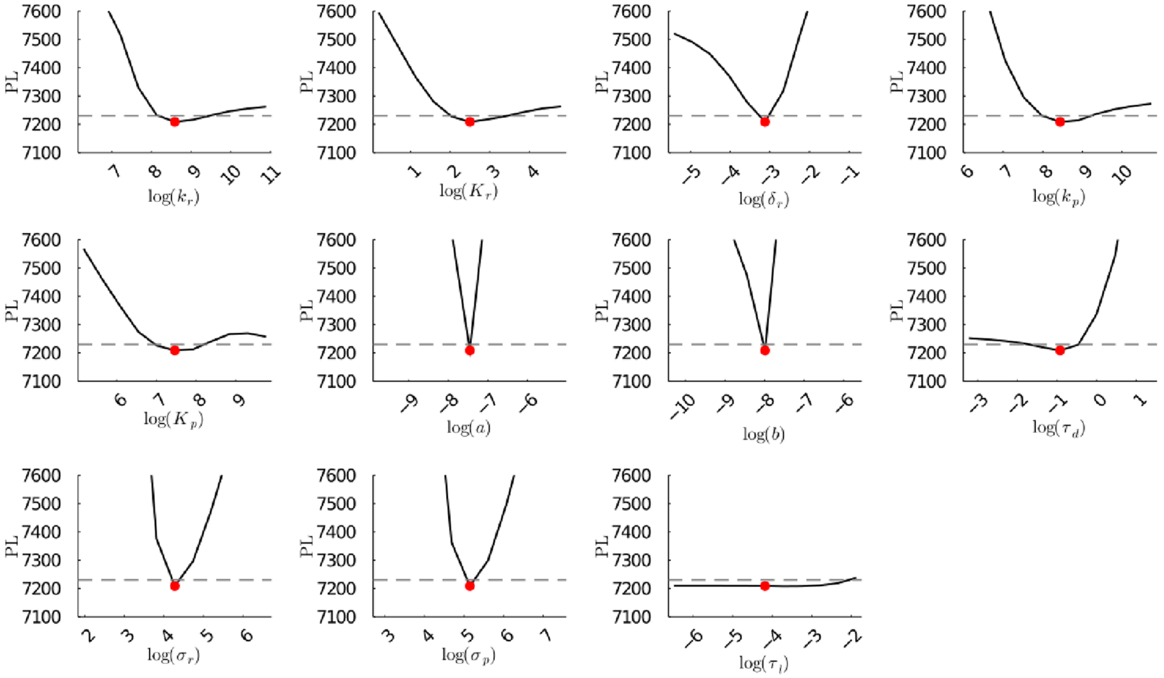

Figure S30a. (Original) Profile likelihoods of parameters from model 6. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

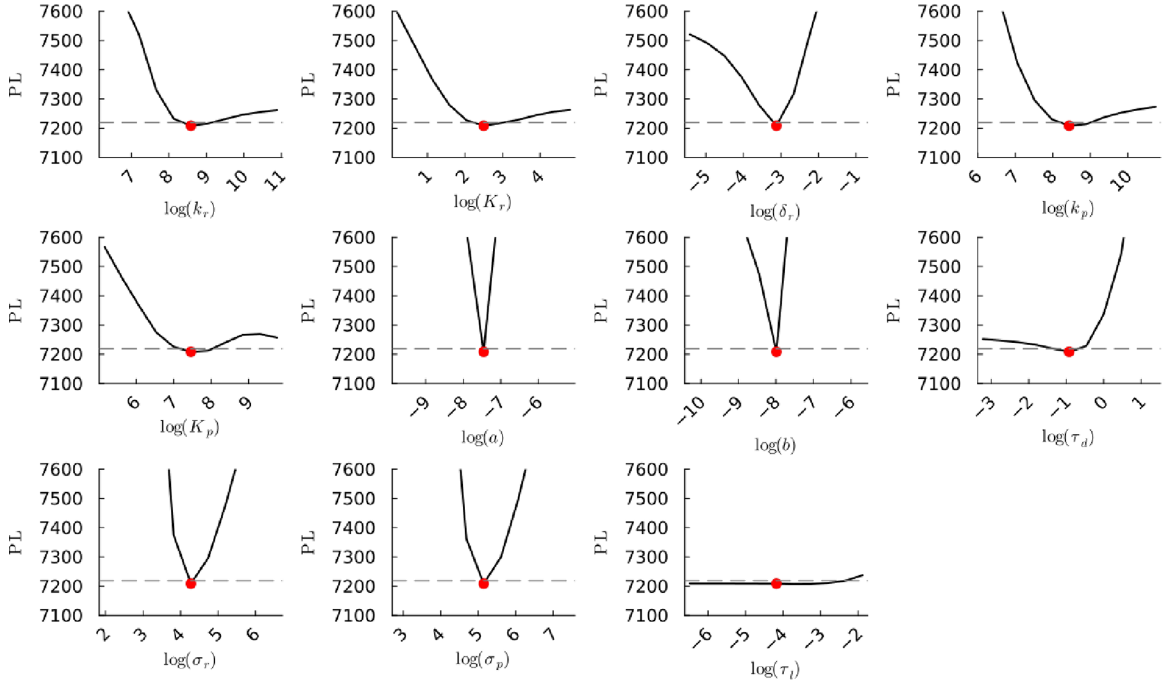

Figure S30b. (Corrected) Profile likelihoods of parameters from model 6. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the negative MLE. The dashed gray line is the 95% significance threshold line. All logarithms are in natural log.

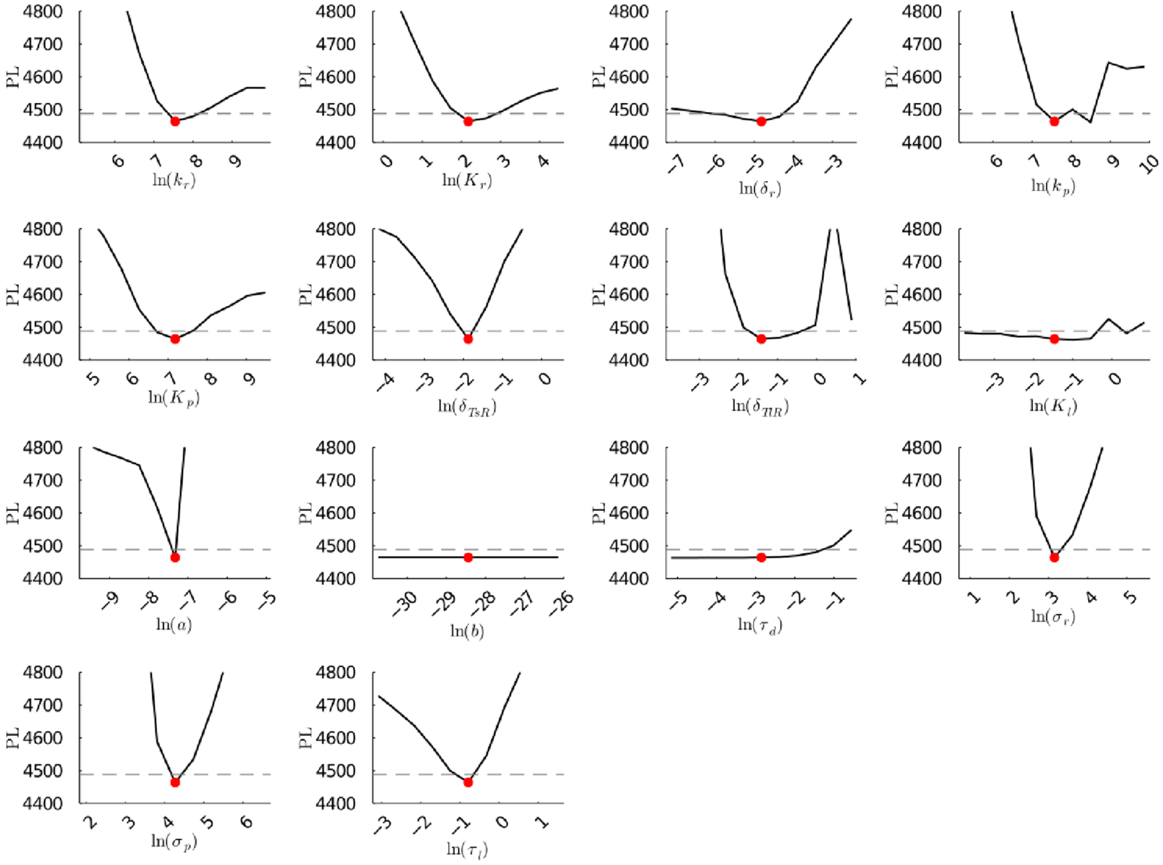

Figure S49a. (Original) Profile likelihoods of parameters from model 2 using synthetic population experiment data. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The *y*-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the *x*-axis. The red dot shows the optimized parameter set with the minimum negative log likelihood. The dashed gray line is the 95% significance threshold line. The intersections of the significance threshold line and profile likelihood are the likelihood-based confidence intervals of the optimized parameter.

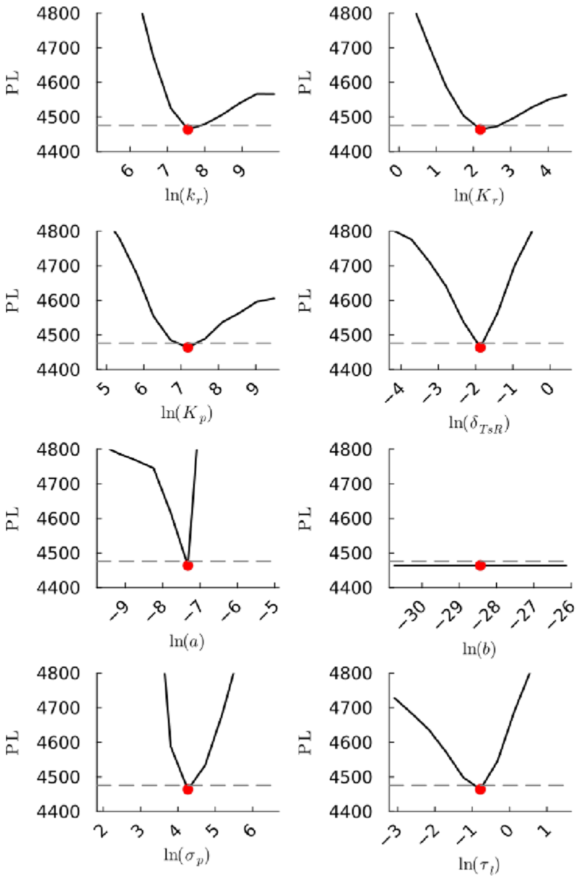

Figure S49b. (Corrected) Profile likelihoods of parameters from model 2 using synthetic population experiment data. Each plot corresponds to a parameter in the model and additional fitting parameters (σ_r, σ_p, τ_d). The y-axis of each plot shows the minimized negative log-likelihood of the model with respect to all parameters except for the parameter given its value in the x-axis. The red dot shows the optimized parameter set with the minimum negative log likelihood. The dashed gray line is the 95% significance threshold line. The intersections of the significance threshold line and profile likelihood are the likelihood-based confidence intervals of the optimized parameter.

parameters. In our original publication, the factor 1/2 with $\chi^2(\alpha,df)$ was omitted in eq 11 and eq S34. Our error resulted in an overestimation of each parameter's 95%-confidence interval. The maximum likelihood estimates of the parameters themselves were not affected by the mistake. After correcting this in our calculations, the confidence intervals became narrower. In one instance, this caused a parameter, which was previously found to be weakly identifiable, to become identifiable (K_l). All original and corrected items are provided.

While the profile likelihoods plotted in Figures S25−S30 and Figure S49 in the Supporting Information were not affected by the mistake, the likelihood thresholds (gray dashed lines) were incorrect. The original and corrected Figures S25−S30 and Figure S49 are provided.

■ AUTHOR INFORMATION

Corresponding Authors

Christoph Zechner − *Max Planck Institute of Molecular Cell Biology and Genetics, 01307 Dresden, Germany; Center for Systems Biology Dresden, 01307 Dresden, Germany; Physics of Life, Cluster of Excellence, TU Dresden, 01603 Dresden, Germany*; Email: zechner@mpi-cbg.de

T-Y. Dora Tang − *Max Planck Institute of Molecular Cell Biology and Genetics, 01307 Dresden, Germany; Center for Systems Biology Dresden, 01307 Dresden, Germany; Physics of Life, Cluster of Excellence, TU Dresden, 01603 Dresden, Germany*; orcid.org/0000-0001-9030-6991; Email: tang@mpi-cbg.de

Authors

David T. Gonzales − *Max Planck Institute of Molecular Cell Biology and Genetics, 01307 Dresden, Germany; Center for Systems Biology Dresden, 01307 Dresden, Germany*

Naresh Yandrapalli − *Max Planck Institute of Colloids and Interfaces, 14476 Potsdam, Germany*; orcid.org/0000-0002-1516-6674

Tom Robinson − *Max Planck Institute of Colloids and Interfaces, 14476 Potsdam, Germany*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acssynbio.4c00583

Funding

Open access funded by Max Planck Society.