The Seventh q-bio Conference Invited Speakers for 2013

Nancy L. Allbritton, University of North Carolina
Naama Barkai, Weizmann Institute of Science
Sydney Brenner, Salk Institute (Opening Banquet Talk)
Leah Edelstein-Keshet, University of British Columbia
Hana El-Samad, University of California, San Francisco
Jim Haseloff, University of Cambridge
Suckjoon Jun, University of California, San Diego
Marc W. Kirschner, Harvard Medical School (Closing Banquet Talk)
Jennifer Lippincott-Schwartz, National Institutes of Health
Zaida (Zan) Luthey-Schulten, University of Illinois, Urbana-Champaign
Rama Ranganathan, University of Texas Southwestern Medical Center at Dallas
Peter K. Sorger, Harvard Medical School
Erik Winfree, California Institute of Technology
Lani Wu, University of Texas Southwestern Medical Center at Dallas

http://www.q-bio.org/wiki/The_Seventh_q-bio_Conference

The Seventh Annual q-bio Summer School

Two Great Campuses (July 21 - August 2, 2013):

St. John's College (Santa Fe, New Mexico, USA)	University of California (San Diego, California, USA)

Converging at:

The q-bio Student Symposium (St. John's College, Santa Fe, New Mexico, USA, August 5-6, 2013)	The Seventh Annual q-bio Conference (Santa Fe, New Mexico, USA August 7-10, 2013)

*** Biomolecular Simulations (Santa Fe, NM)**
*** Cancer (Santa Fe, NM)**
*** Viral Dynamics (Santa Fe, NM)**
*** Computational Neuroscience (San Diego, CA)**
***Stochastic Gene Regulation (Santa Fe, NM)**
*** Cell Signaling (Santa Fe, NM**
*** Synthetic Biology (San Diego, CA**

http://q-bio.org/wiki/The_Seventh_q-bio_Summer_School

Combining quantitative experiments and modeling to understand kinetics of the T cell response

Anton Zilman, Vitaly Ganusov and Alan Perelson
Los Alamos National Laboratory
University of Toronto

Los Alamos NATIONAL LABORATORY EST. 1943

T | Theoretical Division

Center for Nonlinear Studies

Physics
UNIVERSITY OF TORONTO

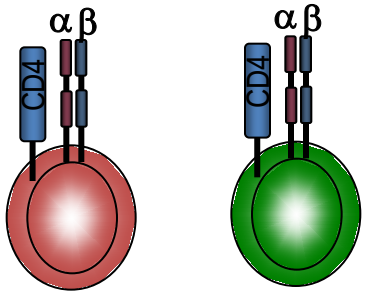
Alena Gallegos and Eric Pamer
Memorial Sloan-Kettering Cancer Center

MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

Model system to study CD4 T cell response to infection

2 TCR tg mice lines

C7 C24



ANTIGEN: ESAT-6

Infecing Bacteria

Listeria moncytogenes

Expresses ESAT-6

Courtesy of Alena Gallegos-Srinivasan (IGGEB)

Experimental procedure

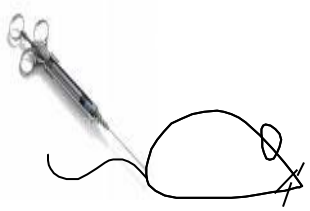
Transgenic mouse on B6 Thy 1.1 background:
CD4 T cells specific for ESAT (TB antigen)

Day -1

Transfer transgenic CFSE labeled CD4 T cells

Transferred cells are pre-sorted to narrow the CFSE peaks

Day 0



Infect the mice i.v. with the ESAT expressing Lysteria

Day x after infection

"Sacrifice" the mice

Extract the T cells from the spleen

Label with anti Thy1.1 antibodies and other activation and death markers

Put on the flow cytometer

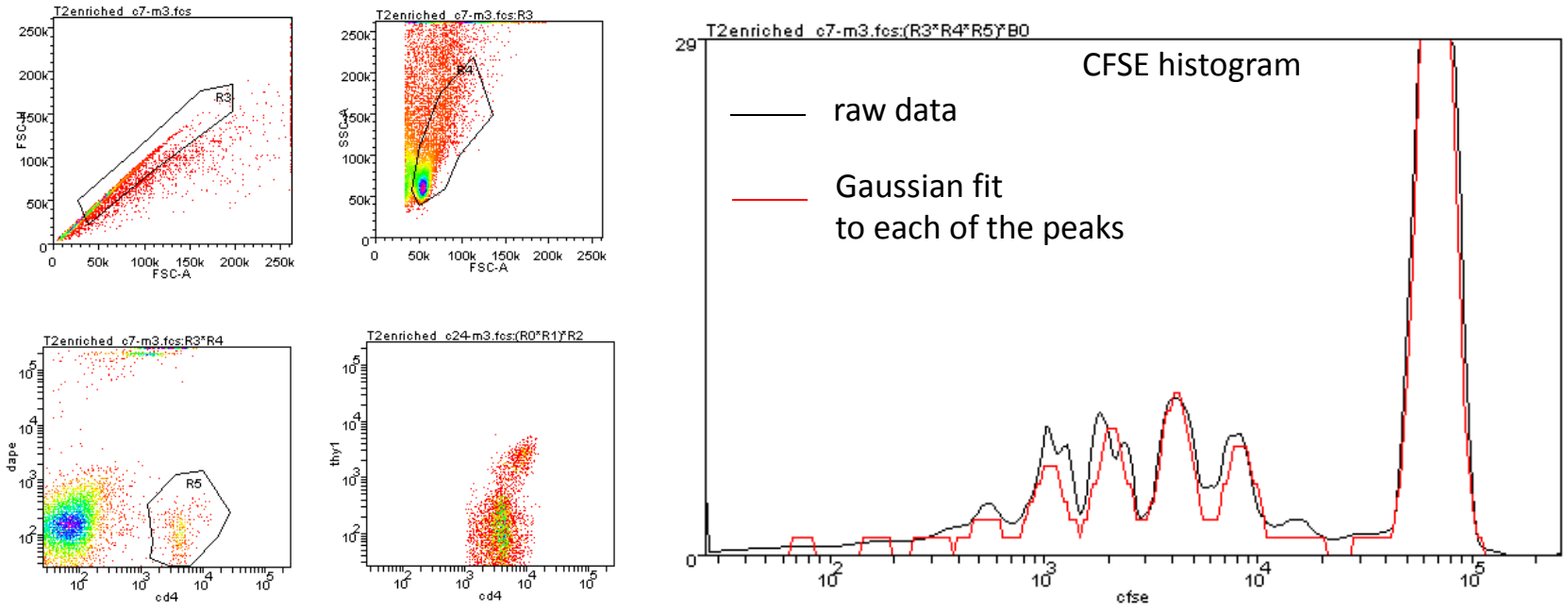
Data is collected every 12 hours from 12 to 96 hours post-infection

Early proliferation kinetics: CFSE profiles

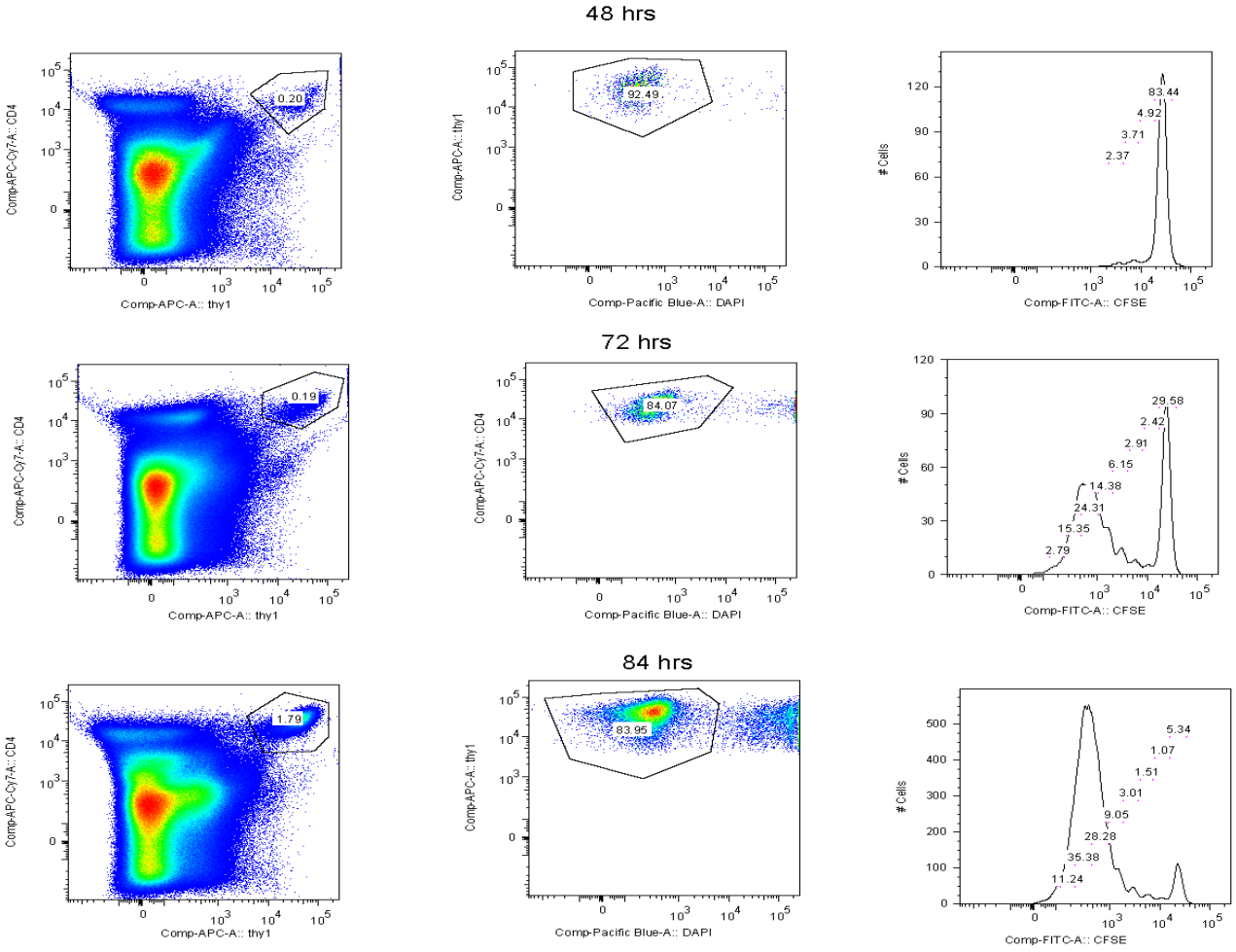
Numbers of cells in different division classes at time *t* are extracted from the CFSE profiles measured in cell transfer experiments

Numbers of cells in different division classes at time *t* are then used as input to the mathematical model

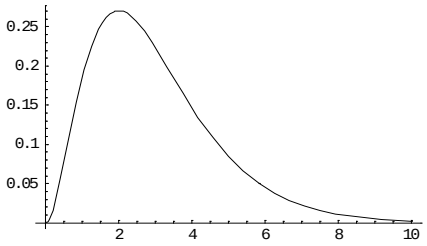
Data fitting: example



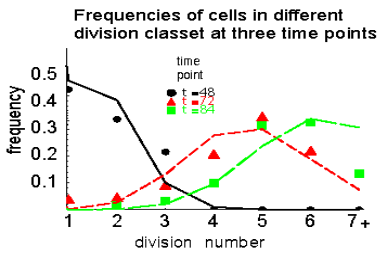
Data analysis

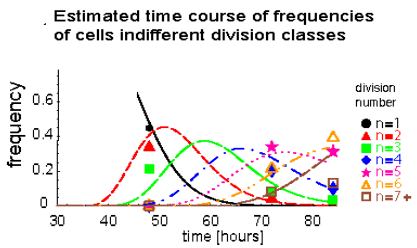


Model assumptions:
the distribution of the inter-division times is a gamma function (similar to log-normal)



(results are relatively insensitive to the precise choice)





Fit results

initial lag 25 hrs

mean time to first division 33.2 hrs

mean subsequent division time 9.3 hrs

Results

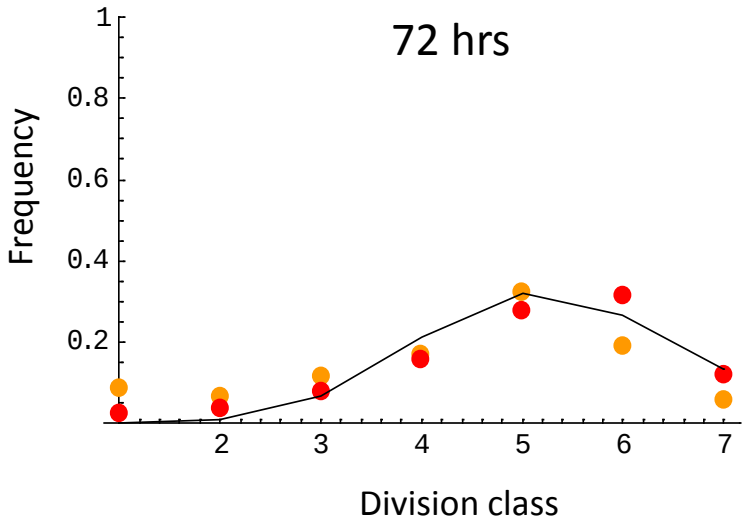
Model parameters:
Inter-division time distribution:

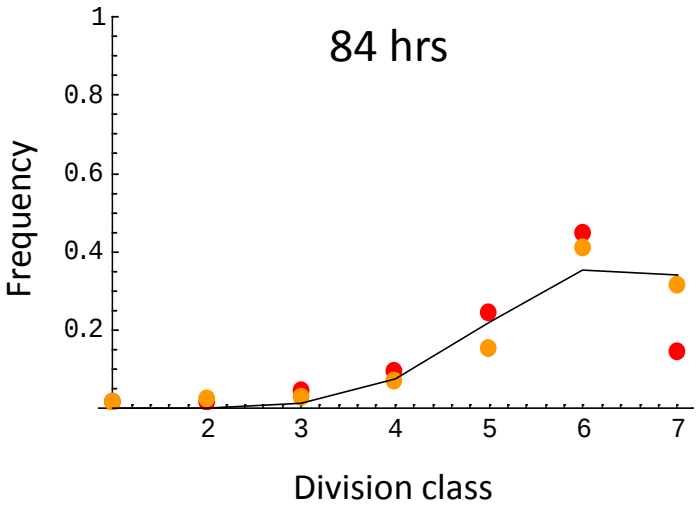
$$P(t) = \frac{1}{2} b^3 t^2 e^{-bt}$$

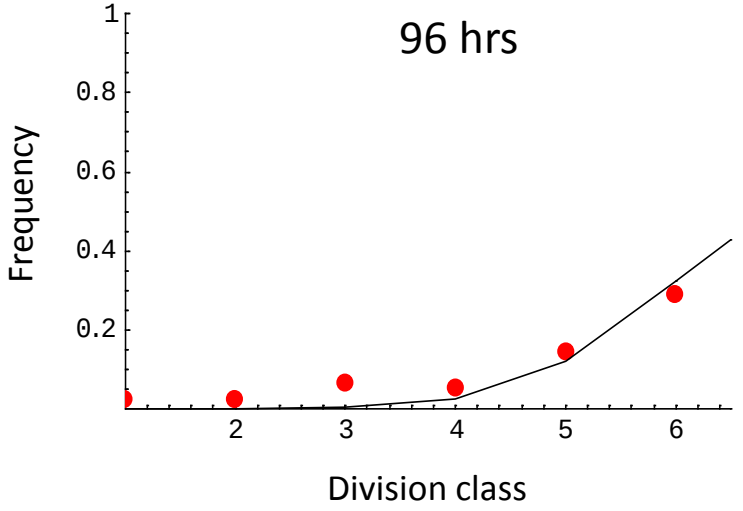
Activation lag: 25 hrs

Mean inter-division time: 8 hrs

- Clone 7
- Clone 24
- model





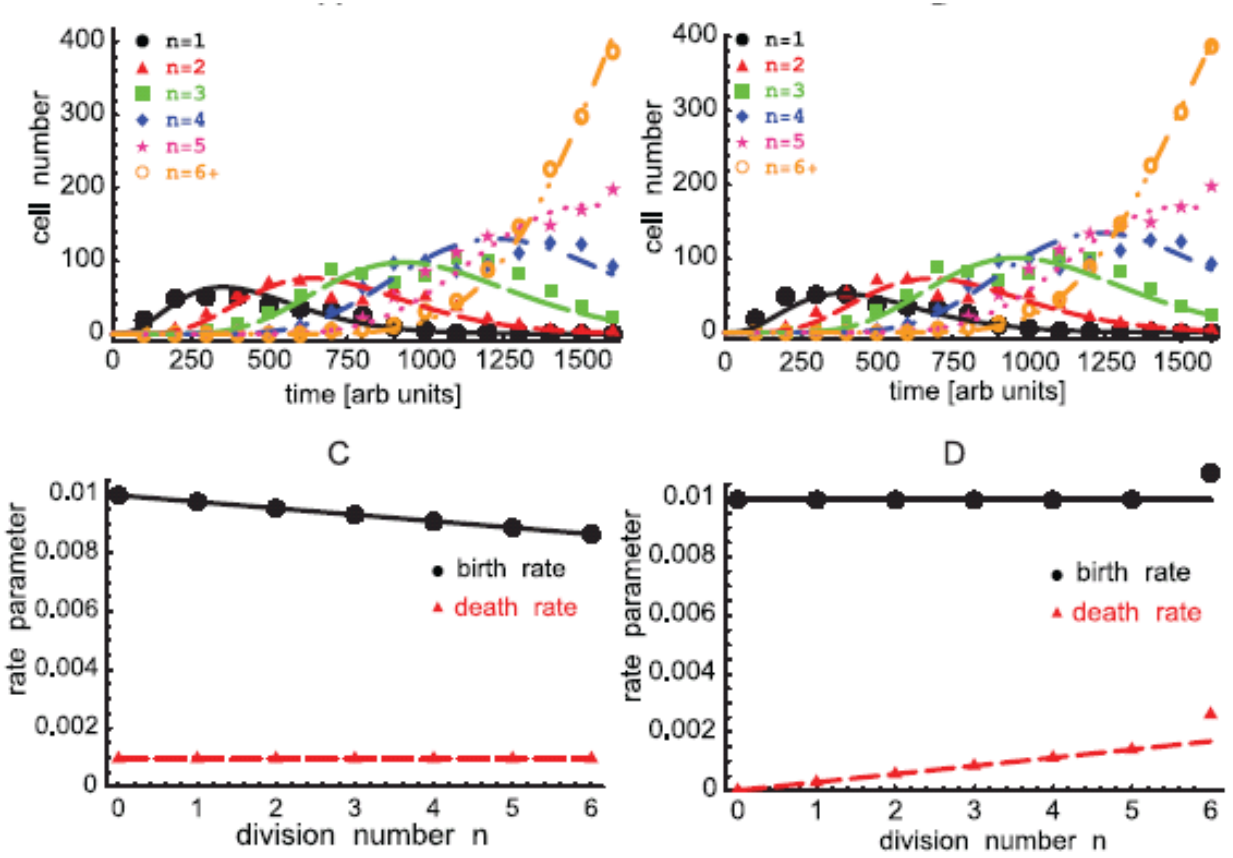


Parameter sensitivity analysis: fitting same data with models with different distributions

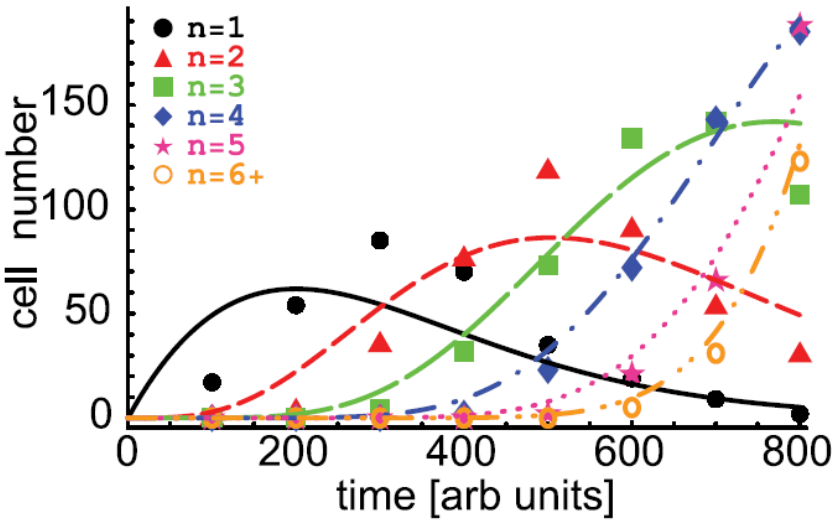
Table 1. Estimates of the parameters providing the best fit to the simulated and experimental data.

	Simulated data		Experimental data	
	Actual	**Estimated**	**Estimated gamma**	**Estimated SM**
T_0, h	66.7	75.5 ± 0.4	50.6 ± 0.6	63.7 ± 0.9
T, h	20	19.3 ± 0.4	16.2 ± 0.2	13.55 ± 0.53
τ, h	0	54.6 ± 0.3	33.2 ± 0.8	21.25 ± 1.62
N_0 cells	100	105.9 ± 12.8	$(0.54 \pm 0.05) \times 10^4$	$(0.50 \pm 0.07) \times 10^4$
d, h^{-1}	0.01	0.007 ± 0.002	0.024 ± 0.002	0.02 ± 0.005

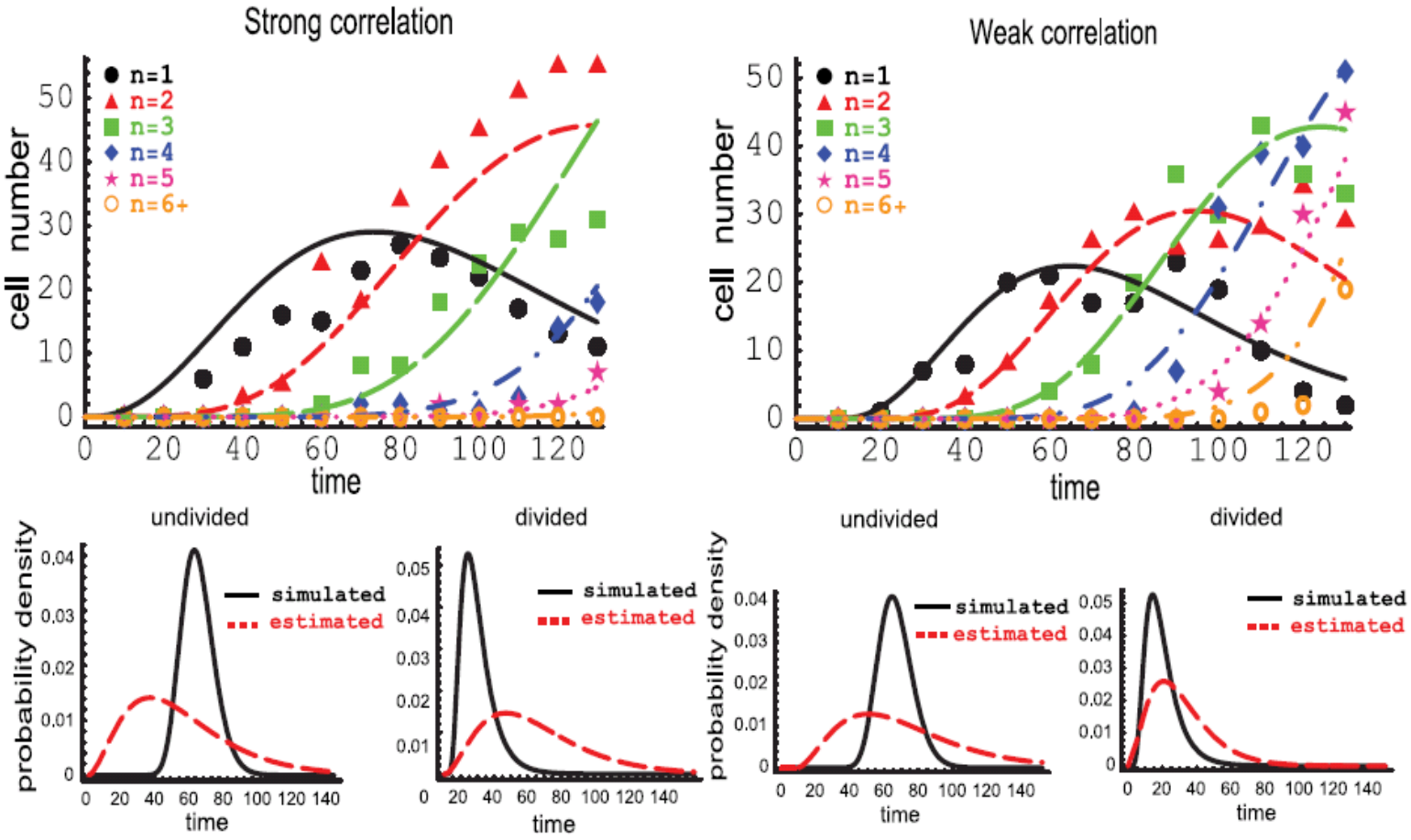
More parameter sensitivity analysis: division-linked births vs. division-linked deaths



More parameter sensitivity analysis: division-linked births vs. time-linked birth



More parameter sensitivity analysis: mother-daughter correlations



Some lessons and questions

In vivo quantification of early kinetics of T cell response is feasible

Comparisons of actual numbers obtained using different models are likely meaningless

How many features can be reliably estimated without over-fitting?

What is model accuracy??