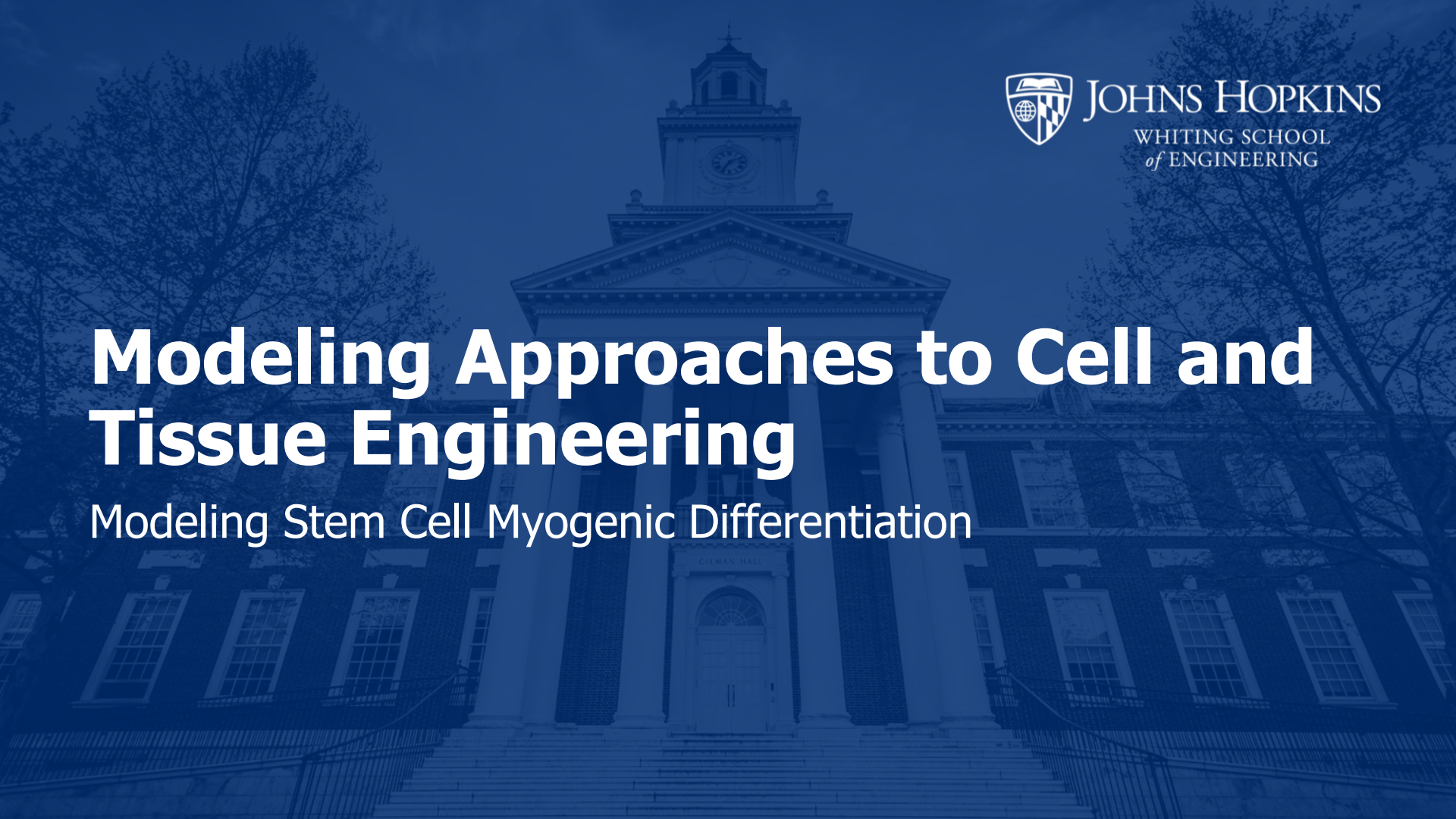


Modeling Approaches to Cell and Tissue Engineering

Modeling Stem Cell Myogenic Differentiation

Modeling Stem Cell Myogenic Differentiation

Alexander A. Spector (From R. Deshpande et al., 2017)

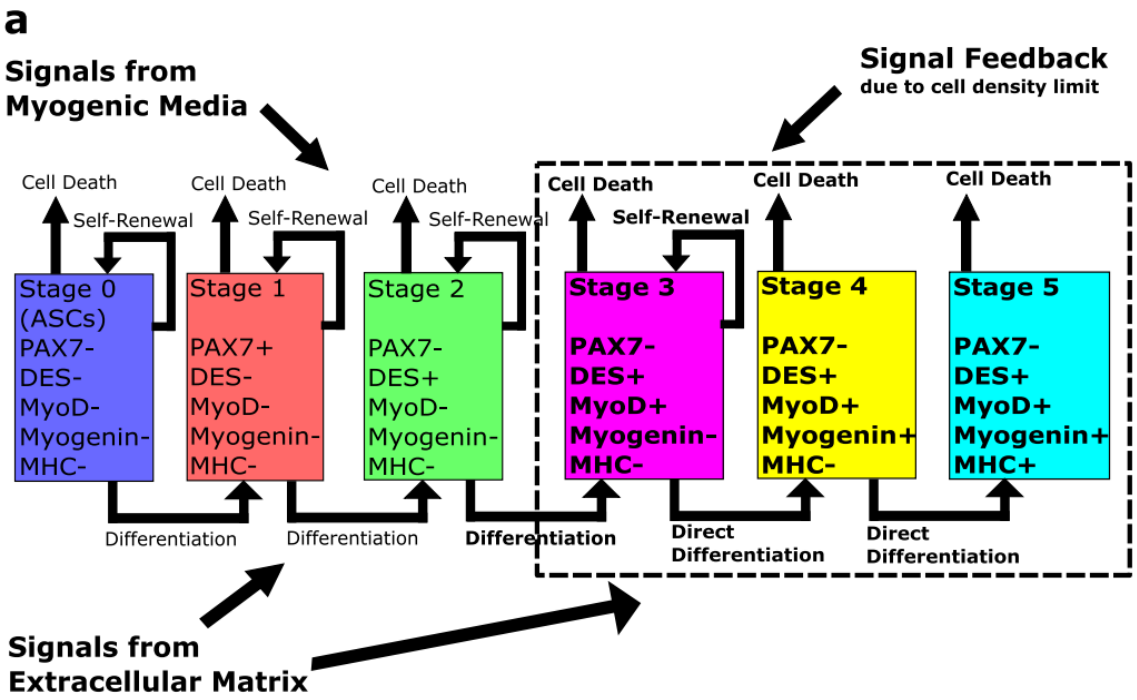
1. Molecular markers involved in the process of myogenic differentiation
2. Multi-stage model
3. Kinetic equations
4. Differentiation functions
5. Comparison with experiment
6. List of optimal parameters
7. Predicted results for longer times
8. Predicted results for different strain

Molecular Markers Involved in Stem Cell Myogenesis

DESMIN, PAX7 (division stage)

myogenin, MyoD, and MHC (differentiation stage)

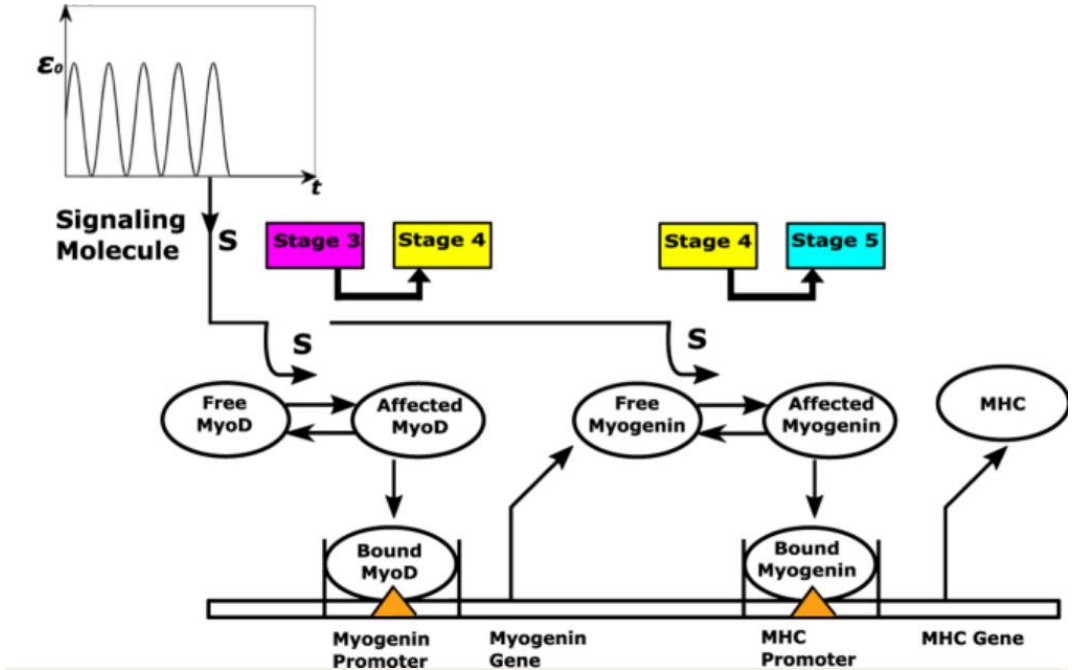
Multi-Stage Model 1



Six stages and the expression of myogenic factors. The first three stages occur via asymmetric cell division, and the latest three stages (shown within the dashed line) proceed through direct differentiation. The multi-stage process of stem cell myogenesis is affected by external signaling from the myogenic medium, extracellular matrix (strain effect), and cell-cell interaction if a cell density threshold is reached.

Multi-Stage Model 2

The proposed mechanism of stem cell myogenic differentiation associated with the interaction among the transcription factors, MyoD and myogenin, and the late myogenic factor, MHC. The strain effect is interpreted as strain-generated signaling molecule, S, that affects the transcriptional activity of MyoD and myogenin.



Kinetics in the Differentiation Stage

$$\frac{dn_3}{dt} = [p_3 n_3 - d_3 n_3 + 2(1 - r_2) p_2 n_2 - D_3(n_3, S)] f(n_{tot}) \quad (1)$$

$$\frac{dn_4}{dt} = [D_3(n_3, S) - D_4(n_4, S) - d_4 n_4] f(n_{tot}) \quad (2)$$

$$\frac{dn_5}{dt} = [D_4(n_4, S) - d_5 n_5] f(n_{tot}) \quad (3)$$

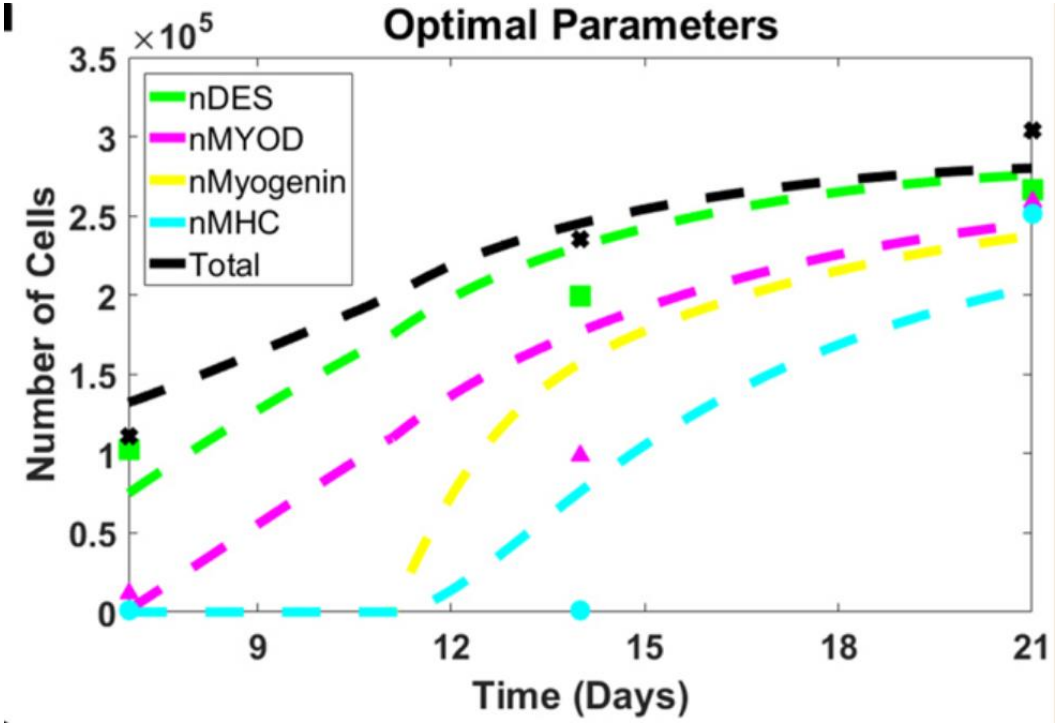
Here, the right-hand sides on equations (1-3) give the sums of fluxes that determine the rates of the cell numbers in stages 3, 4, and 5, respectively. The terms on the right-hand side of equation (1) are associated with symmetric division (proliferation rate, p_3), cell death (death rate, d_3), asymmetric division in previous stage 2 (differentiation coefficient, $1 - r_2$, proliferation rate, p_2), and direct differentiation into next stage 4 (differentiation function D_3). The terms on the right-hand side of equation 2 are determined by direct differentiation from stage 2 (differentiation function, D_3), direct differentiation into next stage 4 (differentiation function, D_4), and cell death (death rate, d_4). The terms on the right-hand side on equation(3) are associated with direct differentiation from previous stage 4 (differentiation function, D_4) and cell death (death rate, d_5). In equations (1-3), all rates have units of time^{-1} (day^{-1}) and the coefficient, $1 - r_2$, describing differentiation via asymmetric division is dimensionless. Both functions describing direct differentiation have units of number of cells/time (number of cells/day). The function $f(n_{tot})$ (dimensionless) describes the feedback signal affecting the rates of cell number in different stages if the total cell number approaches a threshold.

Solutions for Differentiation Functions

$$D_3\left(n_3, S(\varepsilon)\right) = \beta_3 \frac{\frac{\varepsilon n_3}{\varepsilon + k_s^*}}{\frac{\varepsilon n_3}{\varepsilon + k_s^*} + k_3^{**}} \qquad (7)$$

$$D_4\left(n_4, S(\varepsilon)\right) = \beta_4 \frac{\frac{\varepsilon n_4}{\varepsilon + k_s^*}}{\frac{\varepsilon n_4}{\varepsilon + k_s^*} + k_4^{**}} \qquad (8)$$

Comparison with Experimental Data and Determination of Optimal Parameters

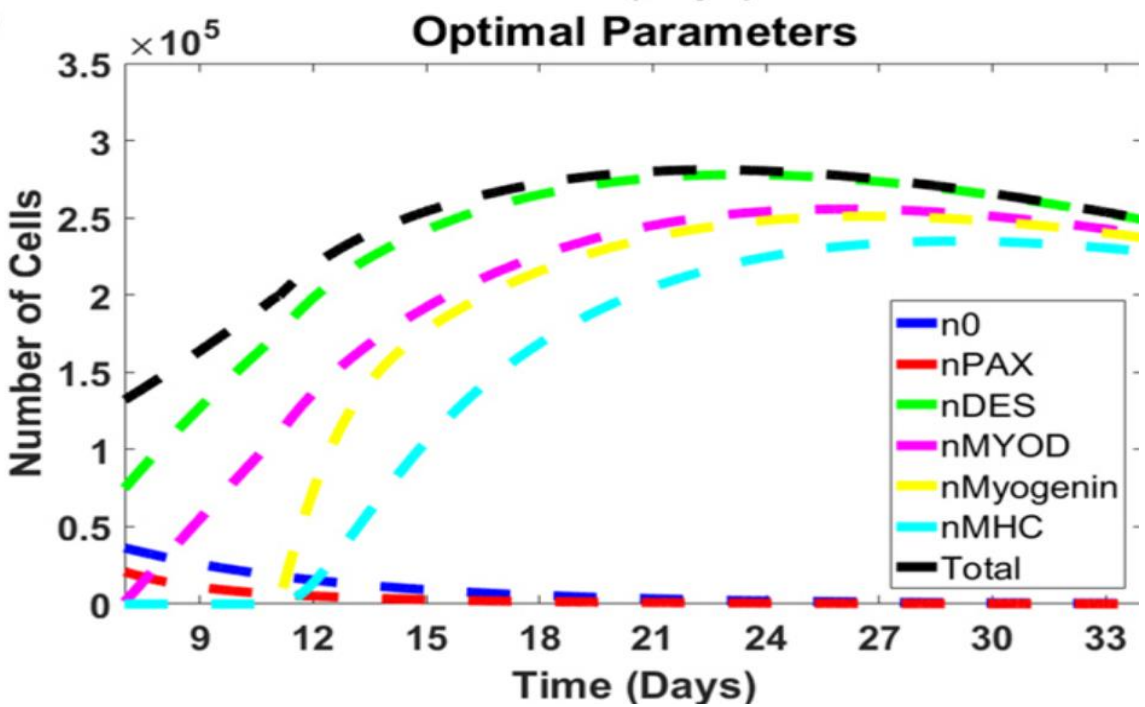


Here, the modeling results are presented in terms of cell numbers expressing particular factors, which is different from cell numbers, n_1–n_5, but has an advantage in the comparison with the experimental data. The computed total cell number is also used for the comparison with the experimental data. The modeling results are shown in dashed lines, and the experimental data for days 7, 14, and 21 and strain magnitude of 10% are shown in squares (number of cells expressing Desmin), triangles (number of cells expressing MyoD), circles (number of cells expressing MHC), and crosses (total cell number). (a) Computed kinetics for the optimal values of the model parameters vs. experimental data for the time interval of the differentiation part of the experiment (from day 7 through day 21)

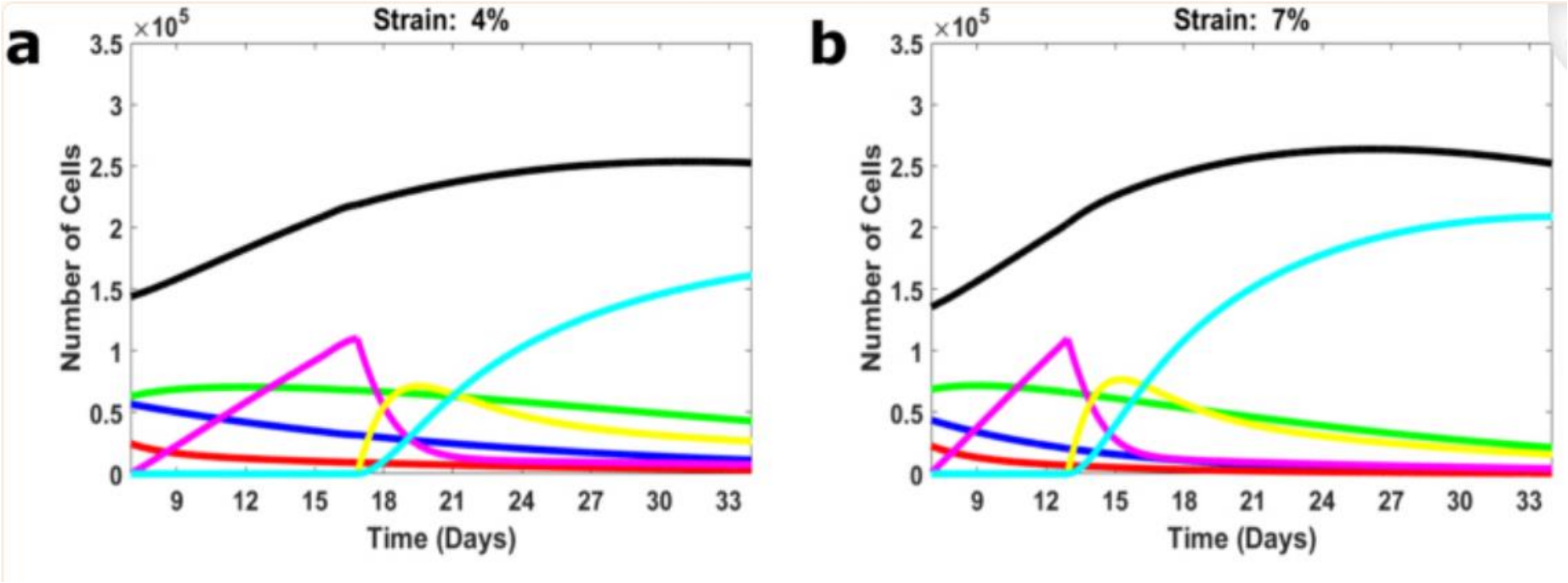
List of Model Parameters

	Parameter	Value
Thresholds	n_3^t	1.1×10^5
	n_{tot}^t	4.0×10^5
Earlier Stages	p_2	0.36
	r_2	0.50
	d_2	0.10
Later Stages	β_3	1.9×10^5
	β_4	0.8×10^5
	k_3^{**}	0.6×10^5
	k_4^{**}	2.0×10^5
	k_s^*	0.75
	d_3	0.20
	$d_4 = d_5$	0.03

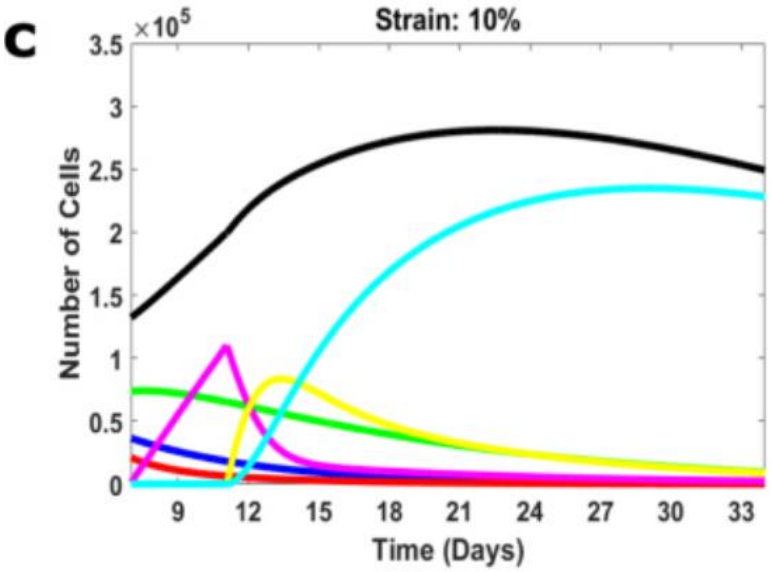
Model Prediction for Longer Times

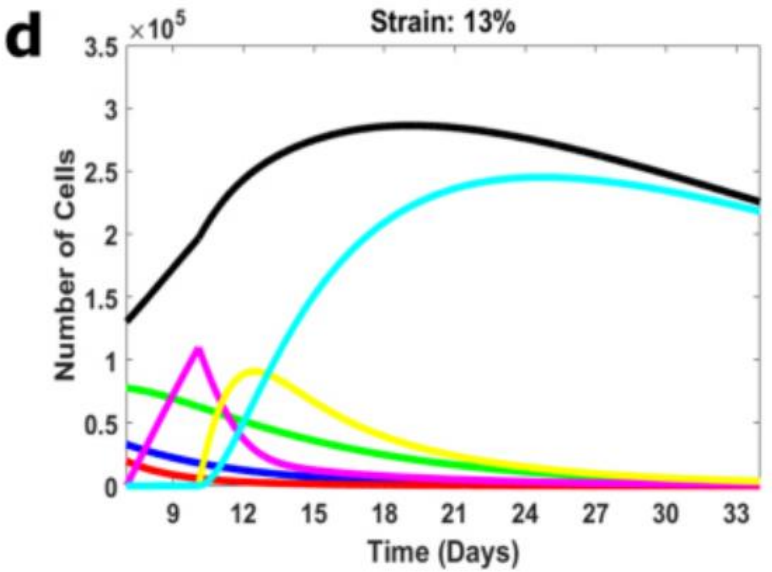


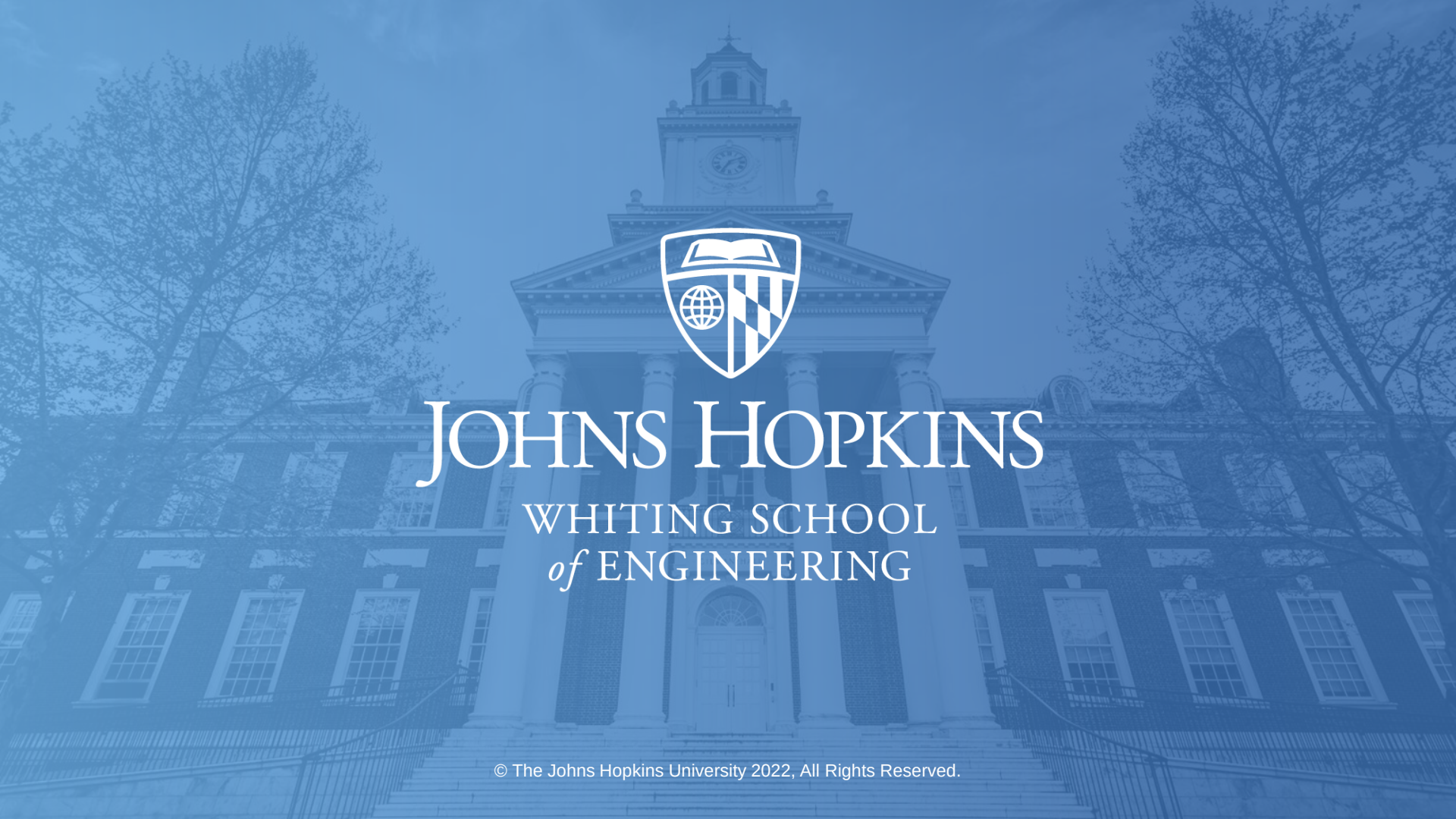
Model Predictions for Different Strains 1



Model Predictions for Different Strains 2







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