Using Linear Cancer Networks to Model Hormone Therapy for Breast Cancer

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- Starting in the epithelial cells of the breast, the cancer spreads to the surrounding tissue, ultimately killing the host.
- There are four types of breast cancer mentioned in the paper by McDuffie:
  - Endocrine receptor positive for estrogen (ER+)
  - Endocrine receptor positive for progesterone (PR+)
  - HER2 positive (HER2+)
  - Negative for each of the three.

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  - Hormone therapy
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- We will be focusing on the treatment of breast cancer via hormone therapy.
- Hormone therapy only works for those forms of cancer that are hormone receptor positive.

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  - Prevents the recurrence of cancer.
  - Slows the spread of cancer.
  - Prevents cancer in women who are at high risk.
- Tamoxifen binds to estrogen receptors on cells, which prevents the receptor from binding to estrogen in breast epithelial tissue. Without bound estrogen, the cells grow and divide much slower.

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- We can consider this network linear, i.e. the cancer cell can either divide into itself or a tumor cell.
- The tumor cells will not divide into more cells, they are considered terminal.

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  - $\dot{z}$ = Healthy cells
- From here we need to determine the best approach to model the interactions and growth of the populations in the system.

A Linear Cancer Network

- This leads us to the following system:

$$\begin{aligned} \dot{x} &= kx\left(1 - \frac{x}{x_c}\right) \\ \dot{y} &= kx\left(\frac{x}{x_c}\right)\left(1 - \frac{y}{y_c}\right) - ny \\ \dot{z} &= qz\left(1 - \frac{z}{z_c}\right) \end{aligned}$$

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- Where x, y, and z have population capacities x_c, y_c, and z_c.
- Where k and q represent the growth rates of cancer cells and healthy cells respectively, and n represents the death rate of tumor cells.

Untreated System Equilibria

- To look for equilibria we set the system equal to $(0, 0, 0)$:

$$\begin{aligned} 0 &= kx\left(1 - \frac{x}{x_c}\right) \\ 0 &= kx\left(\frac{x}{x_c}\right)\left(1 - \frac{y}{y_c}\right) - ny \\ 0 &= qz\left(1 - \frac{z}{z_c}\right). \end{aligned}$$

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- This leaves us with four equilibria in total.
- The only stable equilibrium being the coexistence of the 3 types of cells, the others acting as saddles to send the system to coexistence:

$$\left(x_c, \frac{kx_c y_c}{kx_c + y_c n}, z_c\right).$$

Inclusion of Hormone Treatment

- Introducing the hormone treatment, defining w to represent the current level of estrogen in the system, and w_0 as the level necessary for normal growth:

$$\begin{aligned}
\dot{x} &= \left(\frac{kw}{w_0}\right)x\left(1-\frac{x}{x_c}\right) - d_1\left(1-\frac{w}{w_0}\right)x \\
\dot{y} &= \left(\frac{kw}{w_0}\right)x\left(\frac{x}{x_c}\right)\left(1-\frac{y}{y_c}\right) - ny - d_2\left(1-\frac{w}{w_0}\right)y \\
\dot{z} &= \left(\frac{qw}{w_0}\right)z\left(1-\frac{z}{z_c}\right) - d_3\left(1-\frac{w}{w_0}\right)z \\
\dot{w} &= rw\left(1-\frac{w}{w_0}\right) - sDw.
\end{aligned}$$

- Notice that this creates a number of new interactions in the original system.

Inclusion of Hormone Treatment

$$\dot{w} = rw\left(1 - \frac{w}{w_0}\right) - sDw$$

- Here r represents the growth rate of the receptor binding estrogen, s represents the effectiveness of the drug, and D represents the dosage.

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- The growth rate of the cells is also directly affected by the proportion of estrogen necessary for normal cell growth.

Dimensionless Model

- To make our lives easier, we can simplify the previous system into the dimensionless model shown below:

$$\begin{aligned}
\dot{x} &= wx(1-x) - \delta_1(1-w)x \\
\dot{y} &= \mu w x^2(1-y) - \eta y - \delta_2(1-w)y \\
\dot{z} &= \gamma w z(1-z) - \delta_3(1-w)z \\
\dot{w} &= \rho(1-w)w - \sigma w
\end{aligned}$$

Dimensionless Parameters

$$x = \frac{x}{x_c}, \qquad \delta_i = \frac{d_i}{k}, i = 1, 2, 3,$$

$$y = \frac{y}{y_c}, \qquad \eta = \frac{n}{k},$$

$$z = \frac{z}{z_c}, \qquad \gamma = \frac{q}{k},$$

$$w = \frac{w}{w_0}, \qquad \rho = \frac{r}{k},$$

$$\mu = \frac{x_c}{y_c}, \qquad \sigma = \frac{sD}{k}.$$

Equilibria of the Dimensionless Model

- Similar to before, we can find the equilibria of the system by setting the system equal to $(0, 0, 0, 0)$:

$$
\begin{aligned}
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Equilibria of the Dimensionless Model

- There are five equilibria for this system.

  P_1: $(0, 0, 0, 0)$
  P_2: $(0, 0, 0, \bar{w})$
  P_3: $(\bar{x}, \bar{y}, 0, \bar{w})$
  P_4: $(0, 0, \bar{z}, \bar{w})$
  P_5: $(\bar{x}, \bar{y}, \bar{z}, \bar{w})$

$$\bar{x} = \frac{\rho-\sigma-\delta_1\sigma}{\rho-\sigma} \qquad \bar{y} = \frac{\mu(\rho-\sigma-\delta_1\sigma)^2}{\mu(\rho-\sigma-\delta_1\sigma)^2+(\rho-\sigma)(\eta\rho+\delta_2\sigma)}$$

$$\bar{z} = \frac{\gamma\rho-\gamma\sigma-\delta_3\sigma}{\gamma(\rho-\sigma)} \qquad \bar{w} = \frac{\rho-\sigma}{\rho}$$

- We are only interested in the "cure state" equilibrium, (P_4), where the healthy cells and the level of estrogen coexists.

Dimensionless Model Parameters

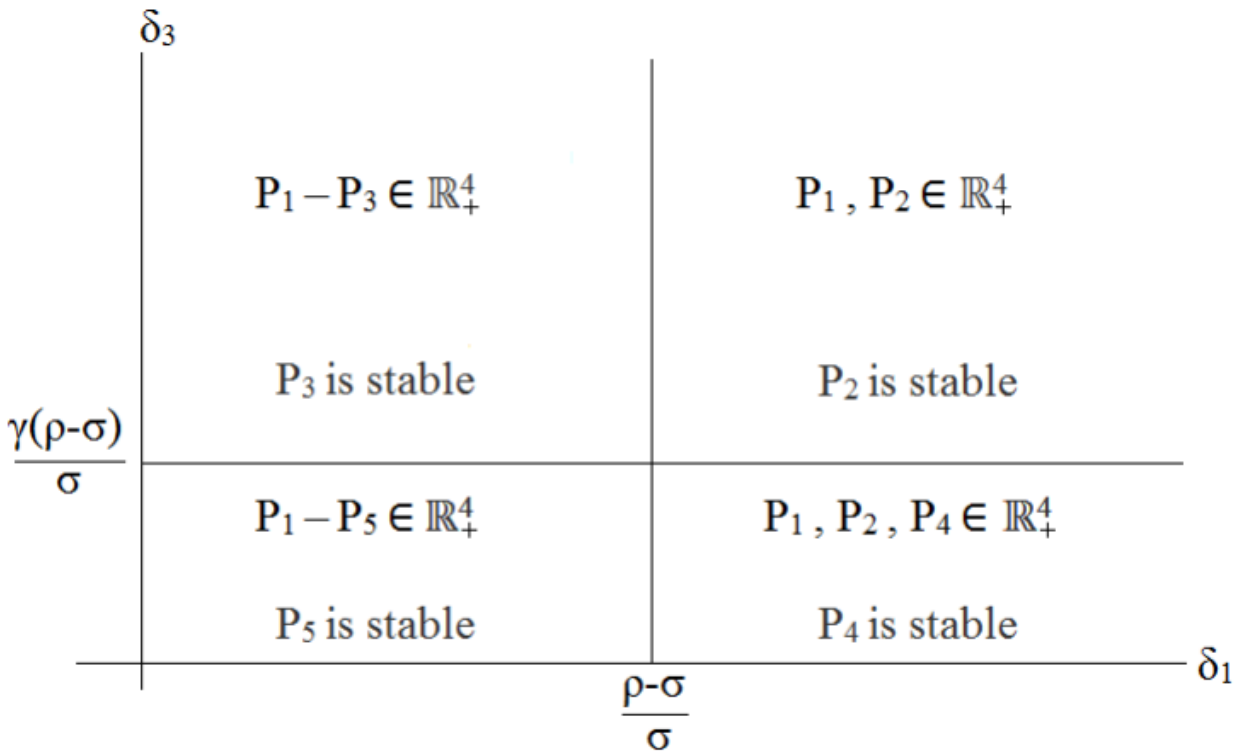
- We decided to focus our stability analysis on σ as it would be the easiest parameter to control in a real situation.
- The following values for the system parameters sets all equations in terms of σ.

Parameter	Values
ρ	0.40
γ	0.75
δ_1	0.55
δ_2	0.65
δ_3	0.20
μ	0.50
η	0.25

Stability of Equilibria

- For the "cure state" to be stable, we require

$$\delta_3 < \frac{\gamma(\rho - \sigma)}{\sigma};\ \delta_1 > \frac{\rho - \sigma}{\sigma}.$$



Stability of the Cure State

- With McDuffie's parameter substitutions, the Jacobian evaluated at the cure state has eigenvalues:

$$\lambda_1 = -0.4 + \sigma,$$
$$\lambda_2 = 1 - 3.875\sigma,$$
$$\lambda_3 = -0.25 - 1.625\sigma,$$
$$\lambda_4 = -0.75 + 2.375\sigma.$$

Stability and σ

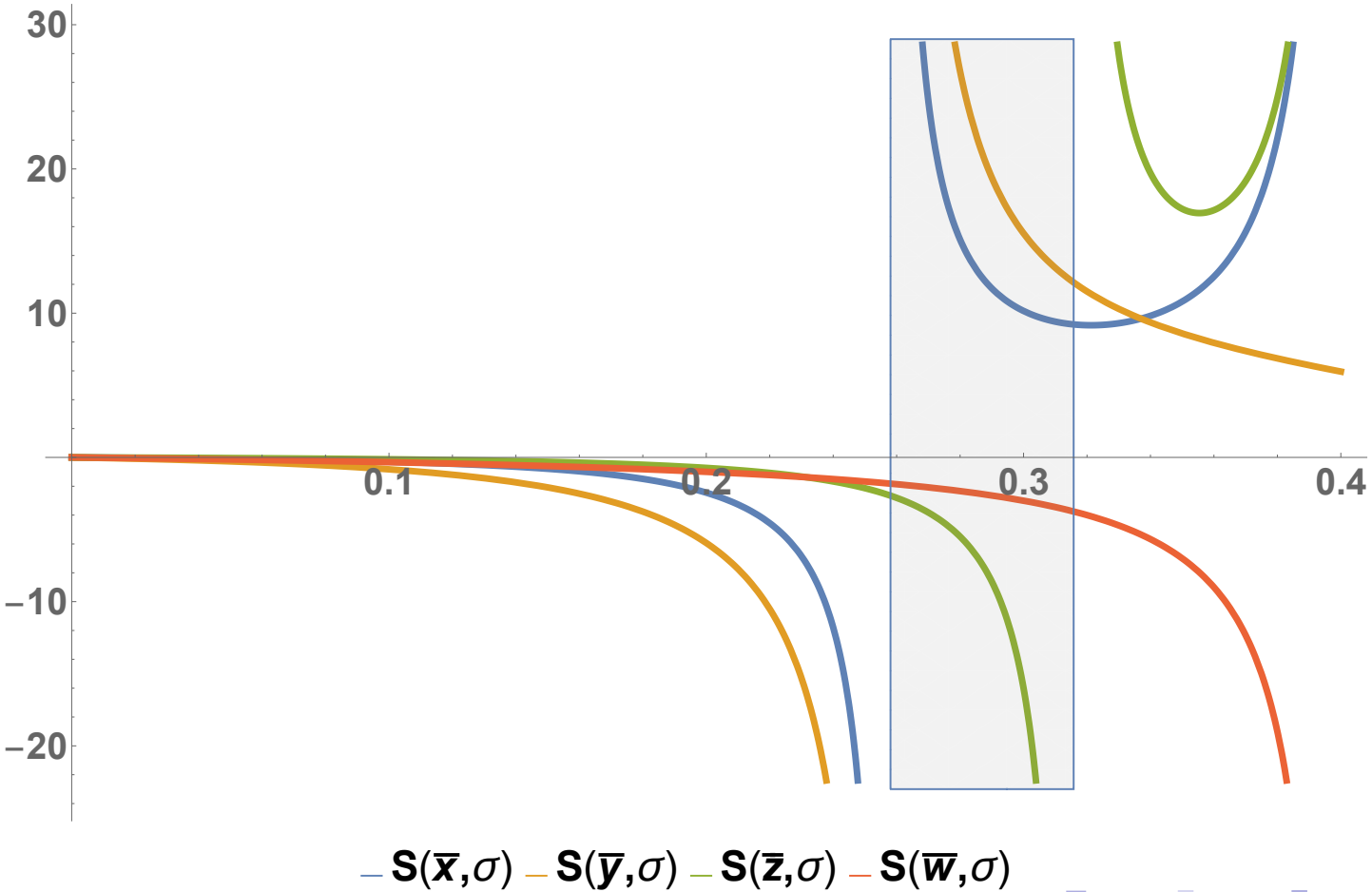
- We conclude that for the cure state to be stable,

$$\sigma \in \left(\frac{0.4}{1.55}, \frac{0.4}{1 + \frac{0.2}{0.75}} \right) \approx [0.26, 0.31].$$

- This satisfies the equations from the previous slide, and ensures all eigenvalues are strictly negative.

Sensitivity to σ

In order to find an optimal value of σ, the dimensionless treatment parameter, we first found the sensitivity of each of the equilibria to σ.



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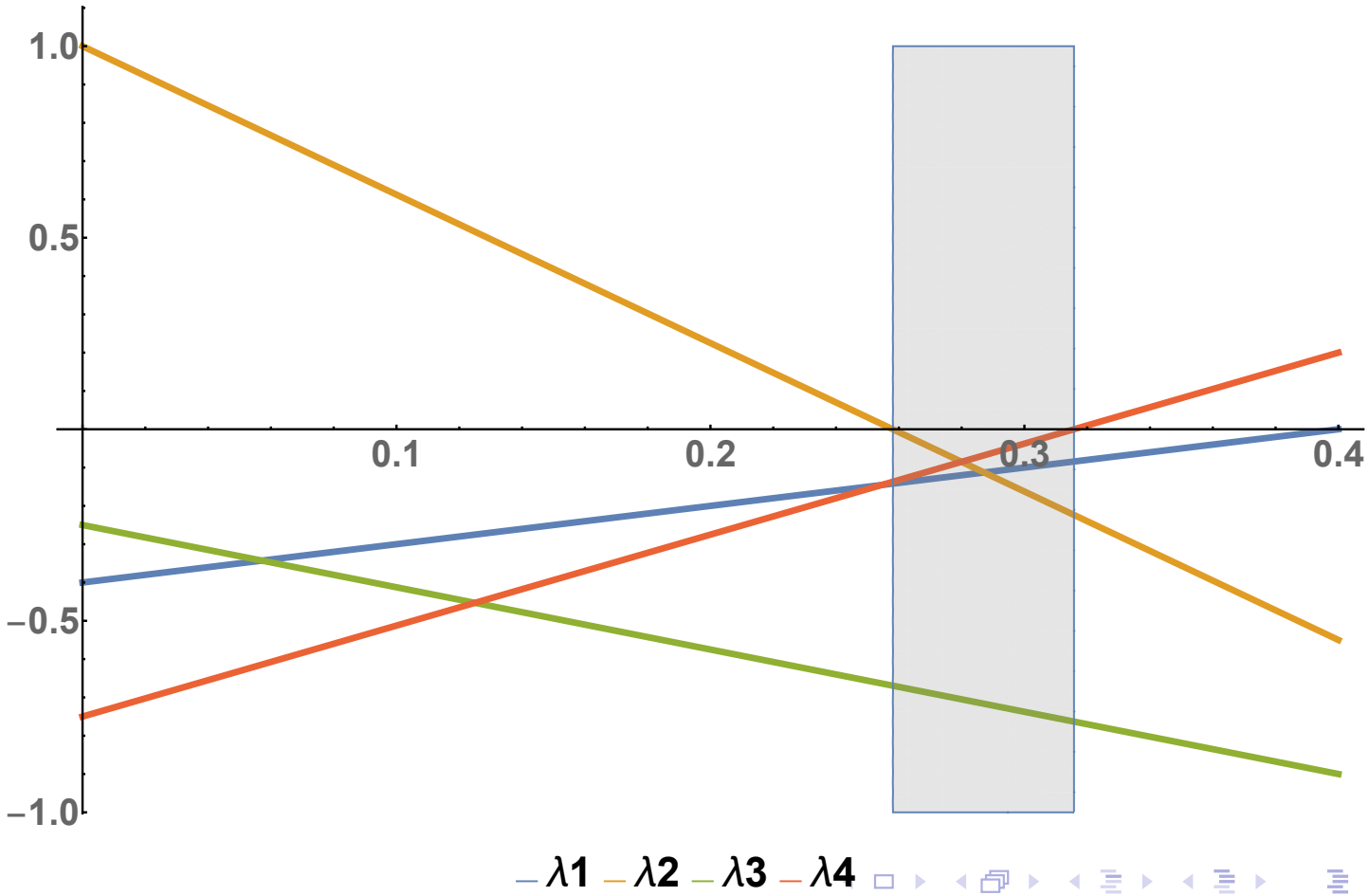

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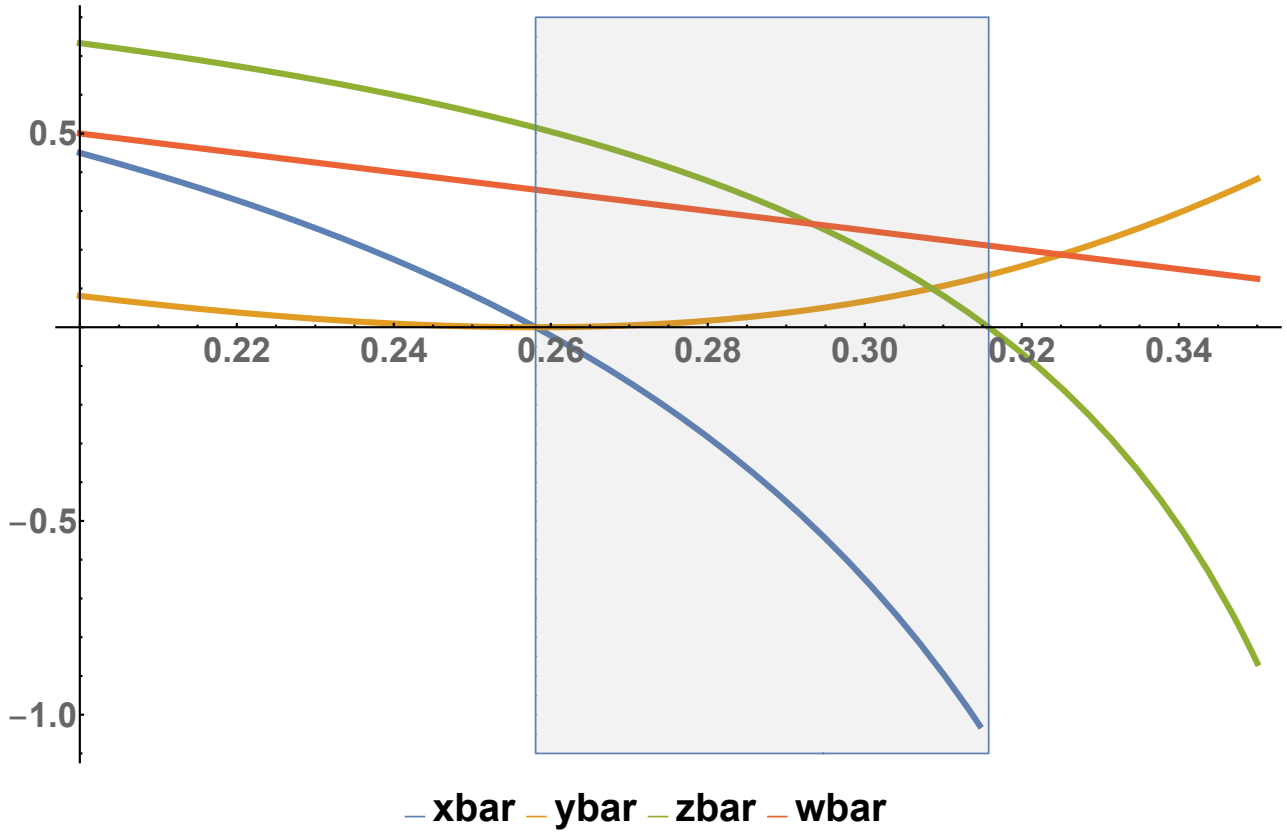

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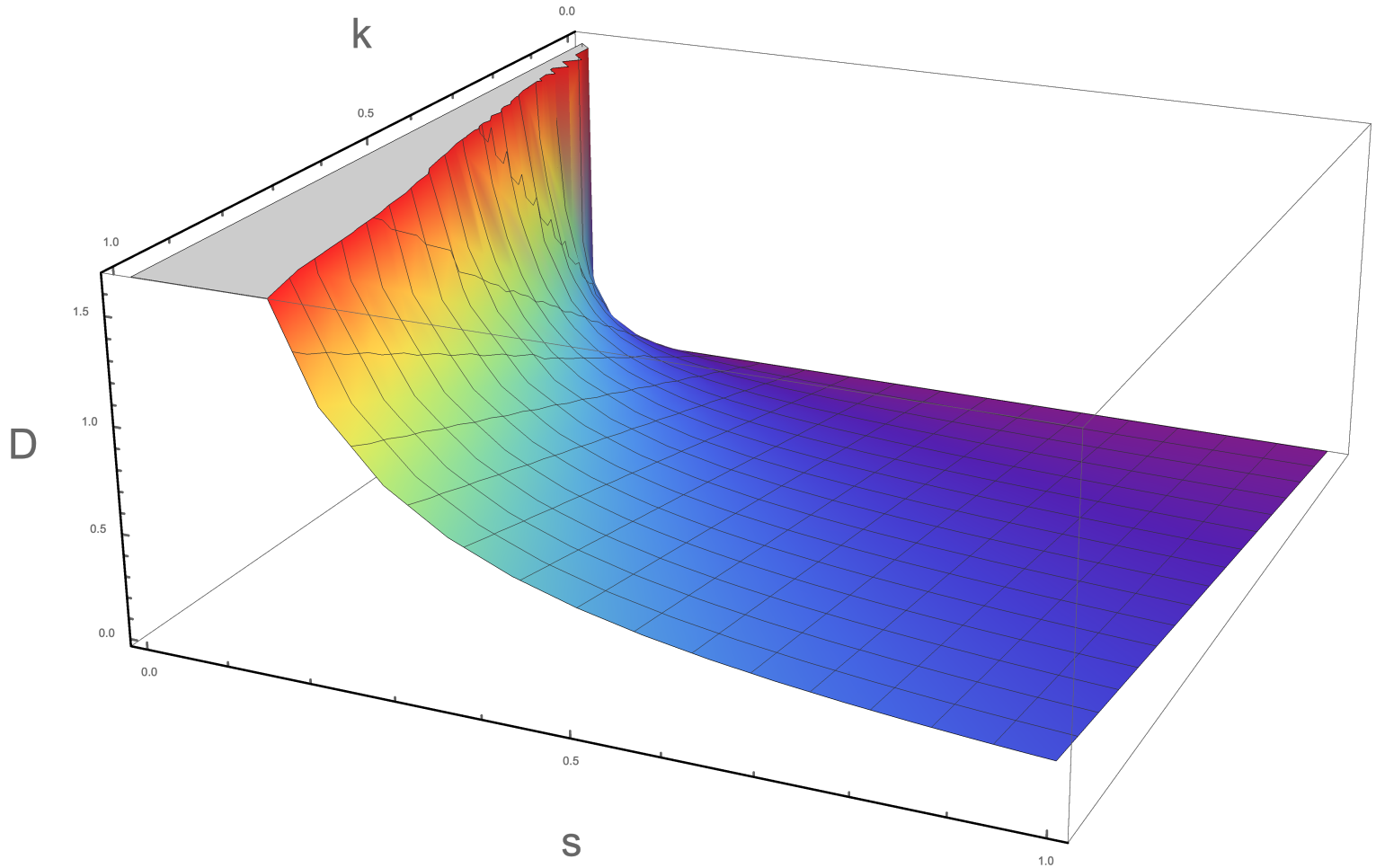

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k	s	Optimal Dosage
0.65	0.15	1.13
0.65	0.45	0.38
0.65	0.60	0.28

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- Conditions exist which make the cancer-free "cure state" asymptotically stable, and these can be expressed in terms of σ, the dimensionless treatment parameter.
- The parameter σ can be expressed in terms of drug dosage, but more information about dimensional analysis is needed for effective treatment decisions.

Strengths and Weaknesses of the Model

- Strengths:
  - This is a great introductory model that gives great insight to the effectiveness of a hormone treatment option for breast cancer.
  - The model takes into account multiple factors for cell biology, and theoretically is a strong system.

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  - This is a great introductory model that gives great insight to the effectiveness of a hormone treatment option for breast cancer.
  - The model takes into account multiple factors for cell biology, and theoretically is a strong system.
- Weaknesses:
  - There are a lot of parameters to consider for this model which make it theoretically strong, but difficult to work with when finding values for the parameters.
  - The model does not account for the side effects of the treatment, as the use of the hormone treatment also increases the risk of getting other forms of cancer.

Questions?