Strategies for Developing Mathematical Models of Cancer

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NEIU

SIMIODE EXPO 2024

Outline

- Building models from data
- Models used for cancer modeling
  - Start with growth models
  - Continue with reduction under therapy
- Examples, free resources, and codes
- References

Functions used to Model Tumor Growth

- An overview of growth functions
  - Parameters
  - Dependent variable
  - Independent variable
  - Shape of the function
  - Units of measurement

Functions used to Model Tumor Growth

- An overview of growth functions
  - Parameters
  - Dependent variable
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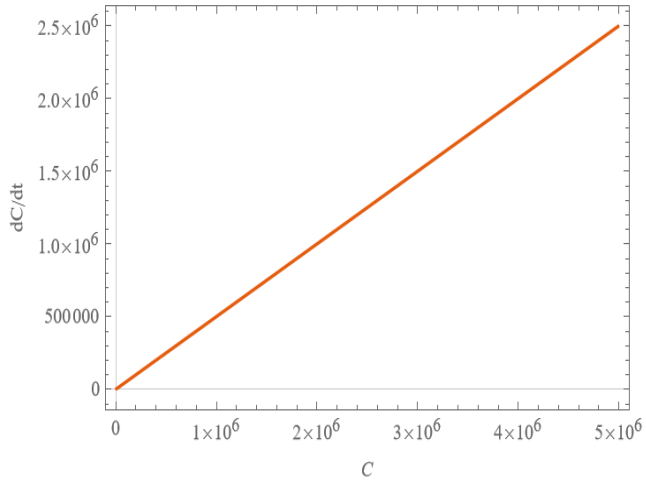
  - Shape of the function
  - Units of measurement
- Analyze Data
  - Try to estimate parameter values from visualizing data
  - Estimate parameters by using regression

Tumor Growth Modeling using the Exponential Function

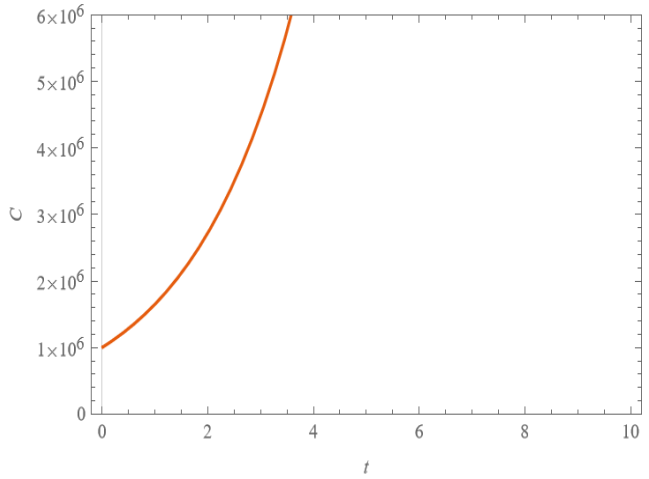
Evolution equation:

$$\frac{dC}{dt} = kC$$



Solution:

$$C(t) = C_0 e^{kt}$$



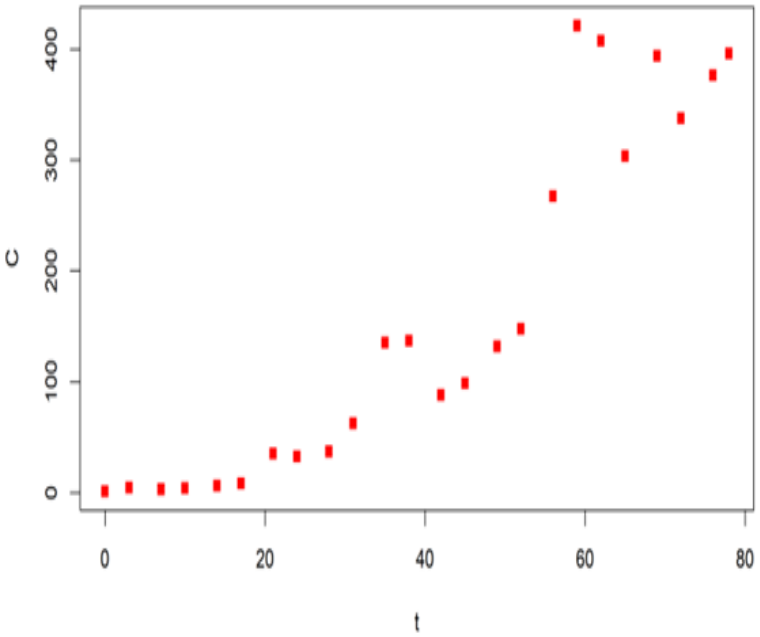
where C is tumor cell density, t is time, and k is the intrinsic growth rate.

C_0 and k are needed for these plots. Some sources:

- $k = \frac{\ln 2}{T_p}$, where T_p is doubling time, C_0=?.
- Experimental literature.
- Lab data.

Exponential: Finding k from Data

Data: Mouse tumor volume, C, in mm^3, as a function of time, t, in *hours*, [4].



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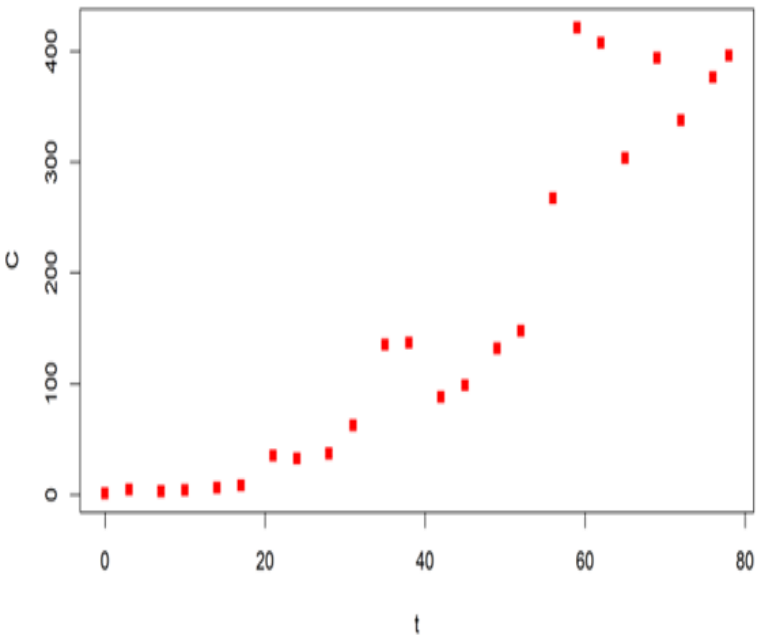


In all cases: $C_0 = 1.041$

Regression	$k = 0.0943$
Solver - SSE	k=0.0804
Solver - Relative SSE	k=0.0826
Dynamic k	k=0.099294

Table: Regression was performed using $C_0 = 1.041$. The relative SSE is $\sum_i^n \frac{(y_i - \hat{y}_i)^2}{y_i^2}$. Here, the dynamic k is the mean (after removing very extreme outliers) of the $k = \frac{1}{C}\frac{dC}{dt}$ by using: $\frac{1}{C_{i-1}}\frac{C_i - C_{i-1}}{t_i - t_{i-1}}$.

Results

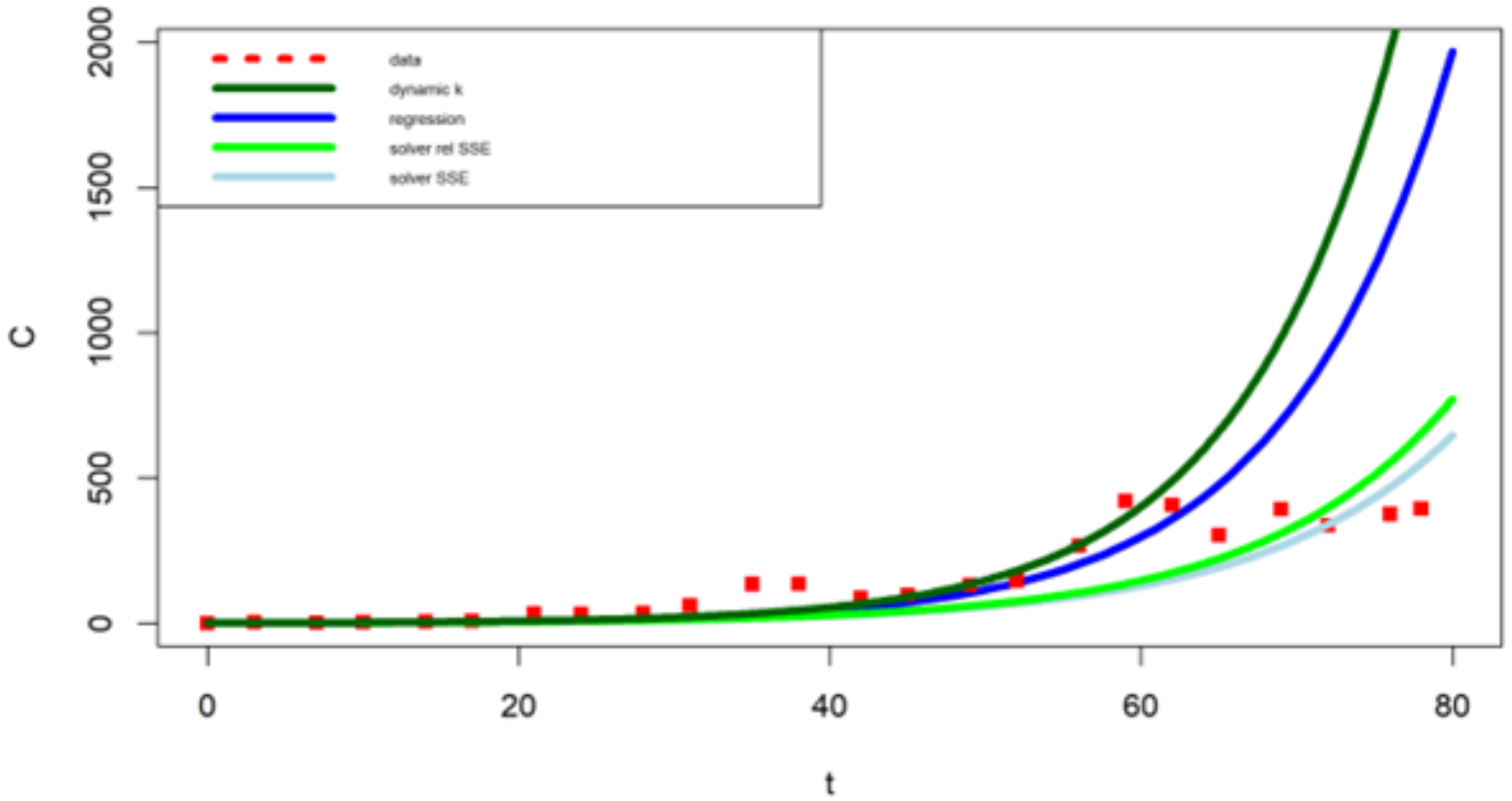


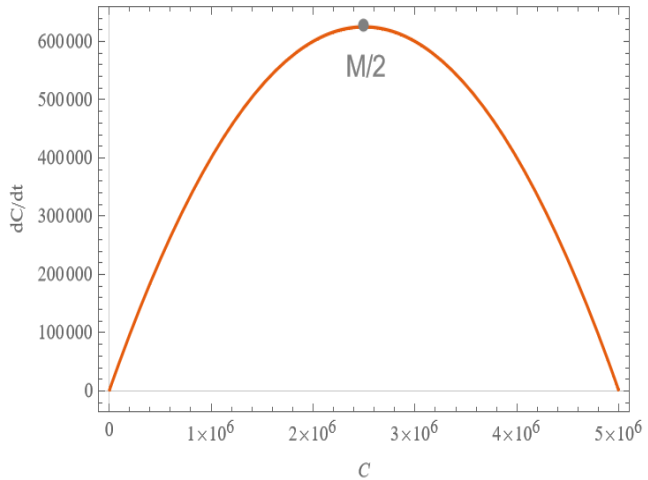
Figure: Exponential functions using different k intrinsic growth rates for a fixed initial tumor volume $C_0 = 1.04mm^3$.

Logistic

- Exponential function does not represent a good fit for the data.
- Need: A model that includes a slow down of the growth rate later on when the tumor is larger, i.e., new rate$= f(C)$.
- Try: Relative growth rate, $\frac{1}{C}\frac{dC}{dt}$, declines linearly with increased tumor size, C, i.e., $k_1 = k\left(1 - \frac{C}{M}\right)$.

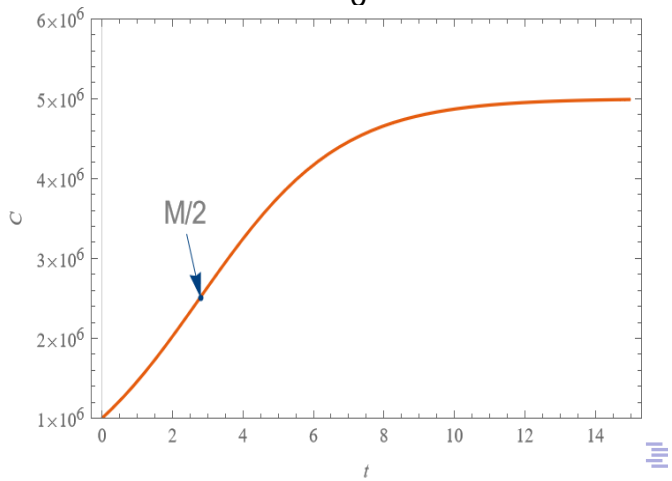
Evolution equation:

$$\frac{dC}{dt} = \left[k\left(1 - \frac{C}{M}\right)\right] C$$



Solution:

$$C(t) = \frac{M}{1 + \frac{M - C_0}{C_0} e^{-kt}}$$



Logistic: Finding k from Data

For the logistic growth: $k = \frac{1}{C}\frac{1}{1-\frac{C}{M}}\frac{dC}{dt}$.

In all cases $M = 421.47$ obtained from regression.

Regression	$k = 0.1086$
Solver - SSE	k=0.1085776
Solver - Relative SSE	k=0.1033
Dynamic k	k=0.173953

Table: Dynamic k: the mean (after removing very extreme outliers) of the k values from: $\frac{1}{C_{i-1}\left(1-\frac{C_{i-1}}{M}\right)}\frac{C_i - C_{i-1}}{t_i - t_{i-1}}$.

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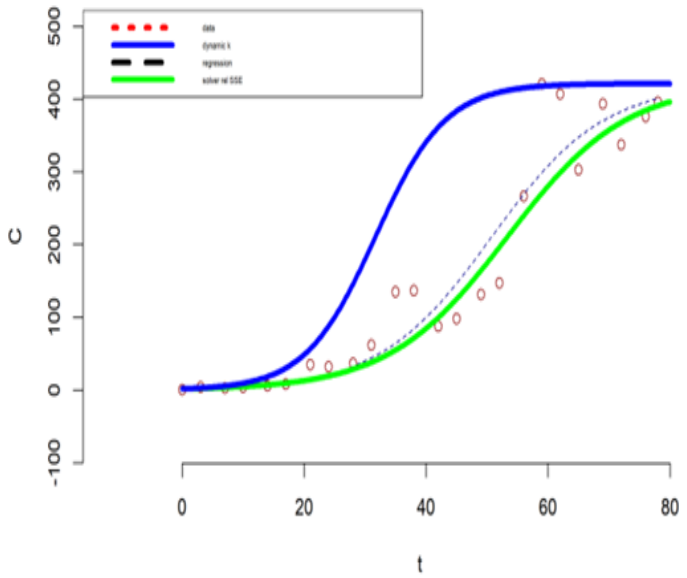

Figure: Logistic growths using different k values.

Random Forests (RF) Algorithm

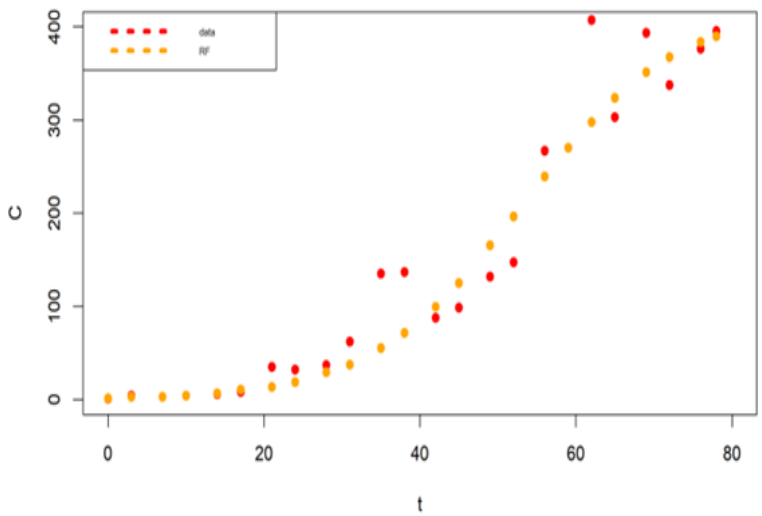

Figure: RF algorithm using random numbers from a normal distribution around points for each subinterval of the logistic regression function as a training data set, and original data values as a testing data set. MAE=30.591 (vs MAE=30.45 for logistic, the green line).

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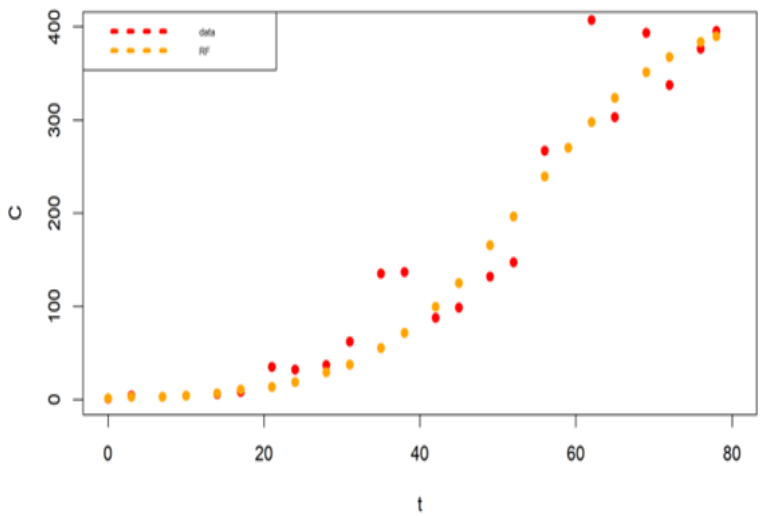

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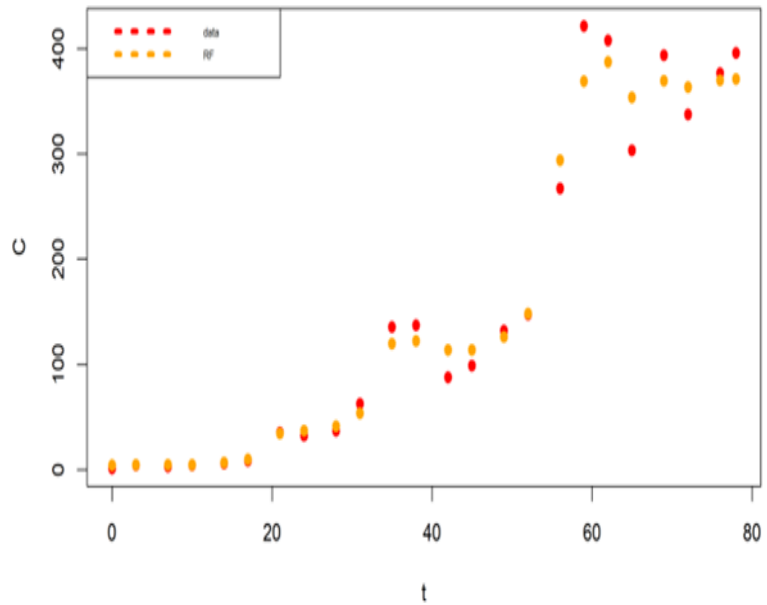


Figure: RF algorithm using randomly generated numbers from an uniform distribution from each subinterval as a training data set, and original data values as a testing data set. MAE=30.6.

Random Forests (RF) Algorithm

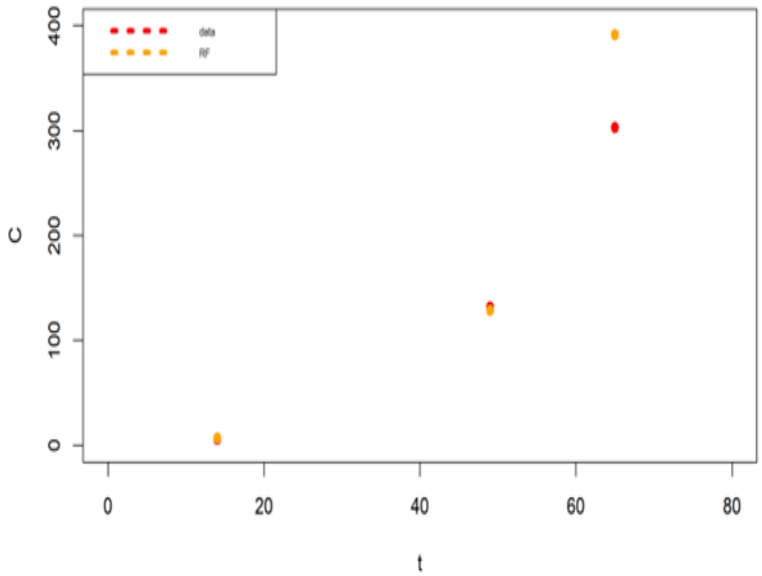
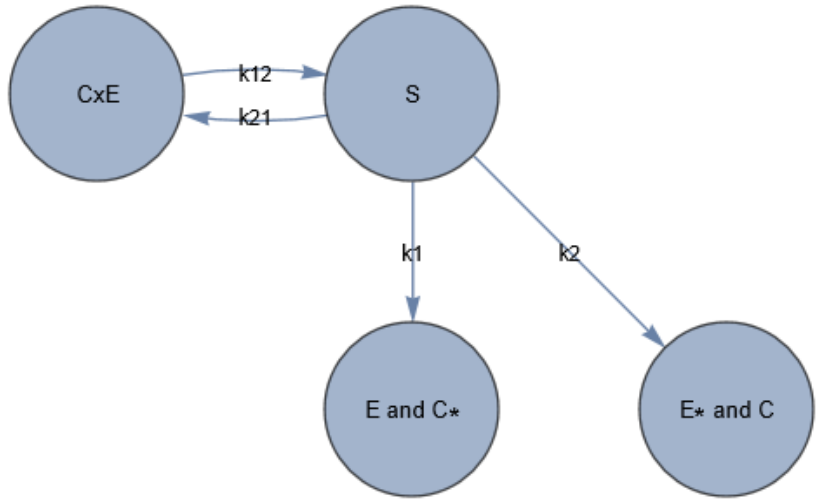


Figure: RF algorithm using original data splitted into train/test using the following percents: 87.5%/12.5%.

Immunotherapy

- Assumption: Tumor growth follows a logistic function.
- Need to add the effect of effector cells, E.
- Terms can be added to the system according to diagram:

Tumor cells, C, and effector cells, E, form a complex, S.



$$\begin{cases} \frac{dC}{dt} = kC\left(1 - \frac{C_{tot}}{M}\right) + \ldots\ldots - \ldots\ldots + \\ \frac{dE}{dt} = \ldots\ldots - \ldots\ldots + \ldots\ldots, \\ \frac{dS}{dt} = \ldots\ldots - \ldots\ldots - \ldots\ldots - \ldots\ldots, \\ \frac{dE_*}{dt} = \ldots\ldots, \\ \frac{dC_*}{dt} = \ldots\ldots \end{cases}$$

Immunotherapy

System of equations becomes:

$$\begin{cases} \frac{dC}{dt} = kC\left(1 - \frac{C_{tot}}{M}\right) - k_{12}CE + (k_{21} + k_2)S, \\ \frac{dE}{dt} = -k_{12}CE + (k_{21} + k_1)S, \\ \frac{dS}{dt} = k_{12}EC - (k_{21} + k_1 + k_2)S, \\ \frac{dE_*}{dt} = k_2 S, \\ \frac{dC_*}{dt} = k_1 S, \end{cases} \tag{1}$$

where $C_{tot} = C + S$.

Immunotherapy

More assumptions:

(a) Constant rate of effector cells, α.

(b) Effector cells are dying (and clearing).

(c) E_*, are clearing.

(d) C_*, are clearing.

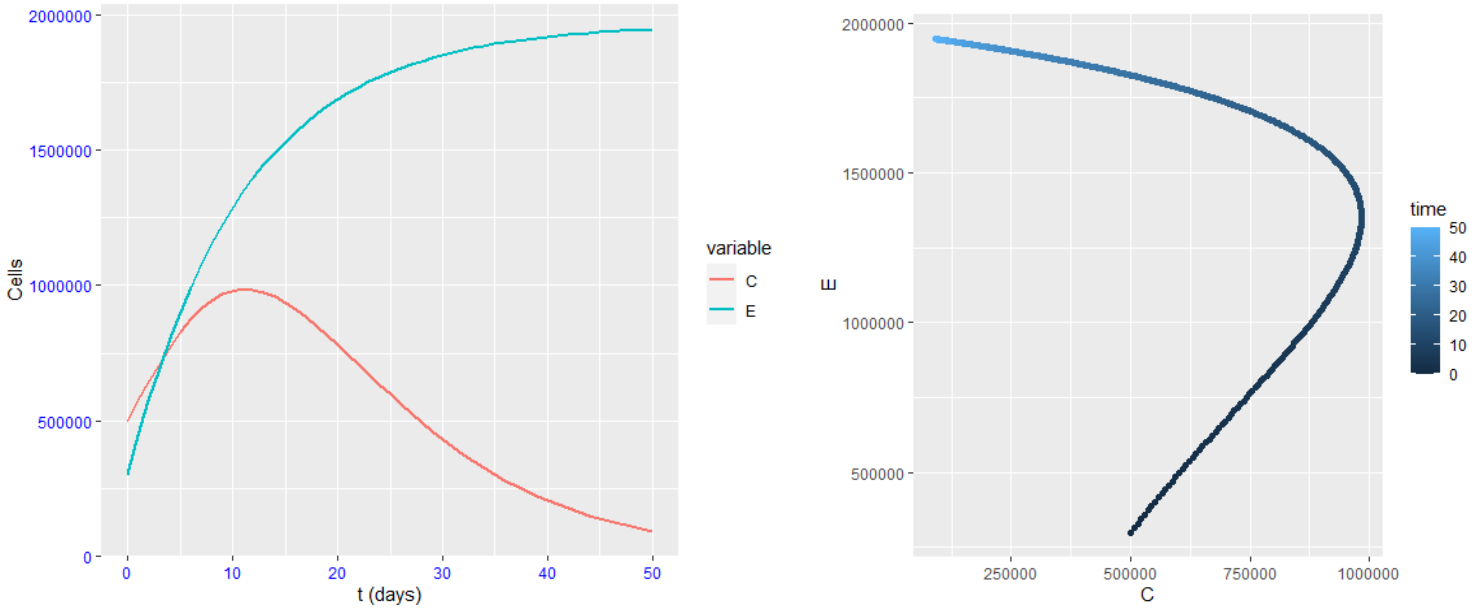
(e) Recruitment of the effector cells to the tumor site.

$$
\begin{cases}
\frac{dC}{dt} = kC\left(1 - \frac{C_{tot}}{M}\right) - k_{12}CE + (k_{21} + k_2)S, \\
\frac{dE}{dt} = \underbrace{\alpha}_{\text{(a)}} + \underbrace{f_{M-M}}_{\text{(e)}} - k_{12}CE + (k_{21} + k_1)S \\
- \underbrace{\delta E}_{\text{(b)}}, \\
\frac{dS}{dt} = k_{12}EC - (k_{21} + k_1 + k_2)S, \\
\frac{dE_*}{dt} = k_2 S, - \underbrace{\beta E*}_{\text{(c)}}, \\
\frac{dC_*}{dt} = k_1 S - \underbrace{\gamma C*}_{\text{(d)}}.
\end{cases}
$$

Immunotherapy: A Two Population Model

Based on experimental observations the system is reduced to:

$$\begin{cases} \frac{dC}{dt} = \underbrace{kC(1 - C/M) - cCE}_{\text{(i)}}, \\ \frac{dE}{dt} = \underbrace{p + \frac{aCE}{b + C} - dE - gCE}_{\text{(ii)}}. \end{cases} \tag{2}$$



Immunotherapy: A Two Population Model - Mosaic Calculus Modules, from Daniel Kaplan, Macalester College: *https://www.mosaic-web.org/MOSAIC-Calculus/*.

Using **mosaicCalc** package in R:

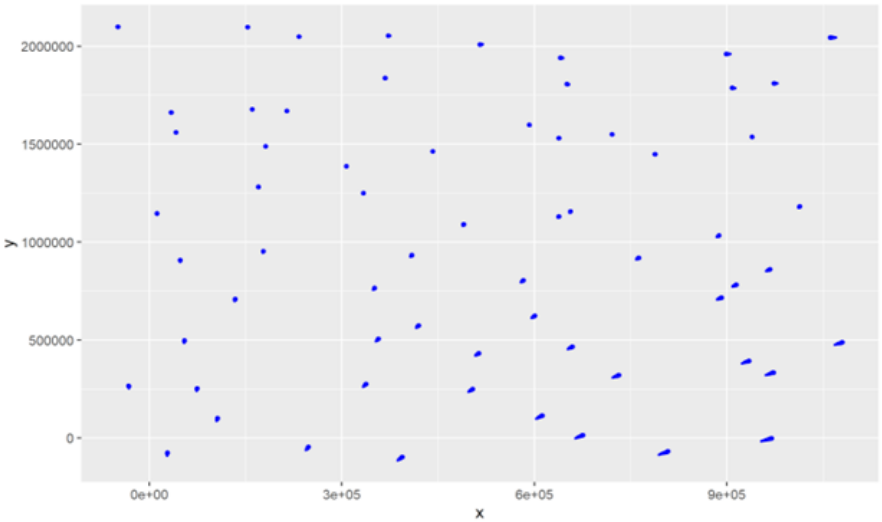


Figure: Streamline field: streamlines(dx $\sim$ (i), dy $\sim$ (ii), domain(x=0:1000000, y=0:2000000), npts = 8, dt = 0.01, nsteps = 10, color = "blue", alpha = 7). Here, (i) and (ii) are the RHS of the Eqs. 2.

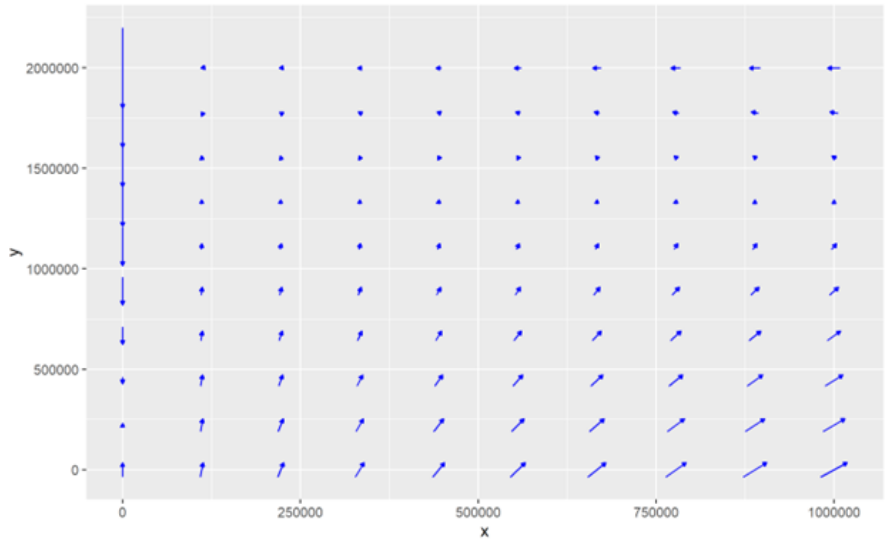


Figure: Flow field: flow_field(dx $\sim$ (i), dy $\sim$ (ii), domain(x=0:1000000, y=0:2000000), npts = 10, scale = 0.9, color = "blue", alpha = 5). Here, (i) and (ii) are the RHS of the Eqs. 2.

Immunotherapy: A Two Population Model - MosaicCalc

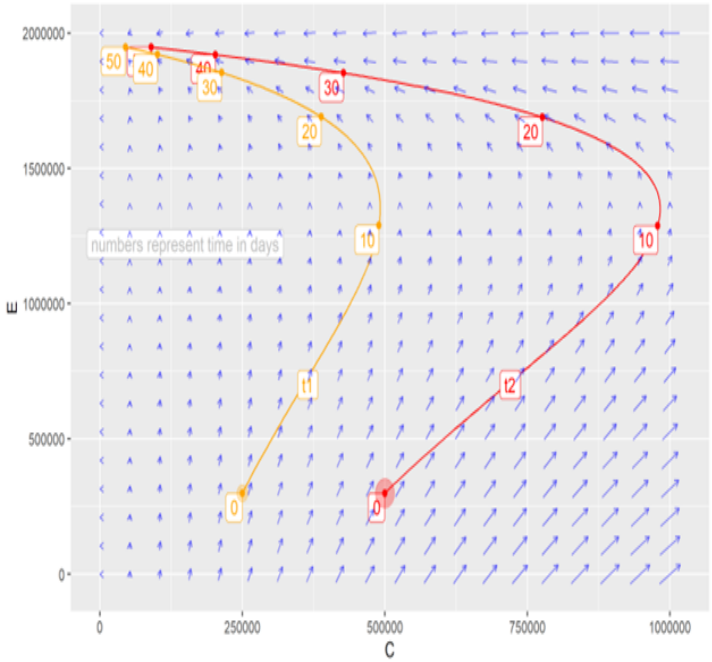


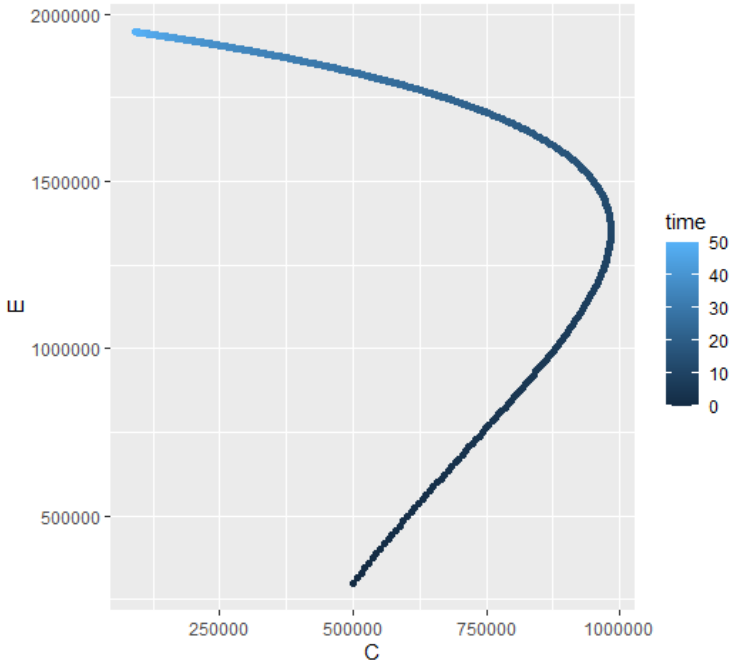
Figure: Vector field and trajectories, T1 and T2, with marked times (in days).

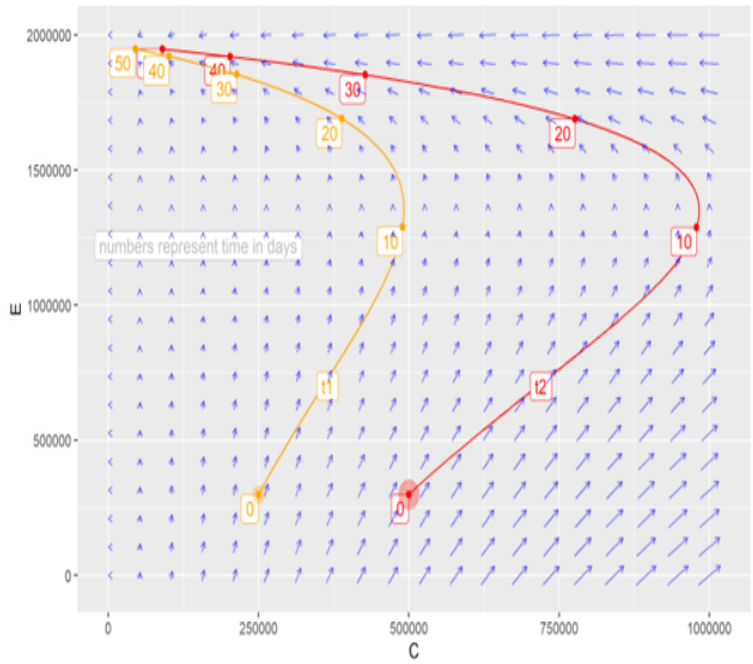
```
library(mosaicCalc)
Pts1 ← tibble(x = 500000, y = 300000)
Pts2 ← tibble(x = 250000, y = 300000)
soln1 = integrateODE(dx ∼ (i), dy ∼ (ii), x=500000, y=300000,
domain(t=0:50))
soln2 = integrateODE(dx ∼ (i), dy ∼ (ii), x=250000, y=300000,
domain(t=0:50))
gf_label(1220000 ∼ 150000, label="numbers represent time in days",
color="gray")% > %
traj_plot(y(t) ∼ x(t), soln1, col="red")% > %
traj_plot(y(t) ∼ x(t), soln2, col="orange")% > %
gf_point(y ∼ x, data = Pts1, color = "red", size=7, alpha=0.3)% > %
gf_label(700000 ∼ 365000, label="t1", color="orange")% > %
gf_point(y ∼ x, data = Pts2, color = "orange", size=4, alpha=0.3)% > %
gf_label(700000 ∼ 720000, label="t2", color="red")% > %
vectorfield_plot(C ∼ (a), E ∼ (b), color="blue",bounds(x=0:1000000,
y=0:2000000))
```

(i) and (ii) are as in Eqs. 2 with $x = C$, and $y = E$.

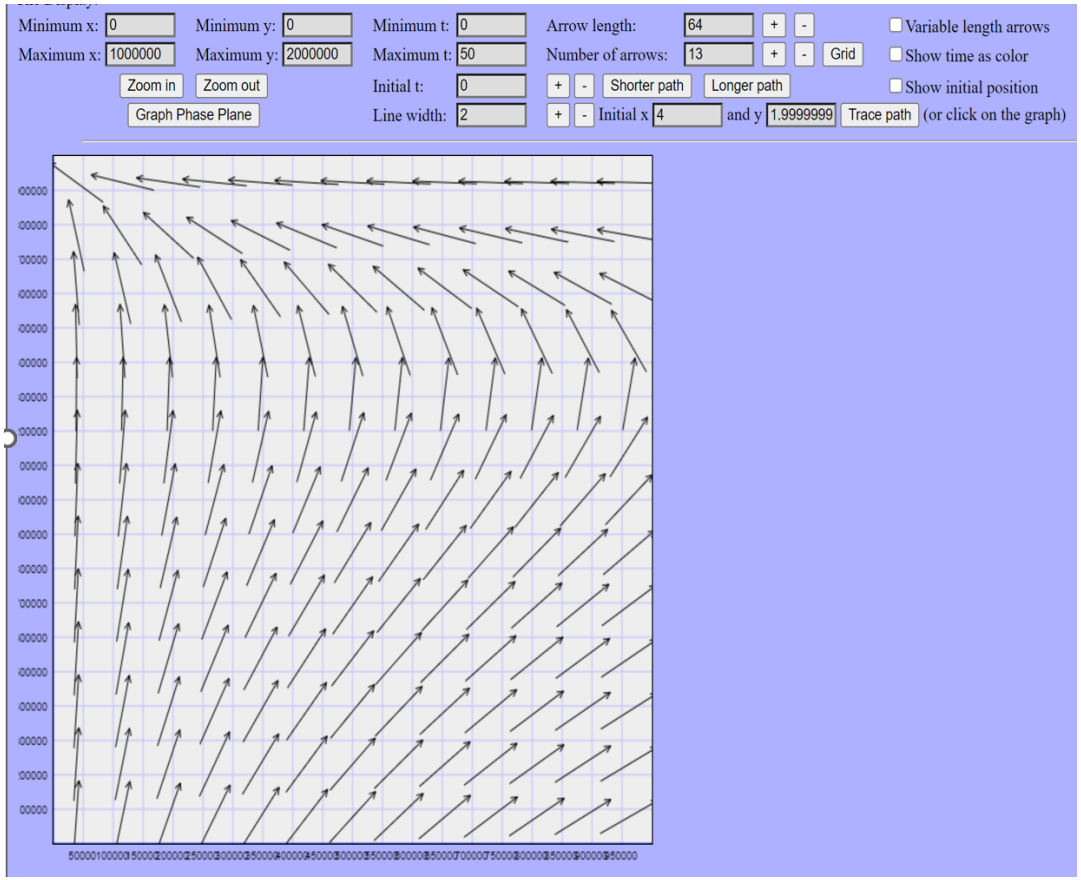
Immunotherapy: A Two Population Model

1. The trajectory shown in the left figure is identical to T1 or T2 (from the figure shown on the right)?
2. What does the vector plot (on the right) suggest? Is tumor dynamic sensitive to the initial tumor size? Is tumor dynamic sensitive to the initial number of effector cells?





Immunotherapy: A Two Population Model



MATLAB plotter written by John C. Polking of Rice University:

https://aeb019.hosted.uark.edu/pplane.html.

Immunotherapy: A Two Population Model

Nondimensional Kuznetsov-Taylor system

$$\begin{cases} \frac{dx}{d\tau} = \sigma + \frac{\rho xy}{\eta + y} - \mu xy - \delta x \\ \frac{dy}{d\tau} = \alpha y(1 - \beta y) - xy \end{cases} \tag{3}$$

- Nullclines:

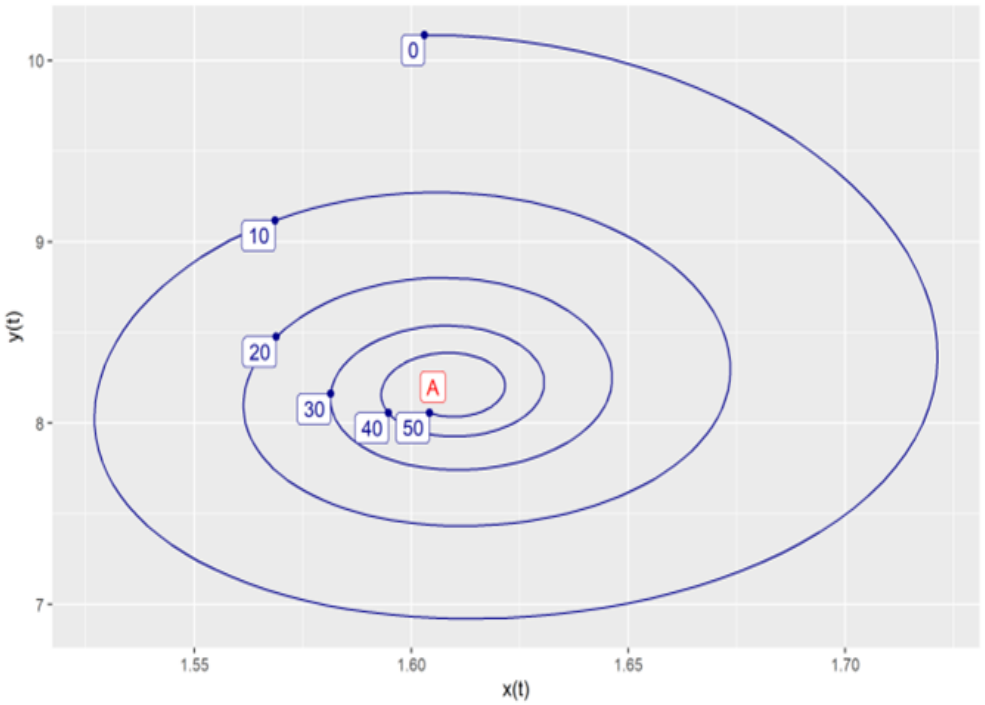
$$\begin{cases} y = 0 \\ x = \alpha(1 - \beta y) \\ x = \frac{\sigma}{\delta - \frac{\rho y}{\eta + y} + \mu y} \end{cases} \tag{4}$$

- There are up to 4 possible steady states (depending on parameter values).
- **Tumor-free equilibrium** given by $(x_e, y_e) = (\frac{\sigma}{\delta}, 0)$, from the intersection of two nullclines.
  - Stability of $(x_e, y_e) = (\frac{\sigma}{\delta}, 0)$ depends on parameter values.

Immunotherapy: A Two Population Model - MosaicCalc

For Eq. (3), J (the Jacobian matrix) =

$$\begin{bmatrix} -\delta - \mu y + \frac{\rho y}{y+\eta} & \left(\frac{\eta\rho}{(y+\eta)^2} - \mu\right) x \\ -y & -x + \alpha - 2\alpha\beta y \end{bmatrix}$$



- At point A: determinant$(J) > 0$ and trace$(J) < 0 \Rightarrow$ A is asymptotically stable.
- Point A is an example of a steady state corresponding to a **dormant tumor**; a relatively low number of tumor cells.

Immunotherapy: A Three Population Model - MosaicCalc

C=tumor cells, E=effector cells, T=$CD8^+$ T-cells

$$\begin{cases} \frac{dC}{dt} = \underbrace{kC(1-C/M) - cCE}_{\text{(a)}} \\ \frac{dE}{dt} = \underbrace{p + \frac{aCE}{b+C} - dE - gCE,}_{\text{(b)}} \\ \frac{dT}{dt} = \underbrace{-mT + \frac{jD^2}{k+D^2}T - qTC + rCE}_{\text{(c)}}. \end{cases} \tag{5}$$

where $D = d\frac{\left(\frac{T}{C}\right)^\lambda}{s+\left(\frac{T}{C}\right)^\lambda}$ is the fractional kill rate for tumor specific $CD8^+$ T-cells (de Pillis-Radunskaya Law).

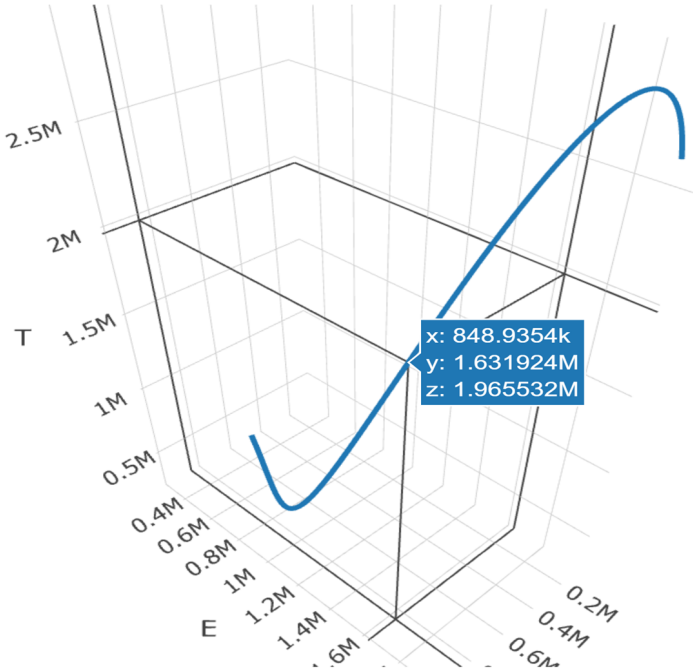


Figure: 3D trajectory: library(mosaicCalc), soln3=integrateODE(dC ~ (a), dE ~ (b), dT ~ (c), C=500000, E=300000, T=300000, domain(t=0:50)), traj_plot_3D(C, E, T, soln3, npts=5000). (a), (b), and (c) are as in Eqs. 5.

References

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- 2. Kuznetsov, V. A., Makalkin, I.A., Taylor, M. A., & Perelson, A. S. (1994). Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. *Bulletin of mathematical biology, 56*(2), 295-321.
- 3. Kuznetsov, V. A. & Knott, G. D. (2001). Modeling tumor regrowth and immunotherapy. *Mathematical and Computer Modelling, 33*(12-13), 1275-1287.
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THANK YOU!

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