Drexel University

Office of the Dean of the College of Engineering

ENGR 232 – Dynamic Engineering Systems

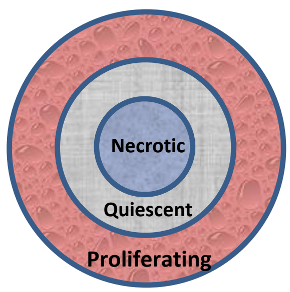
Lab 1: Bertalanffy Model of a Tumor

Summer 2022

Background: In this lab, we will investigate the use of direction fields to evaluate solutions to first-order differential equations and introduce many important MATLAB commands for working exactly with integrals and differential equations. We will explore these qualitative and exact analysis tools via the example of tumor growth. A very general model of tumor growth is that the volume rate of growth is based on the difference between a growth term and a degradation (or necrosis) term.

$$\frac{dV}{dt} = \underbrace{aV^{\alpha}}_{\text{Growth}} - \underbrace{bV^{\beta}}_{\text{Degradation}}$$

Different choices of the four parameters a, b, α *and* β give many important growth models including the **logistic** equation, the **Gompertz** equation and the **Bertalanffy** equation. Let's focus on the Bertalanffy model, which can be explained using this conception of a tumor as composed of three layers.



Multicellular tumor spheroid (MTS)

The central core of the tumor is **necrotic** (dead) having been starved of nutrients. This is surrounded by a nonproliferating layer (**quiescent**) and finally on the outside is the layer of rapidly **proliferating** cells. This third layer is where all the growth occurs.

The Bertalanffy model assumes that growth rate is proportional to the surface area, and the degradation rate is proportional to the entire volume. Since volume is proportional to r^3 and surface area of the tumorous sphere is proportional to r^2, the above general equation reduces to:

$$\frac{dV}{dt} = \overbrace{aV^{2/3}}^{\text{Area}} - \overbrace{bV}^{\text{Volume}}$$

Bertalanffy Model of Tumor Growth

Equilibrium Values: When the tumor achieves an equilibrium size, we must have $\frac{dV}{dt} = 0$.

The parameters a and b determine the final size $V(\infty)$.

$$aV^{2/3} = bV \quad \rightarrow \quad a = b\,V^{1/3} \quad \rightarrow \quad \left(\frac{a}{b}\right)^3 = V(\infty)$$

Let's now choose b so that the final volume is $V(\infty) = 8$ cubic centimeters, a good-sized tumor!

The DE becomes:

$$\frac{dV}{dt} = a \cdot V^{2/3} - \frac{a}{2} \cdot V$$

Here a is the growth rate and $b = \frac{a}{2}$ is the degradation rate. We will set $a = 1$ to fix this parameter for now.

Part A. Open MATLAB and review basic techniques like symbolic integration and solution of differential equations using dsolve. It is always a good idea to initialize your workspace when you start a new problem. This helps clear out any variables that may have been used in previous problems. Just to review how the clear command works, enter the following two values for the growth rate and decay rate for our Bertalanffy tumor.

```
a = 1;   b = a/2;
```

If you type in either a or b, MATLAB returns the value you just entered. OK, let's clear these values. Enter clear, then see if MATLAB still knows a and b. Next type in clc. What does it do? Explore the help facility by entering: help clear and help clc.

Solving differential equations usually involves finding integrals. MATLAB's int command can help! First, get help on the int command. >> help sym/int

Note: You must always declare any symbolic variables before attempting a symbolic integration.

Example 1: Find the indefinite integral of $y = 3x^2$ and denote it using Y.

```
syms x c  % Constant of integration c.
y = 3*x^2
Y = int(y, x) + c
```

Try it, and verify the integral is $Y = x^3 + c$. It's always a good idea to verify your work and check the answer.

```
% Let's check our answer is correct.
check = diff(Y,x) - y % This should be zero.
simplify(check)
```

You can use the **int** command to find just about any integral which has a closed-form expression.

Question 1: Find the indefinite integral of $y = \frac{75+25x^2}{1-x^4}$. and display the answer in the box below. Find: $Y = \int \frac{75+25x^2}{1-x^4} dx + c$

Note that by default, MATLAB does not display the constant of integration c. You should include that in your answer explicitly.

Question 1: The integral Y is: _ _ _

Paste code here:

Using the **diff** command, verify your answer is correct.

MATLAB can also solve many differential equations exactly using the dsolve command. First clear your variables and command window, then get help on the dsolve command. Spend a few minutes reviewing that help info. There is lots of good stuff!

Example 2: **a.** Solve the second-order differential equation: $\frac{d^2x}{dt^2} = -4x$

You may recognize this as simple harmonic motion and should expect two constants of integration.

```
syms x(t)   % x is the dependent variable, t is independent.
DE = diff(x,t,t) == -4*x    % Use == to separate the LHS and RHS of the DE
sol = dsolve(DE)            % Solve the DE.
```

Note the use of == to separate the LHS and RHS of equations.

Record your answer here: _ _ _ _ _ _ _ _ _ _ ___ _ _ _ _ (Not graded)

b. Now find the solution with the initial conditions $x(0) = 1,\ x'(0) = 4$. We'll start from scratch.

```
clear, clc
syms x(t)           % x is the dependent variable, t is independent.
Dx = diff(x)        % the derivative of x wrt time
DE = diff(x,t,t) == -4*x        % Use == to separate the LHS and RHS of the DE
dsolve(DE, x(0)==1, Dx(0)==4)   % Solve the DE with initial conditions
```

Specify initial conditions after the DE.

Record your answer here: _ _ _ _ _ _ _ _ _ _ _ ___ _ _ _ _ (Not graded)

Question 2: Find the general solution to this new differential equation. Place your code and answers in the numbered box below. No initial condition is given so your answer will involve a constant *c* which MATLAB will helpfully generate for you.

$$\frac{dy}{dt} + 5y = 13 + 15t$$

Question 2. The general solution is: _ _ _

Paste your code here:

Question 3: Find the specific solution to the DE $\frac{dy}{dt} + 5y = \ 13 + 15t$ with the initial condition that: $y(0) \ = 0$
Also, paste your code at the bottom of the box.

Question 3. The solution satisfying $y(0) = 0$ is: $y(t) \ = \ \_\_\_$

Paste your code here:

Ungraded Practice: Now find the specific solution satisfying $y'(0) \ = 3$ instead. Note the derivative!
You do not need to record the answer. You should find it's just the straight line: $y(t) = 3t + 2$
Hint: Define `Dy = diff(y,t);` then specify `Dy(0)==3` inside the `dsolve` command.

Question 4: The **Bertalanffy** differential equation on the first page is a challenging non-linear, autonomous differential equation. But let's see if MATLAB can solve it exactly. No harm in at least trying.

Clear all your variables. Now enter the values for the growth rate and the degradation rate of the tumor once again.

```
a = 1;  b = a/2;
```

The volume $V(t)$ of the tumor is a function of time – it's growing!

```
syms V(t);
```

Now enter the **Bertalanffy** differential equation into MATLAB and name it **DE**. You can directly use `a` and `b` in your code.
MATLAB uses `log` for the natural log.
Don't forget to use `==` to denote equality in the equation.

Karl Ludwig von Bertalanffy
Father of Systems Theory

DE = _____

$$\frac{dV}{dt} \ = \ aV^{2/3} \ - \ bV$$

Now solve the DE <u>exactly</u> using `dsolve` and record your command and the specific solution starting with a volume of 1 at time 0. That is, find the solution starting with $V(0) = 1$. The solver may return three solutions because of the two-thirds power. Ignore the two solutions containing complex numbers. We know the volume must be a real number.
Record your code and the answer in the box below. Express your answer as the cube of a term containing an exponential.

Question 4. The solution satisfying the initial condition $V(0) = 1$ is: $V(t) = \ \_\_\_$

Paste your code here:

```
a = 1; b = a/2;
syms V(t)
% Now enter the Bertalanffy differential equation & name it DE. Find solution using dsolve.


% Take only the  real solution. Ignore the two imaginary solutions.
```

Question 5: Plot the Tumor's Growth:

If you stored the answer in a variable, say using: sol = dsolve(_ _ _ _)
you can convert that answer to a MATLAB function using:

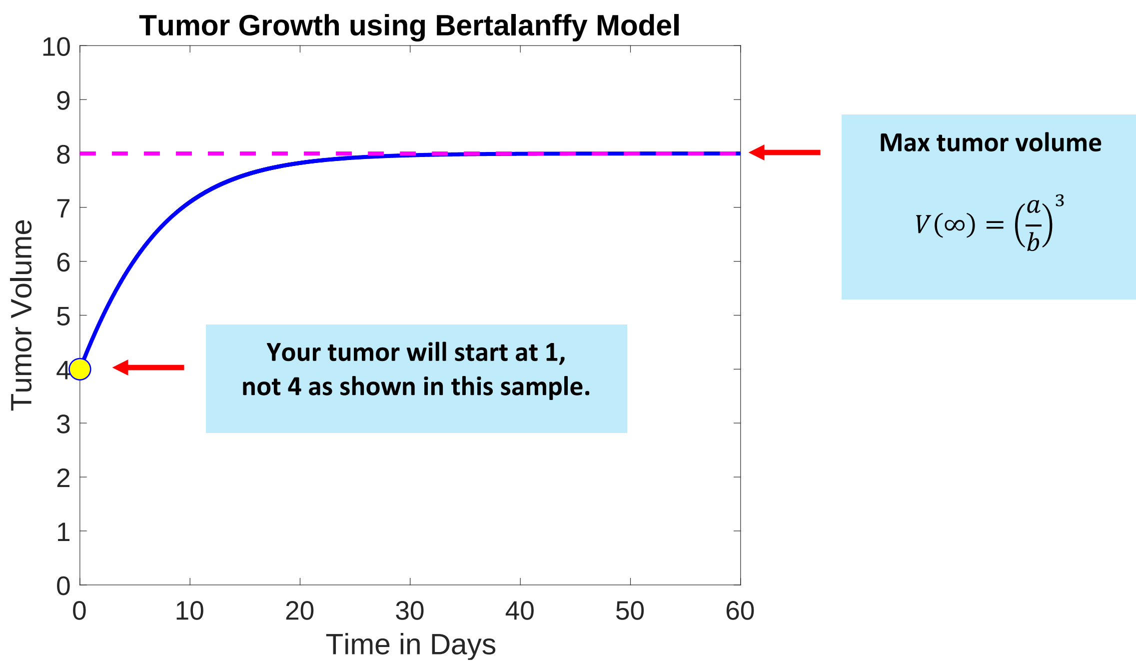
V = matlabFunction(sol(1));

Above, take only the real solution, which is likely the first. That's why you see sol(1).

Now create a plot of your tumor's growth using a **blue** line with **'LineWidth'** of 3. Add a **title** as shown and label both axes using **xlabel** and **ylabel**. Turn on the **grid** and adjust the **'fontsize'** to 20. Use the **axis** command to set limits as shown.

Alert: Unlike the sample curve below, your tumor will start with the smaller volume of $V(0) = 1$ cubic centimeter, not the (initially) much larger tumor shown which has started at half its maximum volume.

Sample



Start your figure as follows. Then add the plot for $V(t)$.

```
close all
figure('Name','Lab 1: Bertalanffy Model', 'NumberTitle','off');
Tmax = 60  % Plot the tumor for 60 days or about two months
```

Some customization ideas for your plot are in the second box. Only use these after you have added the solution curve.

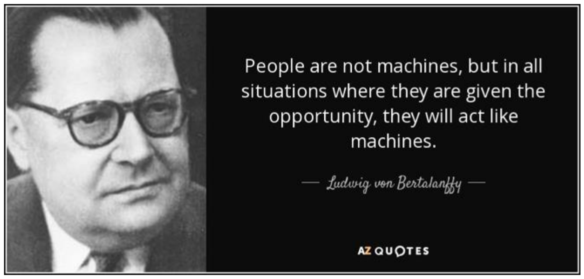
```
ax = gca;  % current axes
ax.FontSize = 20;
% set(gca, 'fontsize', 20)  % An alternative approach

% Customize the figure
grid on
axis([0 Tmax 0 10])
```

Q5. Paste your completed graph in the answer template.

Part B: Qualitative Analysis

The **Bertalanffy** differential equation is somewhat difficult to solve, but as we just saw, MATLAB quickly dispatched with the challenge. That's really impressive raw power! Now let's explore the solutions graphically to get a better intuition about the Bertalanffy model.



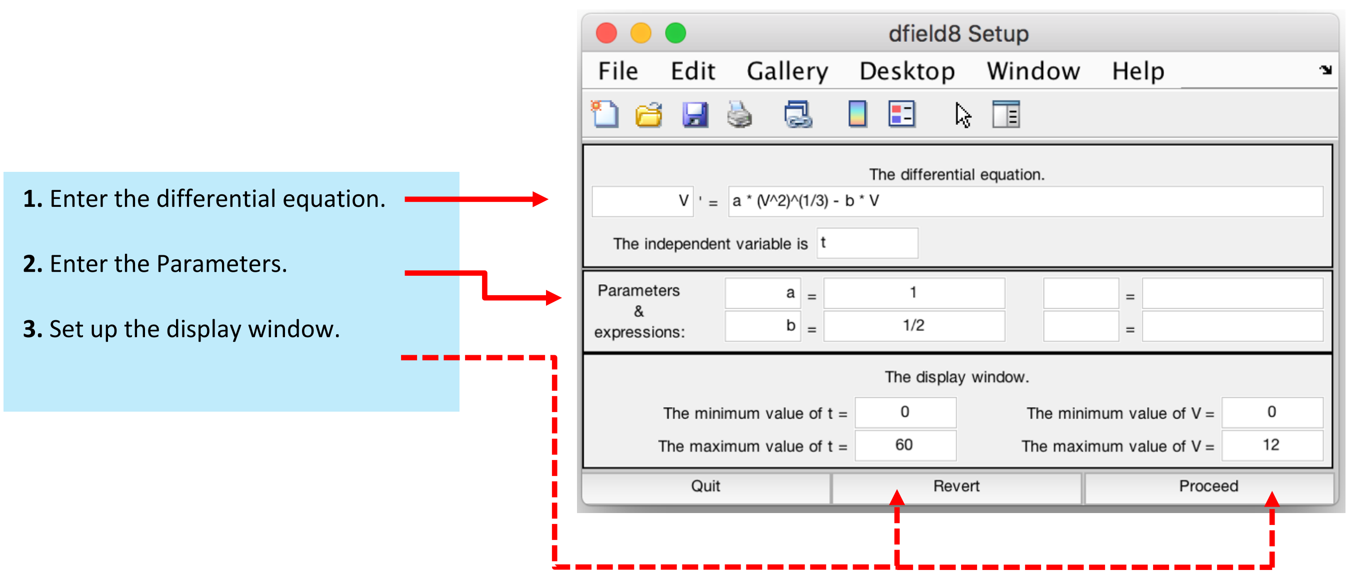
We will now use the direction field tool to examine the solution.
Download the dfield8.m file available in the **Software** folder. Look in the subfolder:

MATLAB Versions of pplane8 and dfield8

Place in MATLAB's present working directory or pwd, then run it by entering: dfield8
in your MATLAB command window. Do <u>not</u> type the suffix .m
OR run it by double clicking on the dfield8 file.

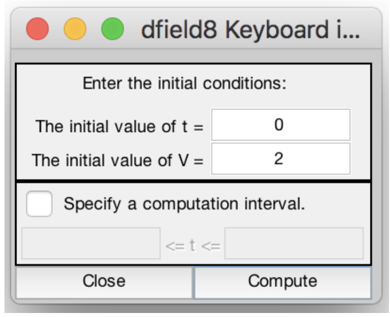
Plot the direction field for the **Bertalanffy** differential equation using dfield8.m. Set time from 0 to 60 (two months), and V from 0 to 12. Let $a = 1$ and $b = 0.5$ as before, using the **Parameter Expressions** fields.

$$\frac{dV}{dt} = aV^{2/3} - bV$$

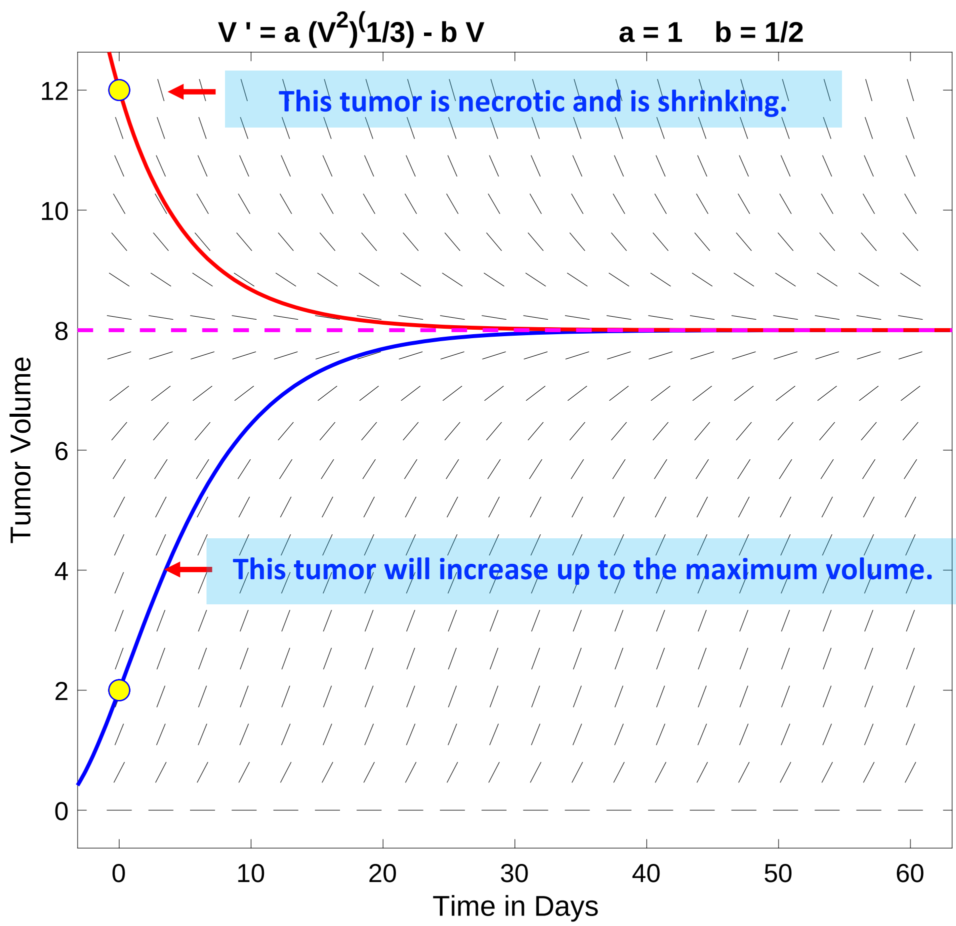


Alert: Extremely important: Notice how I entered the $V^{2/3}$ term as: **(V^2)^(1/3)** instead of **V^(2/3)**
This prevents the annoying appearance of complex numbers when the server steps backwards into negative volume – which will fatally crash the solver and force you to start all over!!

The graph below shows two solutions starting at V(0) = 2 and V(0) = 12 obtained using the **<u>keyboard input</u>** option available under the **Option** menu.



The top curve represents a large tumor, which has lost some of its former blood supply due to necrosis and is now shrinking to its **<u>new</u>** limiting value of 8 cubic centimeters.



Questions 6-7: Growing and shrinking tumors

a. Add 5 more solutions so that the volume at times 10, 20, 30, 40, and 50 days is 2 cc. These tumors are growing.
b. Add 5 more solutions so that the volume at times 10, 20, 30, 40, and 50 days is 12 cc. These tumors are shrinking.
Use the **View > Property Editor** so **<u>all</u>** the necrotic curves are shown in **red** and the growing tumors are shown in **blue**.

Questions 6-7: Paste your completed image in the Answer Template. Also, <u>insert</u> a copy of your completed image as a picture into you Live Script for submission.

Question 8: The critical values for this equation are $V = \left(\frac{a}{b}\right)^3 = 8$ cc and $V = 0$ cc. The equilibrium point at the origin is **semistable**. Is the critical point at $V = \left(\frac{a}{b}\right)^3 = 8$ stable, unstable or semistable?

Question 8: Stability: Stable or Unstable?

The critical value $V = \left(\frac{a}{b}\right)^3 = 8$ is: ___

Hint: This phase plot for the next question, might also help you with the above question.
It plots $f(V) = aV^{2/3} - bV$ versus V for our Bertalanffy differential equation.

The Stability Theorem.

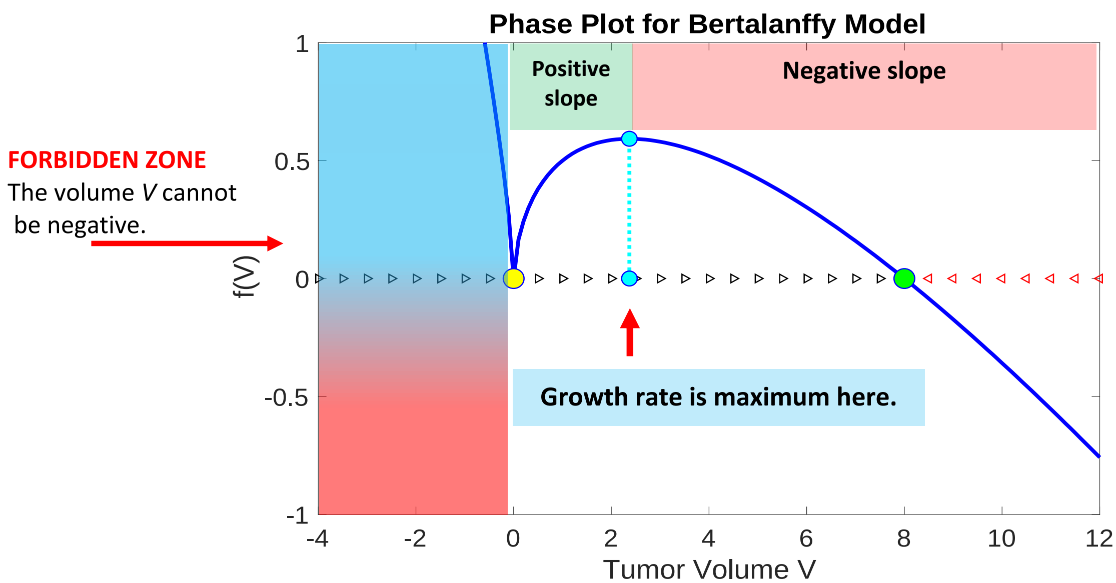
Stability Theorem: Let $\frac{dy}{dt} = f(y)$ be an autonomous 1st-order differential equation and let $f(y)$ be differentiable.
Suppose y^* is a critical point, that is, $f(y^*) = 0$.
If $f'(y^*) < 0$, the equilibrium point is **stable**. On a graph, $f(y)$ changes from positive to negative, moving left to right.
If $f'(y^*) > 0$, the equilibrium point is **unstable**. On a graph, $f(y)$ changes from negative to positive, moving left to right.

If the derivative at the critical point is also zero, i.e. $f'(y^*) = 0$ apply these criteria: (moving left to right)
$+-$ (Stable) $-+$ (Unstable) $++$ or $--$ (Semi-stable)

Question 9: Fastest Growth

The tumors are growing the fastest at the maximum for $f(V)$ below, since $f(V)$ gives their rate of change:

$$\frac{dV}{dt} = f(V) = aV^{2/3} - bV$$



The maximum growth rate occurs at the volume satisfying: $0 = \frac{df}{dV} = \frac{2a}{3} V^{-1/3} - b$

This maximum growth rate is at:

$$\frac{2a}{3b} = V^{1/3} \quad \rightarrow \quad V = \boxed{\left(\frac{2a}{3b}\right)^3}$$

Since we set $b = a/2$, the maximum growth rate is at:

$$V = \left(\frac{4}{3}\right)^3 = \frac{64}{27} = 2.3704$$

Derive the volume V at which the growth rate of the tumor is maximum using MATLAB. We just derived it by hand above – see light blue box. Your formula should work for any value of the parameters a and b. Use diff() and solve().
Here's some starter code.

```
% Find at what volume the tumors are growing the fastest.
clear, clc
syms a b V
f = a * (V)^(2/3) - b * V ;  % The RHS of the Bertalanffy DE.

% The tumors grow the fastest when f(V) is a  maximum.
% That's when the derivative of f(V) wrt V is zero.
% Add code here.
```

Question 9: Paste in the code you added to solve for the volume V at which the tumor grows the fastest.
Label the result **V_max_growth**. Then paste in MATLAB's answer for **V_max_growth**.
Answer must use both *a* and *b* as symbols.
Tip: Since there are three symbols, be sure to provide **V** as the second argument to your **solve()** command.

Question 9: Paste your code here.

```
df = diff(f,V)

% Using solve, find the volume where the tumor grows the fastest.
```

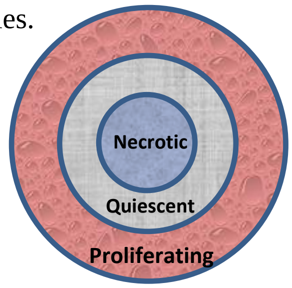
Paste in MATLAB's answer for **V_max_growth**.

V_max_growth = _ _ _ ←

Question 10: Exact Solution Analytically

The Bertalanffy equation can be solved analytically using a simple change of variables.

$$\frac{dV}{dt} = f(V) = aV^{2/3} - bV$$



Recall it models a multicellular tumor spheroid (MTS).

Let's introduce the new parameter $r(t)$ which corresponds to the radius of a sphere with the same volume as the tumor spheroid. Thus:

$$V(t) = \frac{4\pi}{3}\, r^3(t) \qquad \text{and by the chain rule} \qquad \frac{dV}{dt} = 4\pi\, r^2 \cdot \frac{dr}{dt}$$

Substituting r and $\frac{dr}{dt}$ into the Bertalanffy equation gives:

$$4\pi\, r^2 \cdot \frac{dr}{dt} = a\left(\frac{4\pi}{3}\right)^{2/3} \cdot r^2 - b \cdot \frac{4\pi}{3}\, r^3$$

Divide both sides by $4\pi\, r^2$ and simplify:

Linearized Bertalanffy DE $$\boxed{\frac{dr}{dt} = a\left(\frac{1}{36\pi}\right)^{1/3} - \frac{b}{3} \cdot r}$$ **Linear, 1st-order and autonomous**

At equilibrium, $\frac{dr}{dt} = 0$, so that: $\frac{3a}{b}\left(\frac{1}{36\pi}\right)^{1/3} = r(\infty) \;\rightarrow\; V(\infty) = \frac{4\pi}{3} r^3 = \frac{4\pi}{3}\left(\frac{3a}{b}\right)^3 \left(\frac{1}{36\pi}\right) = \boxed{\left(\frac{a}{b}\right)^3}$

Now let's solve our linear equation step-by-step. This will also serve as a preview of the **method of integrating factors**. First, we rewrite out linearized Bertalanffy equation in standard form with all r terms on the left.

$$\frac{dr}{dt} + \frac{b}{3} \cdot r = a\left(\frac{1}{36\pi}\right)^{1/3}$$

The trick is to multiply both sides by the integrating factor $\mu = e^{bt/3}$, so that the LHS can be rewritten as a single derivative.

$$e^{bt/3} \cdot \left(\frac{dr}{dt} + \frac{b}{3} \cdot r\right) = a\left(\frac{1}{36\pi}\right)^{1/3} \cdot e^{bt/3}$$

Using the product rule, the LHS can be written as the derivative of a product of two terms:

$$\frac{d}{dt}\left(e^{bt/3} \cdot r(t)\right) = a\left(\frac{1}{36\pi}\right)^{1/3} \cdot e^{bt/3}$$

Next integrate both sides:

$$e^{\frac{bt}{3}} \cdot r(t) = \frac{3a}{b}\left(\frac{1}{36\pi}\right)^{\frac{1}{3}} \cdot e^{\frac{bt}{3}} + c$$ where c is the constant of integration.

Finally, solve for $r(t)$ explicitly:

$$r(t) = \frac{3a}{b}\left(\frac{1}{36\pi}\right)^{\frac{1}{3}} + c \cdot e^{-\frac{bt}{3}}$$

Since the exponent is negative, after a long time the tumor spheroid reaches a mean radius of $r(\infty) = \frac{3a}{b}\left(\frac{1}{36\pi}\right)^{\frac{1}{3}}$

giving a final volume of $V(\infty) = \frac{4\pi}{3} r^3(\infty) = \frac{4\pi}{3}\left(\frac{3a}{b}\right)^3 \frac{1}{36\pi} = \left(\frac{a}{b}\right)^3$ as we saw earlier.

Question 10: Linearized Bertalanffy DE: Let $a = 1$ and $b = a/2$ as before. Now enter the linearized Bertalanffy DE:

$$\frac{dr}{dt} = \underbrace{a\left(\frac{1}{36\pi}\right)^{1/3}}_{\textbf{a1}} - \underbrace{\frac{b}{3}}_{\textbf{b1}} \cdot r$$

Find the exact solution matching the initial condition $V(0) = 1$ cc. Since $V(0) = \frac{4\pi}{3}\, r^3(0) = 1$, then: $r(0) = \left(\frac{3}{4\pi}\right)^{1/3}$

Here's some starter code.

Alert: Notice we declared pi itself to be symbolic, to prevent MATLAB from replacing it with a rational approximation.

```
%% Question 10. Linearized Bertalanffy Differential Equation
clear, clc
a = 1, b = a/2
syms r(t) pi  % Be sure to make pi symbolic!
a1 = sym(a * (1/(36*pi))^(1/3)),  b1 = sym(b/3)

% Enter the linearized Bertalanffy DE here using a1, b1 and r.

% Use dsolve to find the solution with r(0)==(3/(4*pi))^ (1/3)

% Compute and simplify V(t) using the formula for the volume of a sphere of radius r.

# Paste your completed code in the answer template.
```

When you are done Q10, the final answer will be equivalent to:

$$V = e^{-t/2} \cdot \left(2e^{t/6} - 1\right)^3 = \left(2 - e^{-t/6}\right)^3$$

Notice this exactly matches the answer we found in Question 5 above.

Ready to Submit?

Be sure all ten questions are answered. When your lab is complete, be sure to submit three files:

1. Your **completed Answer Template** as a PDF file
2. A copy of your **MATLAB Live Script**
3. A **PDF** copy of your **MATLAB Live Script** (Save-Export to PDF…)

The due date is the day after your lab section by **11:59pm** to receive full credit. You have one more day, to submit the lab (but with a small penalty), and then the window closes for good and your grade will be zero.