

Underflow and Overflow

- Sometimes the choice of algorithm will lead to underflow or overflow problems.
- Example: Probability (Box 1.3, Ch. 3 combinatorics)

Box 1.3: Selecting subjects for a clinical trial

- Double blind clinical trial to test a vaccine.
- 100 healthy volunteers: 50 women and 50 men.
- Volunteers will be divided into 2 groups: one group will receive the test vaccine, the other group will receive placebo.
- Each group will contain 25 women and 25 men.
- In how many different ways can these groups be formed?

Box 1.3: Selecting subjects for a clinical trial

- The solution is: $\check{N} = \check{C}_{25}^{50} \times \check{C}_{25}^{50}$,
where $\check{C}_r^n = \frac{n!}{r!(n-r)!}$.
- Thus, $N = \frac{50}{25}C \times \frac{50}{25}C = \frac{50!50!}{(25!)^4}$.

**Binomial coeff.
“50 choose 25”**
- And evaluating the factorials...

$$N = \frac{3.0414 \times 10^{64} \times 3.0414 \times 10^{64}}{(1.551 \times 10^{25})^4} = \frac{9.2501 \times 10^{128}}{5.784 \times 10^{100}}$$

Box 1.3: Selecting subjects for a clinical trial

$$N = \frac{3.0414 \times 10^{64} \times 3.0414 \times 10^{64}}{(1.551 \times 10^{25})^4} = \frac{9.2501 \times 10^{128}}{5.784 \times 10^{100}}$$

- In single precision, the range of recognizable numbers extends from:
 -3.403×10^{38} to 3.403×10^{38}
- Try `realmax('single')` in Matlab to see this!
- Note that the correct answer is 1.598×10^{28} , within the defined range for single precision.

So how can we modify our algorithm?

- We add lines of code that check when the number is too large or small...
- ... and then simply divide or multiply the product by a large number to keep it in range.
- If we keep track of the number of times we do this...
- ... We can recover the final result!

One more example (for now)

- Sometimes problems are ill conditioned and no algorithm can avoid numerical error!
- Suppose we want the roots to a polynomial, such as:

$$(x - 2/3)^4 = 0$$

- This has the repeated root: $x = 2/3$
- Now suppose we solve this by attacking the polynomial when multiplied out...

One more example (for now)

$$x^4 - \left(4 + \frac{2}{3}\right)x^3 + \left(6 + \frac{4}{9}\right)x^2 - \left(4 + \frac{8}{27}\right)x + \frac{16}{81} = 0$$

and we store all numbers to single precision (floating point representation)

- If we solve the resulting problem, we get:

0.6861

0.6663 + 0.0191i

0.6663 – 0.0191i

0.6480

or an error of 2.8% !

- Why? The problem was ill conditioned.

One more example (for now)

- The computer solved a problem which was very similar to the one we wanted, but had a very different answer!
- Let's see what happens if we plug one of the roots back in:

$$x=0.6861, (x-2/3)^4 = 1.4 \times 10^{-7}$$

Which is within round-off error of zero!

One more example (for now)

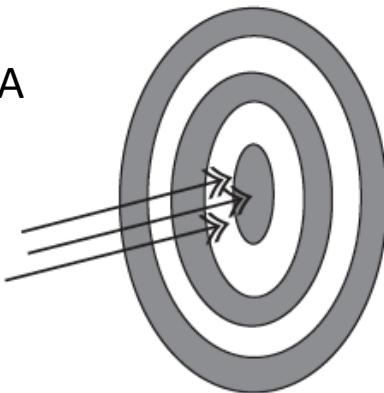
- In an ill-conditioned problem, a small change in the coefficients yields a large change in the result.
- The difficulty is in the problem, not the algorithm.
- Try to avoid ill-conditioned problems as much as possible.
- One focus of this course will be how to avoid all of these types of numerical errors.

Q1: which target demonstrates “accurate on average, but poor precision”?

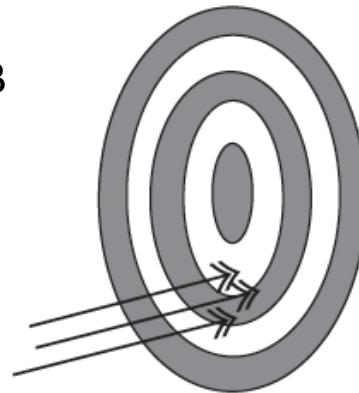
Figure 1.2

The bulls-eye target demonstrates the difference between accuracy and precision.

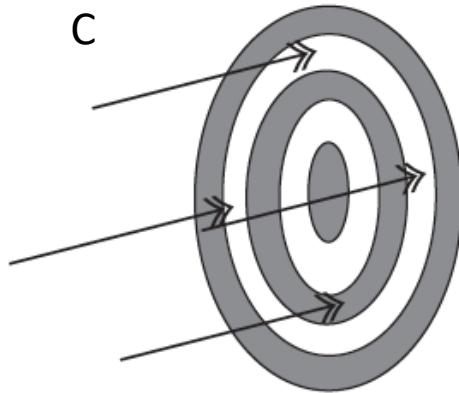
A



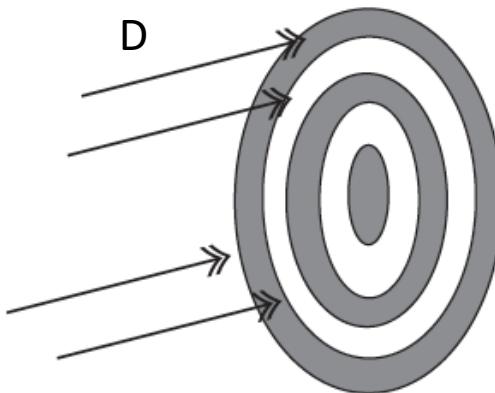
B



C



D



SIGNIFICANT FIGURES in addition

Q2: $10.343 + 4.56743 + 0.62 = ?$

- A. 15.53043
- B. 15.5304
- C. 15.530
- D. 15.53
- E. 15.5

Q3: $0.0000345 + 23.56 \times 10^{-4} + 8.12 \times 10^{-5} = ?$

- A. 24.717×10^{-4}
- B. 24.71×10^{-4}
- C. 24.72×10^{-4}
- D. 24.7×10^{-4}
- E. 2.4×10^{-3}

Q4: $0.23 - 0.1235 = ?$

- A. 0.1065
- B. 0.106
- C. 0.107
- D. 0.10
- E. 0.11

SIGNIFICANT FIGURES in addition

Q2: $10.343 + 4.56743 + 0.62 = ?$

- A. 15.53043
- B. 15.5304
- C. 15.530
- D. 15.53
- E. 15.5

Q3: $0.0000345 - 23.56 \times 10^{-4} - 8.12 \times 10^{-5} = ?$

- A. 24.717×10^{-4}
- B. 24.71×10^{-4}
- C. 24.72×10^{-4}
- D. 24.7×10^{-4}
- E. 2.4×10^{-3}

Q4: $0.23 - 0.1235 = ?$

- A. 0.1065
- B. 0.106
- C. 0.107
- D. 0.10
- E. 0.11

When adding or subtracting two or more numbers, all numbers being added or subtracted need to be adjusted so that they are multiplied by the same power of 10. Next, choose a number (operand) being added or subtracted whose last significant digit lies in the leftmost position as compared to the position of the last significant digit in all the other numbers (operands). The position of the last or rightmost significant digit of the final computed result corresponds to the position of the last or rightmost significant digit of the operand as chosen from the above step. For example:

SIGNIFICANT FIGURES in multiplication and division

Q5: $1.23 \times 0.3045 = ?$

- A. 0.374535
- B. 0.37454
- C. 0.3745
- D. 0.375
- E. 0.37

Q6: $0.00234 / 1.2 = ?$

- A. 0.00195
- B. 0.0019
- C. 0.0020
- D. 0.002
- E. none of the above

Q7: $301 / 0.04545 = ?$

- A. 6622.66
- B. 6622.7
- C. 6623
- D. 6620
- E. 6600

SIGNIFICANT FIGURES in multiplication and division

Q5. $1.23 \times 0.3045 = ?$

- A. 0.374535
- B. 0.37454
- C. 0.3745
- D. 0.375
- E. 0.37

Q6: $0.00234 / 1.2 = ?$

- A. 0.00195
- B. 0.0019
- C. 0.0020
- D. 0.002
- E. none of the above

Q7 $301 / 0.04545 = ?$

- A. 6622.66
- B. 6622.7
- C. 6623
- D. 6620
- E. 6600

When multiplying or dividing two or more numbers, choose the operand that has the least number of significant digits. The number of significant digits in the computed result corresponds to the number of significant digits in the chosen operand from the above step. For example:

Box 1.6

Monod growth kinetics: using finite difference approximations

Bacterial growth



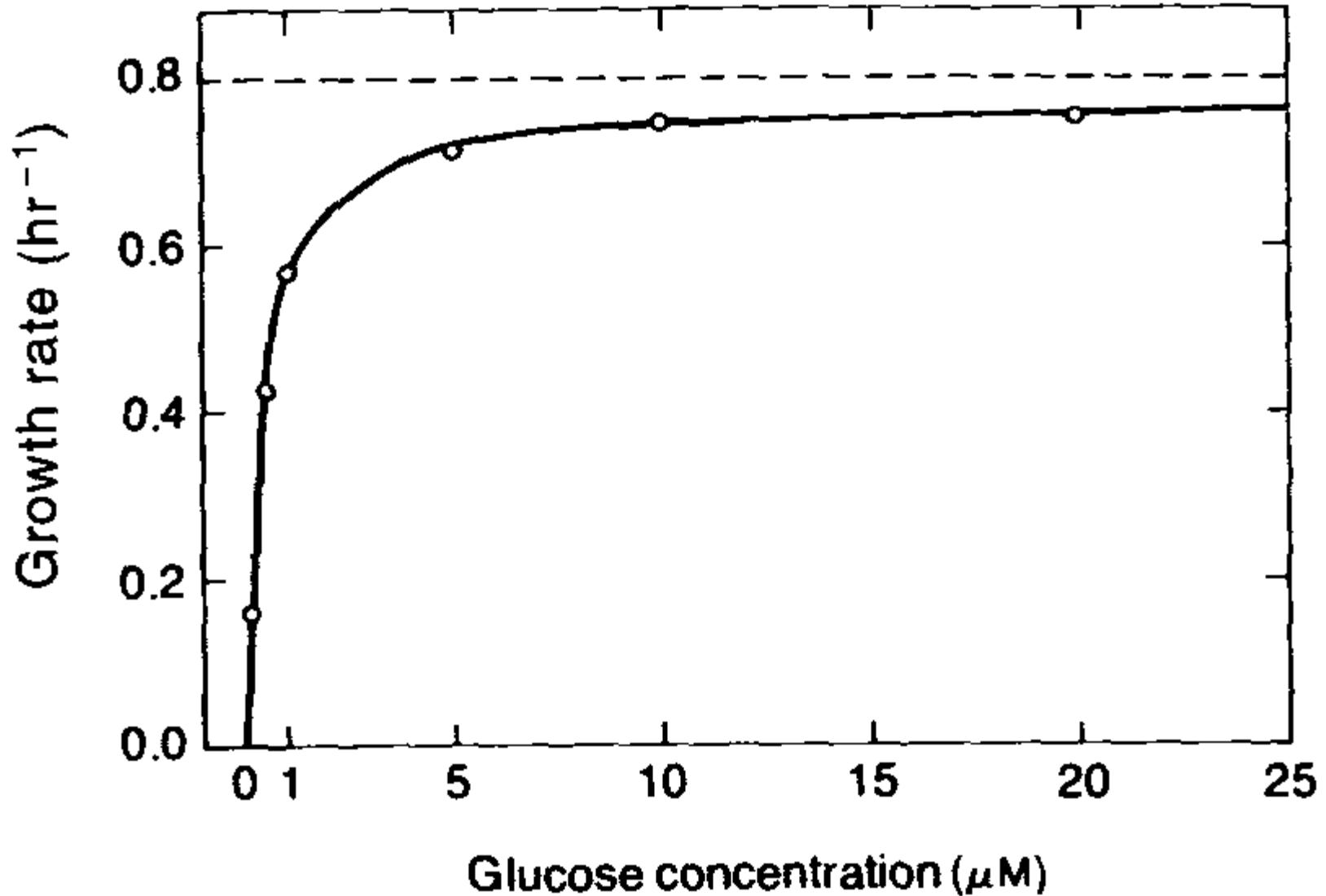
[http://well.blogs.nytimes.com/2012/08/27/
when-the-mango-bites-back/](http://well.blogs.nytimes.com/2012/08/27/when-the-mango-bites-back/)

Unstructured, Nonsegregated Models (Monod)

- Assumptions
 - One limiting substrate
 - Semi empirical relationship
 - Single enzyme system with Michaelis-Menten kinetics is responsible for the uptake of substrate
 - Amount of enzyme is sufficiently low to be growth limiting
 - Low population density
- Most commonly used expression for growth

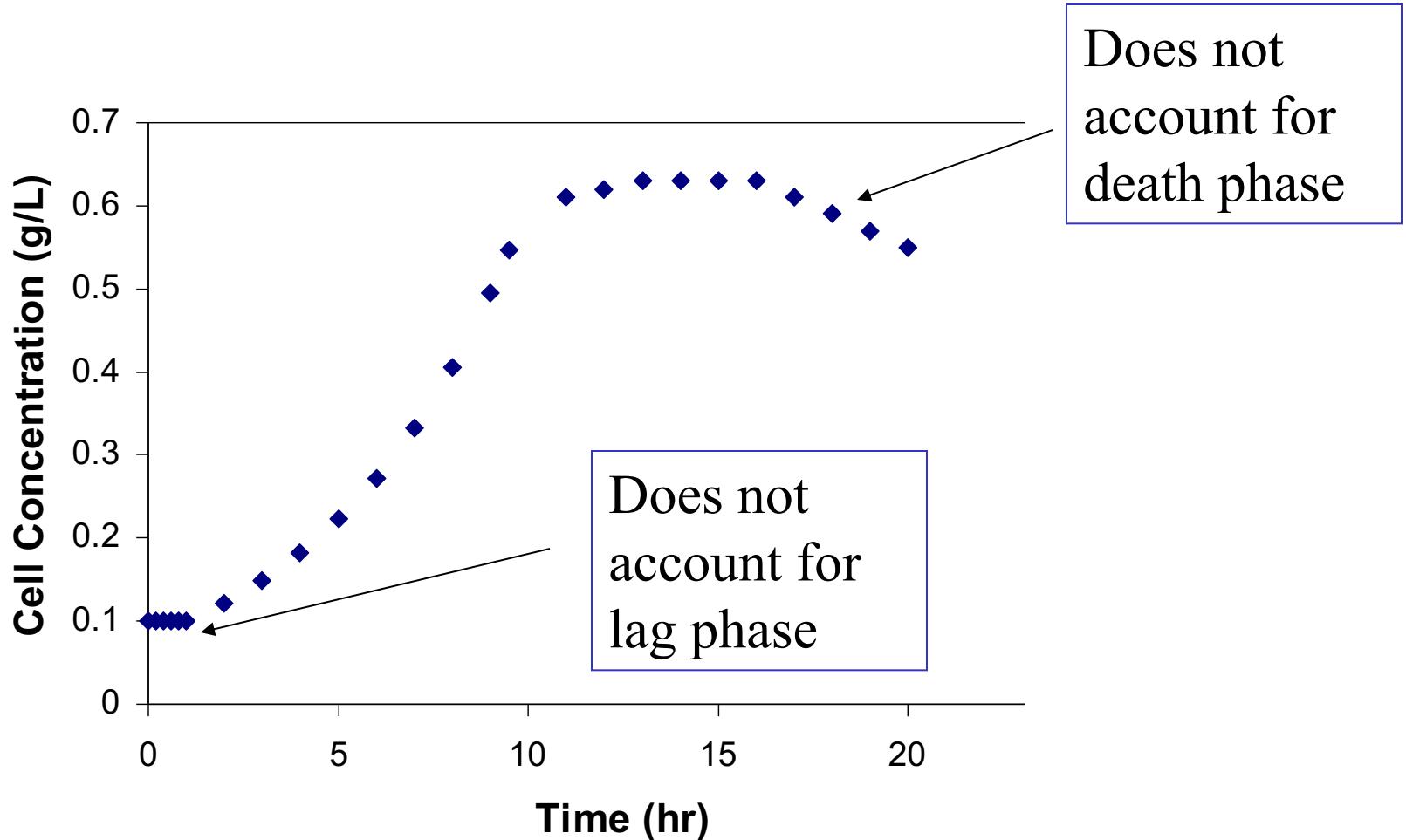
$$\mu = \frac{\mu_m S}{K_s + S}$$

- μ_m - maximum growth rate when $S \gg K_s$
- K_s - saturation constant - concentration of the rate-limiting substrate when the specific rate of growth is equal to one half of the maximum.
- $K_s = S$ when $\mu = 1/2\mu_m$
- In general $\mu = \mu_m$ for $S \gg K_s$ and $\mu = \frac{\mu_m S}{K_s}$ for $S \ll K_s$



Monod type saturation growth kinetics

Cell Growth - Monod



Next topic: Linear systems of equations, Ch. 2

- (You can skip 2.4, 2.5 on matrix inversion.)
- LINEAR REGRESSION
- Consider the parabola: $y = ax^2 + bx + c$
- If fitting to 3 points, there is only one answer.
- Often in data analysis you want to fit a curve to many data points.
- How do we do this? Usually use linear regression.
- This does not mean that we fit data with a line, rather that we use an algorithm which reduces the problem to a set of linear equations!



Article

Piezo1 Mechano-Activation Is Augmented by Resveratrol and Differs between Colorectal Cancer Cells of Primary and Metastatic Origin

Joshua D. Greenlee **Kevin Liu**, **Maria Lopez-Cavestany** and **Michael R. King** *

Department of Biomedical Engineering, Vanderbilt University, PMB 351631, 2301 Vanderbilt Place, Nashville, TN 37235-1631, USA

* Correspondence: mike.king@vanderbilt.edu; Tel.: +1-615-875-8384

Abstract: Cancer cells must survive aberrant fluid shear stress (FSS) in the circulation to metastasize. Herein, we investigate the role that FSS has on colorectal cancer cell apoptosis, proliferation, membrane damage, calcium influx, and therapeutic sensitization. We tested this using SW480 (primary tumor) and SW620 cells (lymph node metastasis) derived from the same patient. The cells were exposed to either shear pulses, modeling millisecond intervals of high FSS seen in regions of turbulent flow, or sustained shear to model average magnitudes experienced by circulating tumor cells. SW480 cells were significantly more sensitive to FSS-induced death than their metastatic counterparts. Shear pulses caused significant cell membrane damage, while constant shear decreased cell proliferation and increased the expression of CD133. To investigate the role of mechanosensitive ion channels, we treated cells with the Piezo1 agonist Yoda1, which increased intracellular calcium. Pretreatment with resveratrol further increased the calcium influx via the lipid-raft colocalization of Piezo1. However, minimal changes in apoptosis were observed due to calcium saturation, as predicted via a computational model of apoptosis. Furthermore, SW480 cells had increased levels of Piezo1, calcium influx, and TRAIL-mediated apoptosis compared to SW620 cells, highlighting differences in the mechano-activation of metastatic cells, which may be a necessary element for successful dissemination *in vivo*.



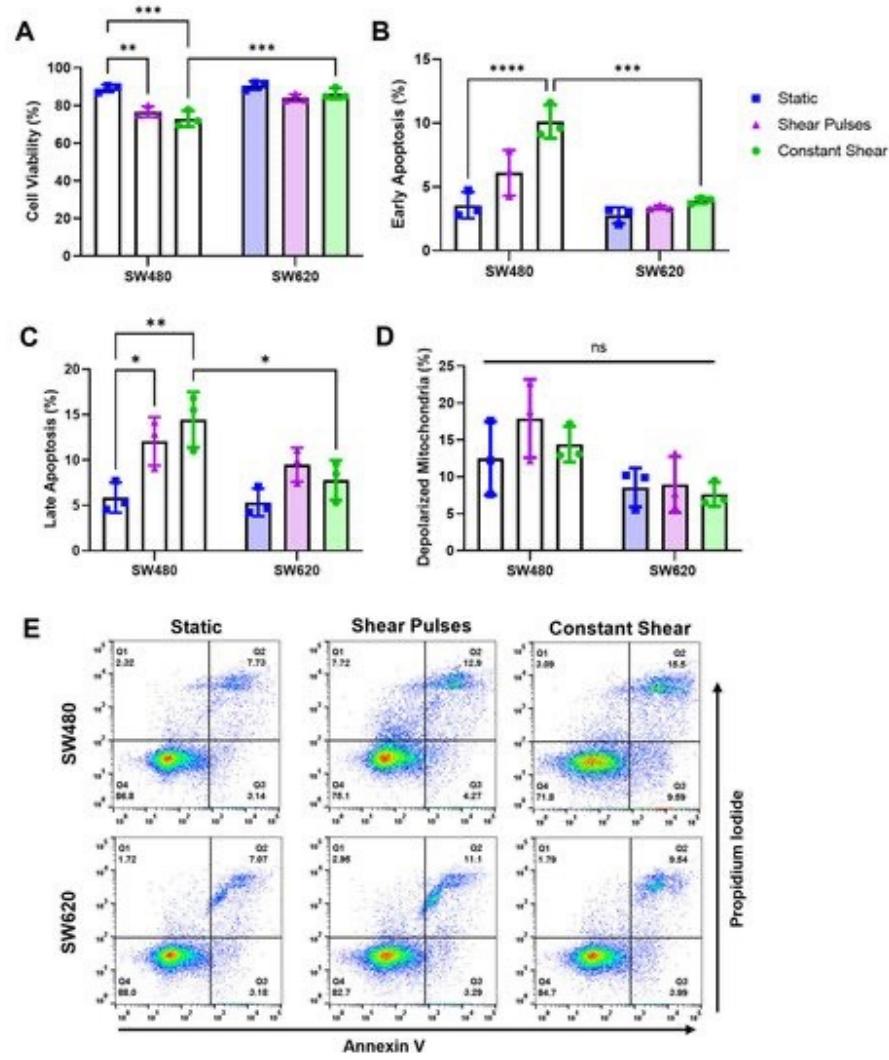
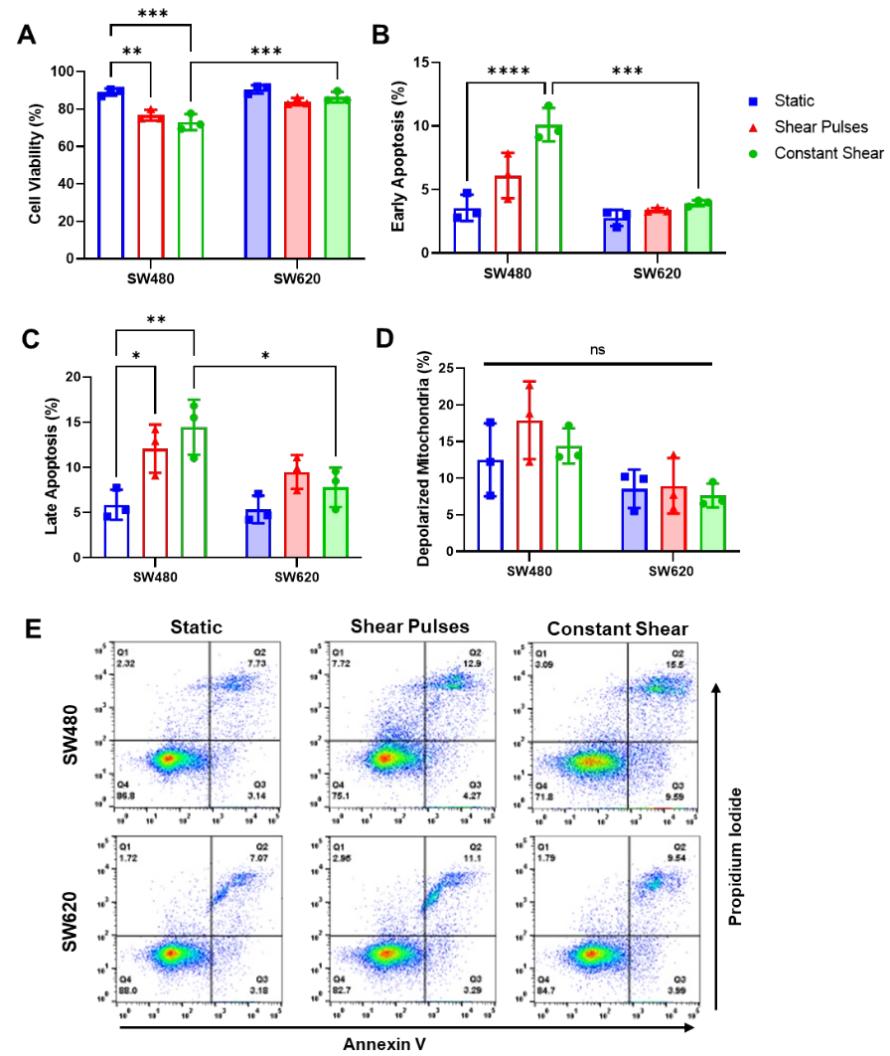
Citation: Greenlee, J.D.; Liu, K.; Lopez-Cavestany, M.; King, M.R. Piezo1 Mechano-Activation Is Augmented by Resveratrol and Differs between Colorectal Cancer Cells of Primary and Metastatic Origin. *Molecules* **2022**, *27*, 5430. <https://doi.org/10.3390/molecules27175430>

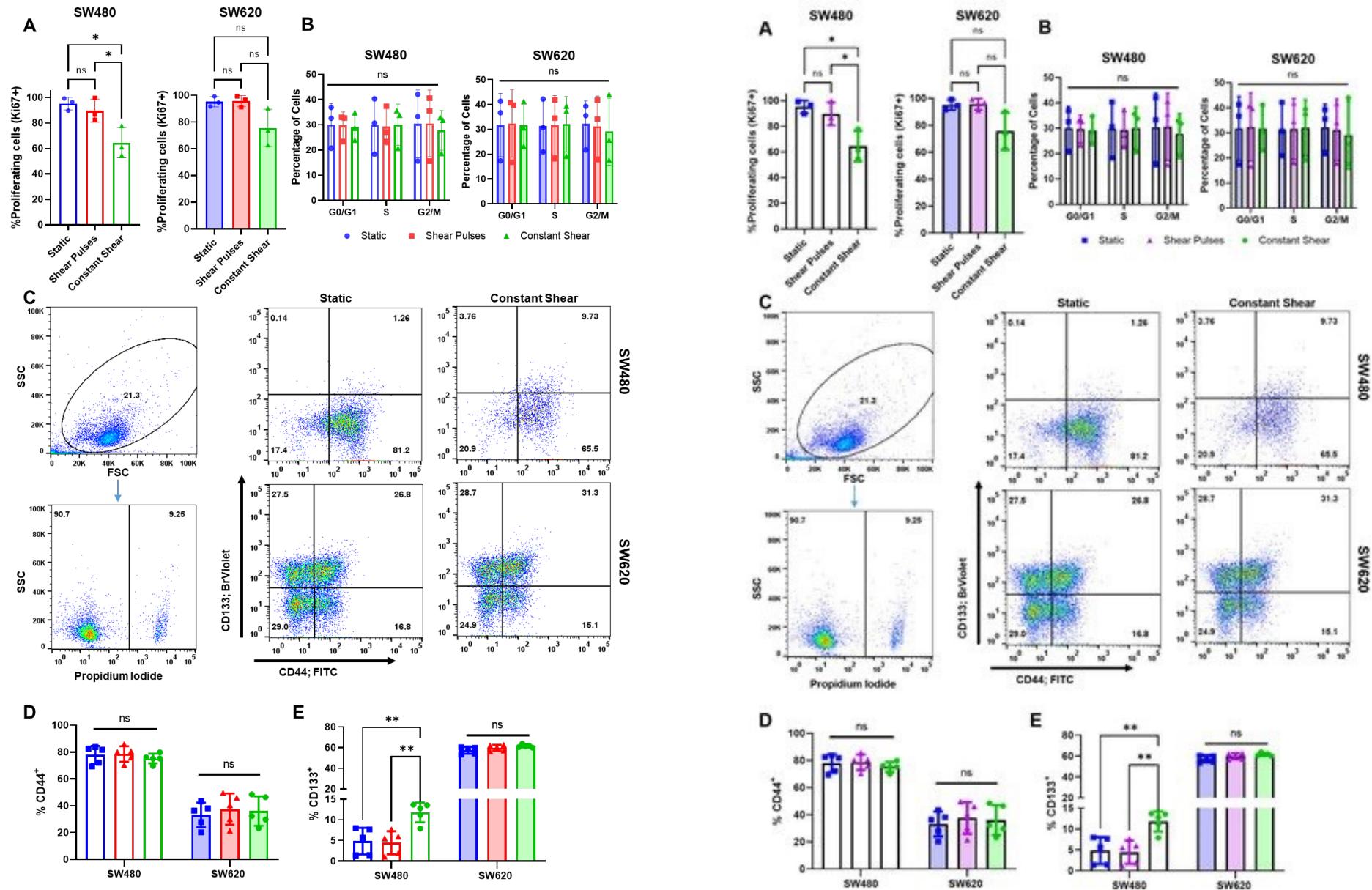
Keywords: mechanotransduction; metastasis; shear stress; Piezo1; colorectal cancer; TRAIL; calcium; resveratrol

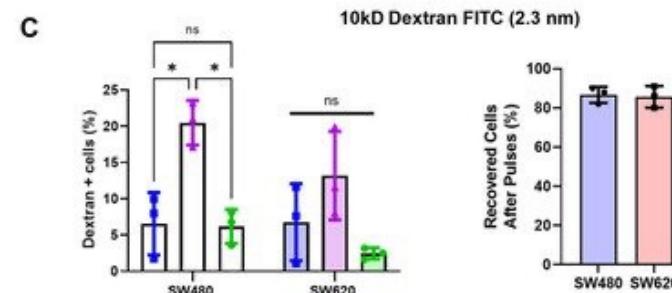
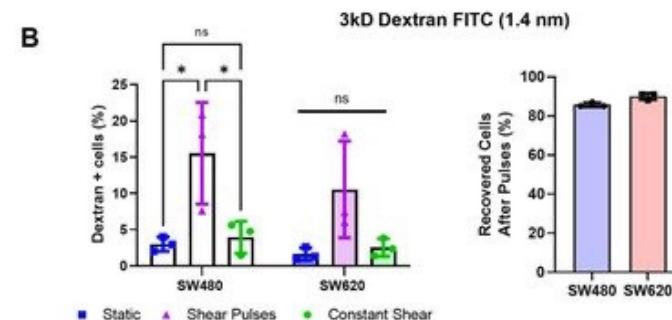
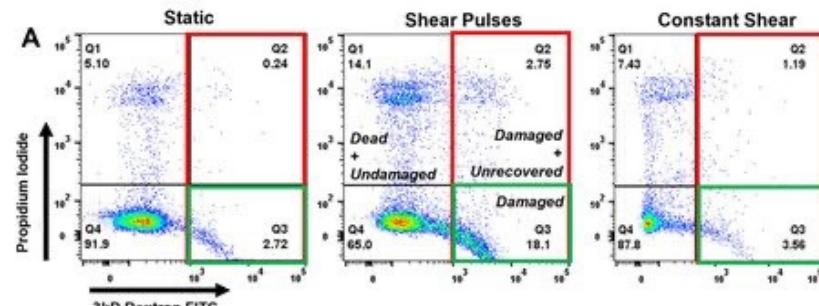
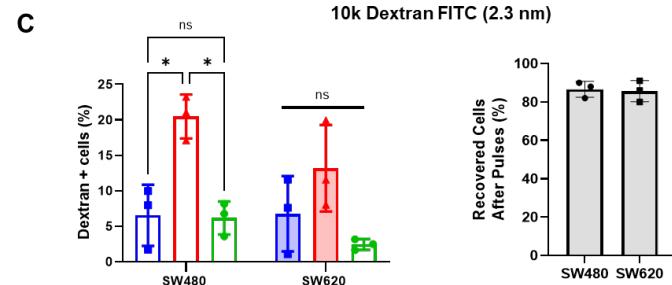
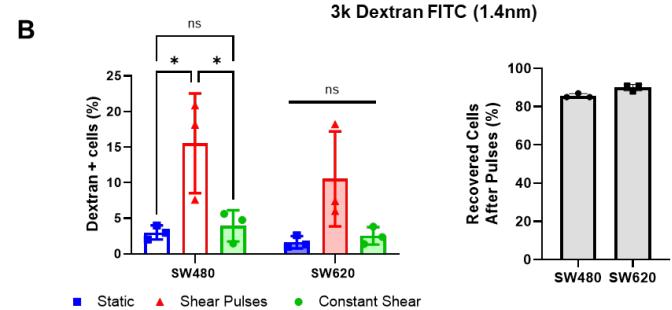
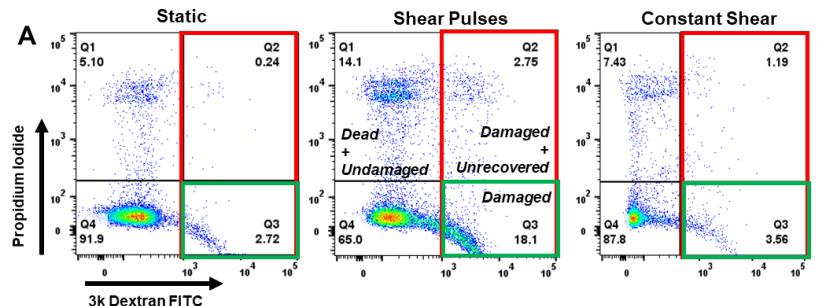
Background info for final (extra-credit) project

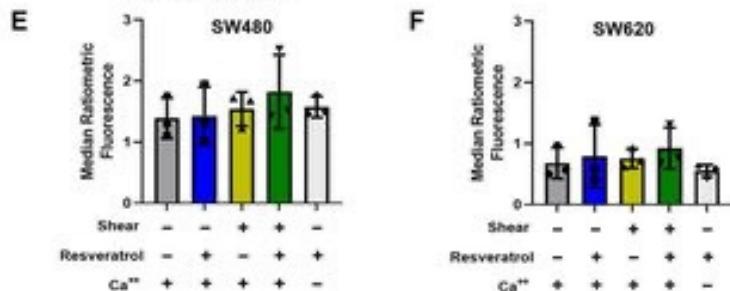
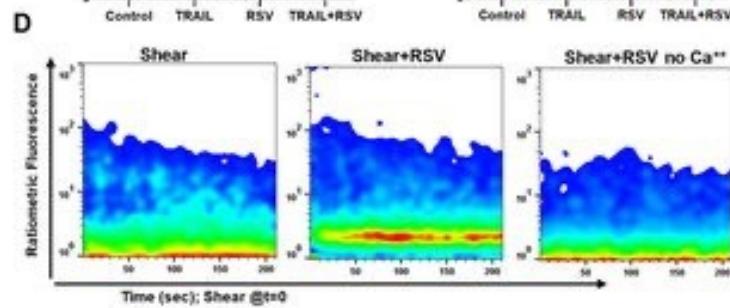
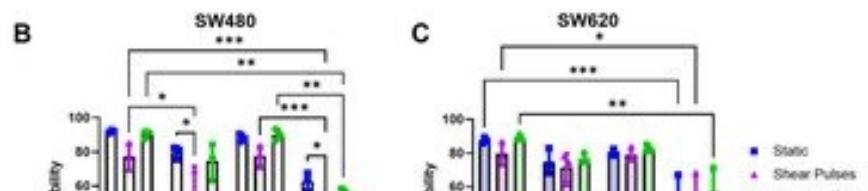
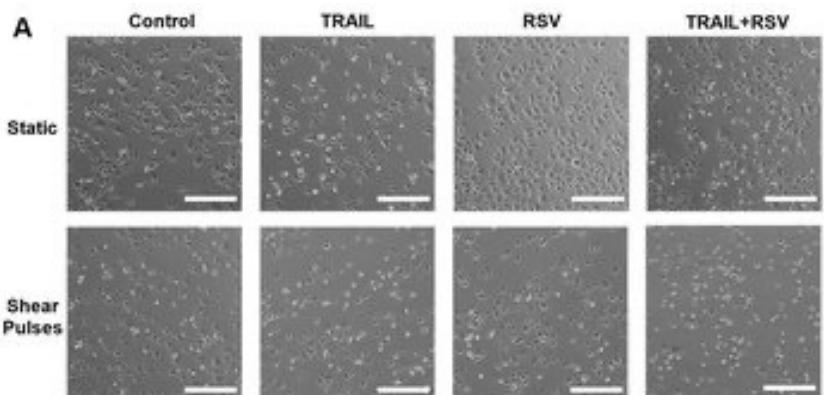
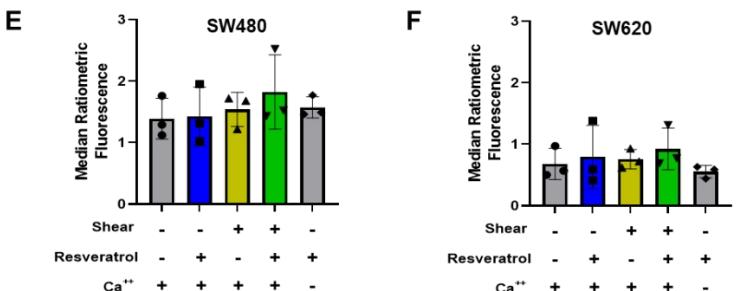
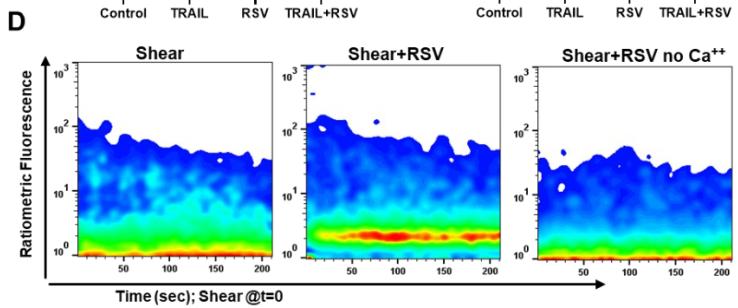
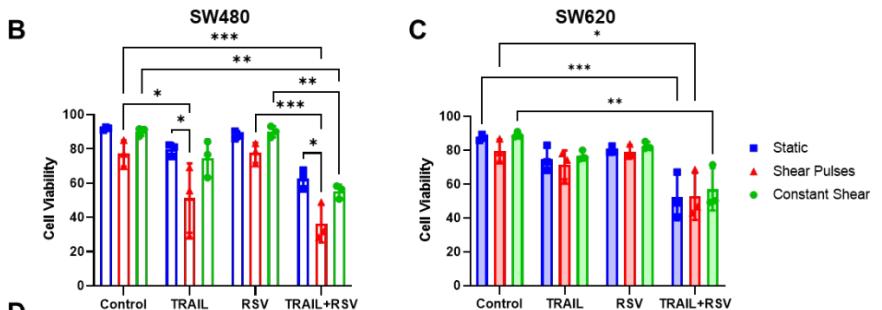
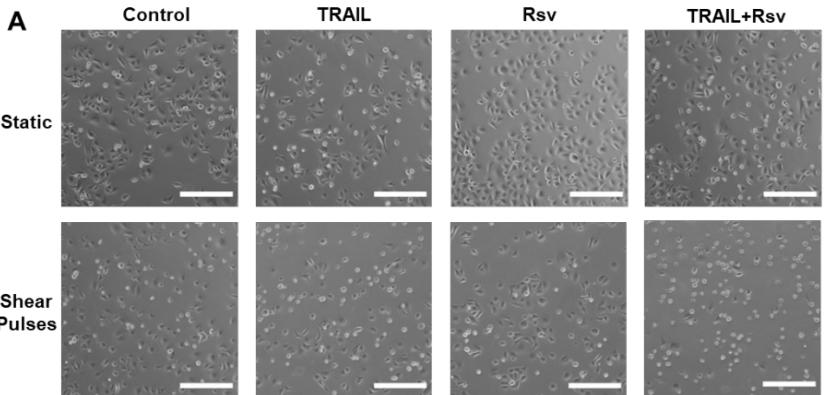
2. The use of the RGB (red/green/blue) colors in the schemes and graphics reported in the manuscript is unreadable for color-blind people and as such no longer acceptable in today's publishing. The authors should consider popular scientific coloring guides (such as <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199239>) and must change the color palette of the schemes.

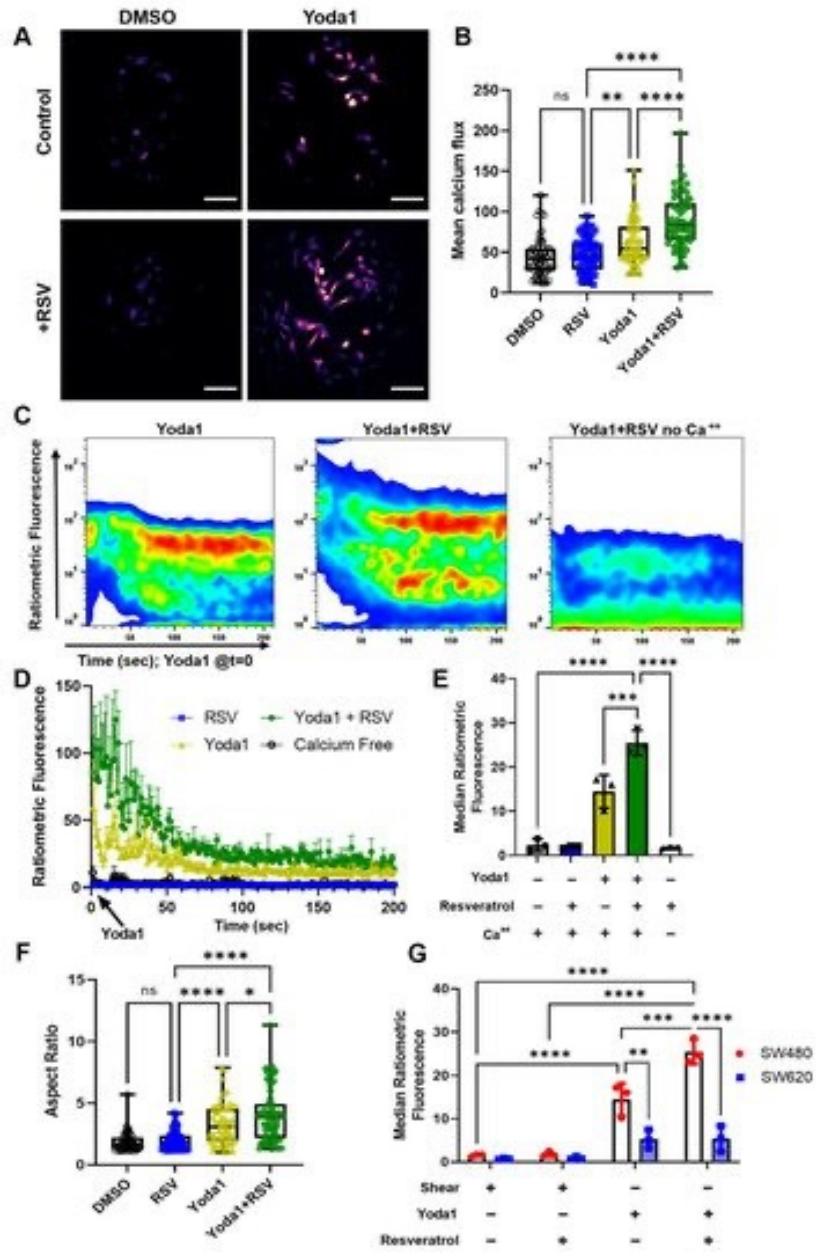
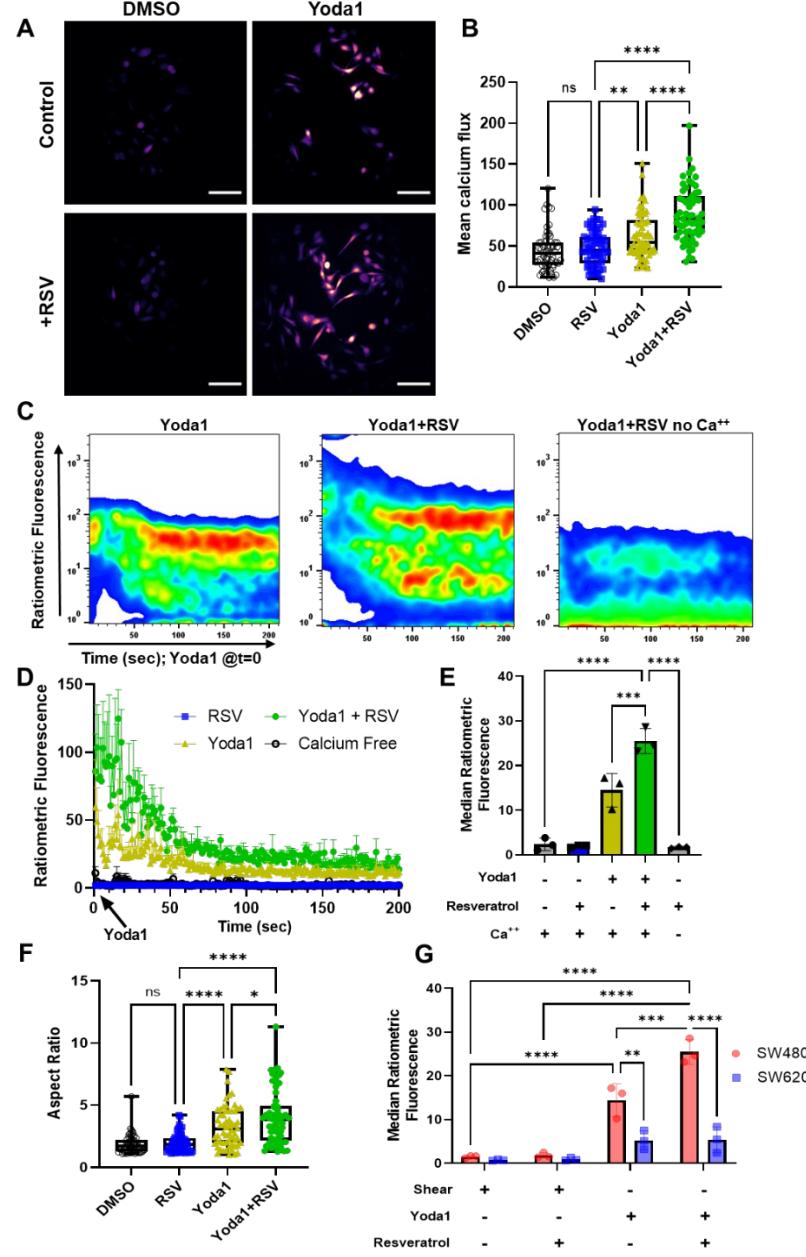
We agree that the use of red/green/blue color schemes for the indication of FSS treatments was an oversight on our part and not inclusive for colorblind readers. We have changed the schemes on all figures, changing the red scheme for “shear pulses” to magenta (new color scheme being blue, magenta, green) to make it appropriate for users with deutanopia and/or protanopia (<https://www.ascb.org/science-news/how-to-make-scientific-figures-accessible-to-readers-with-color-blindness/>). We also darkened the tone of green in the “Yoda1+RSV” condition (i.e. Figure 6D) to make it more distinguishable from the “Yoda1” condition in yellow. Additionally, even in grayscale, all conditions can be identified from different symbol shapes (i.e square for static, triangle for shear pulses, and circle for constant shear).

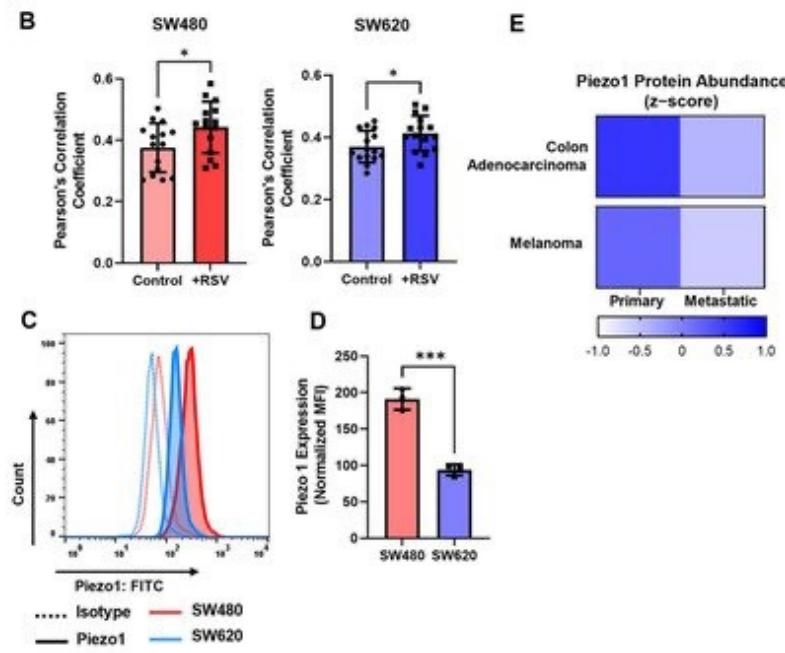
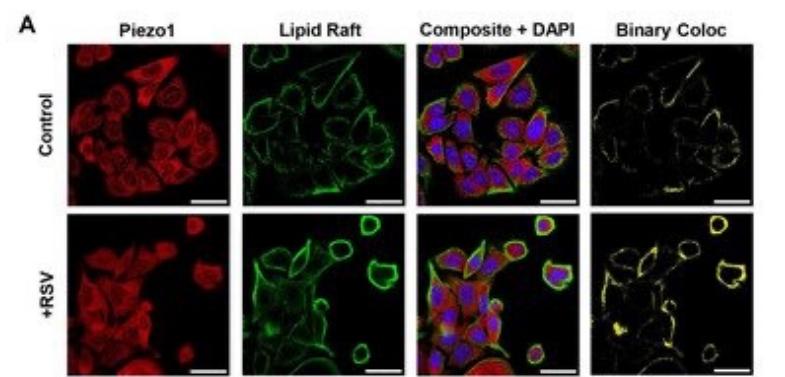
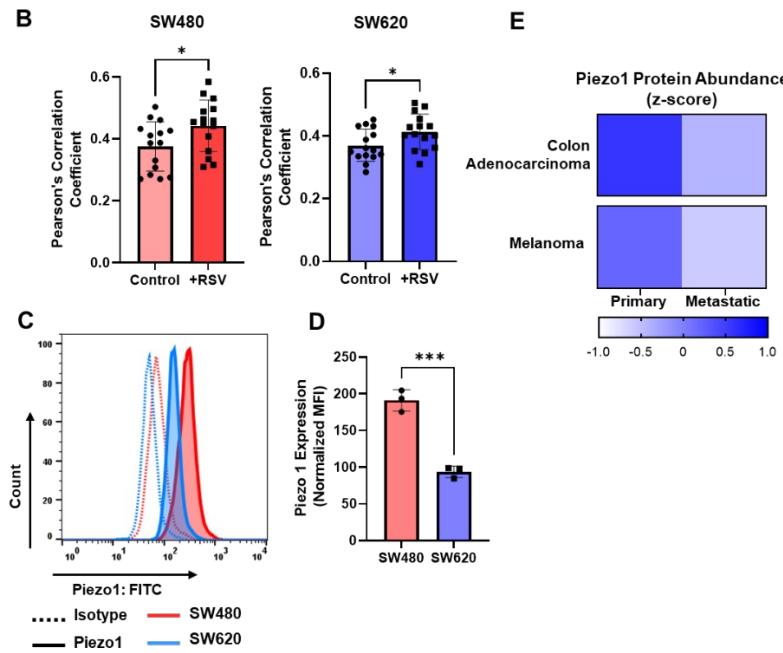
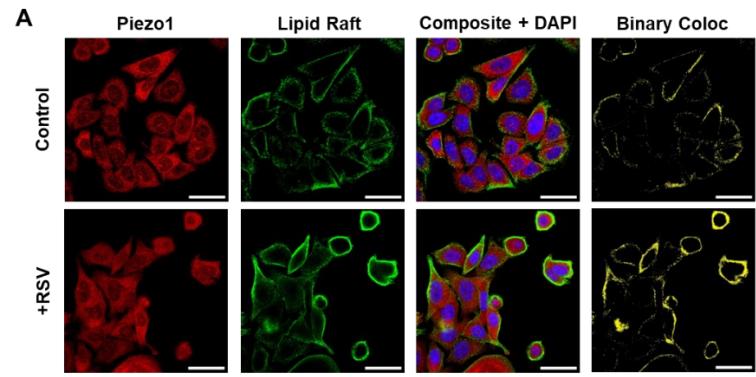


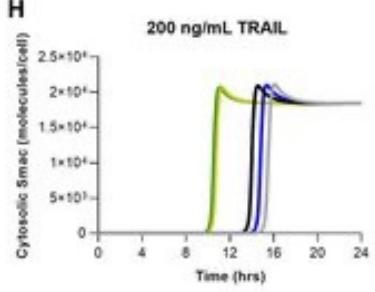
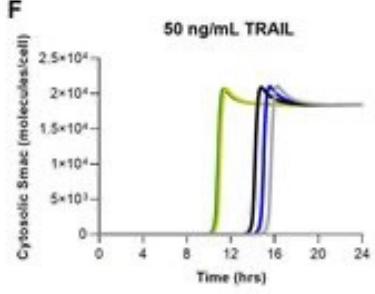
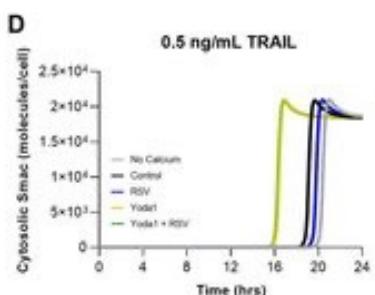
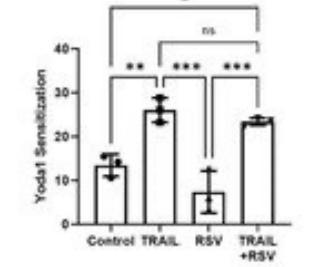
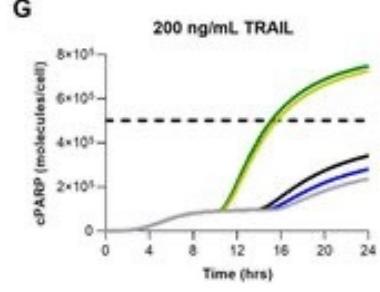
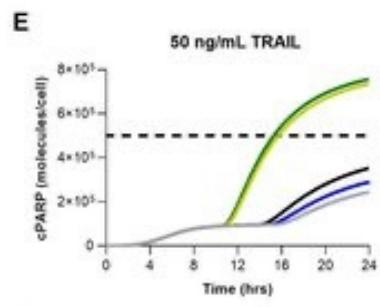
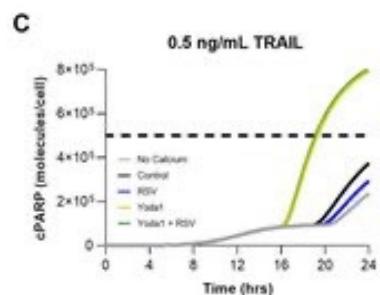
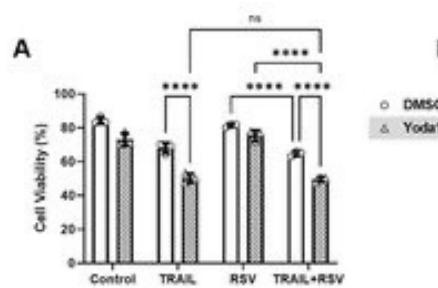
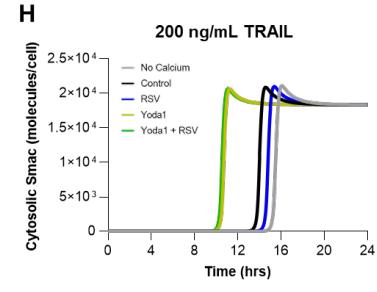
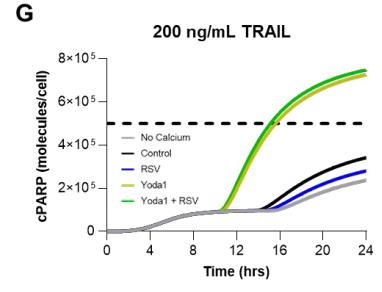
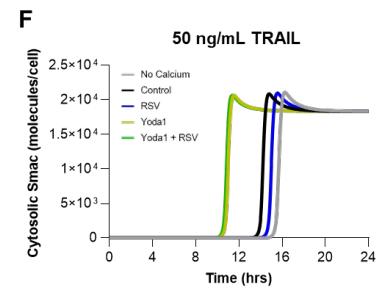
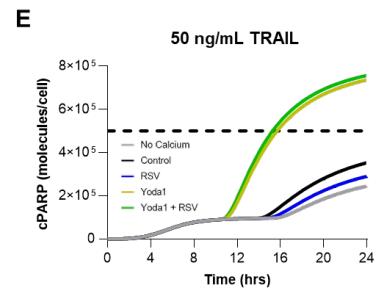
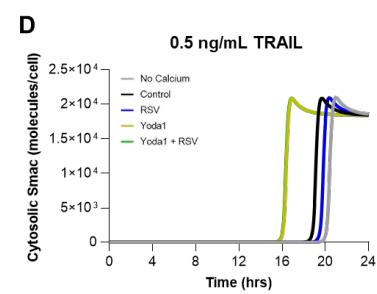
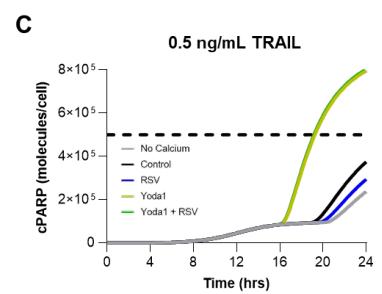
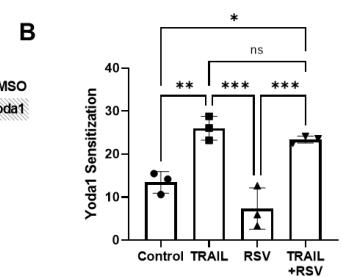
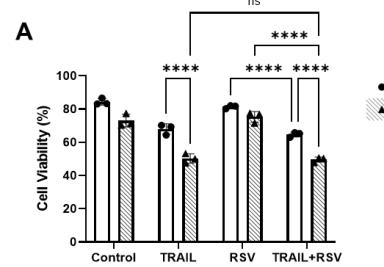


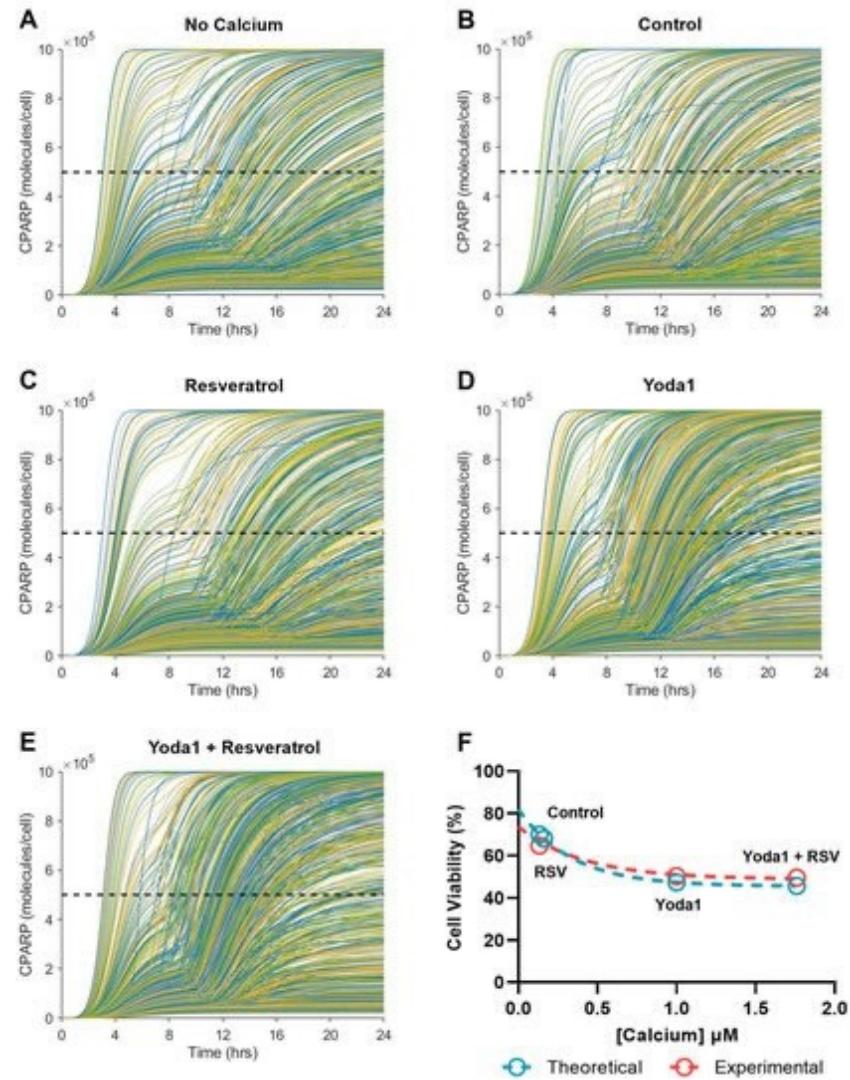
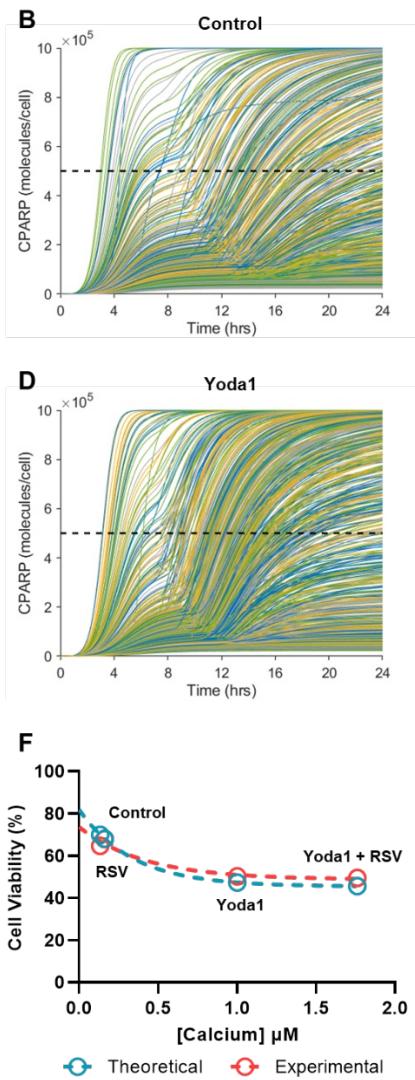
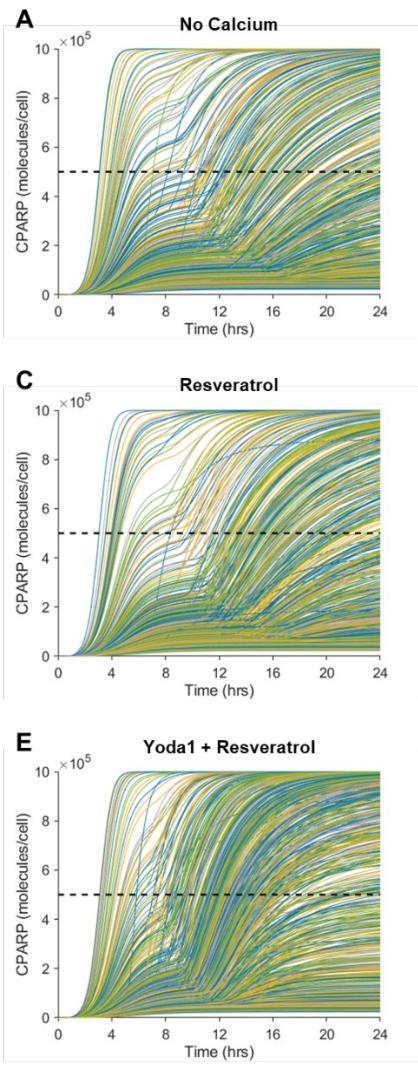












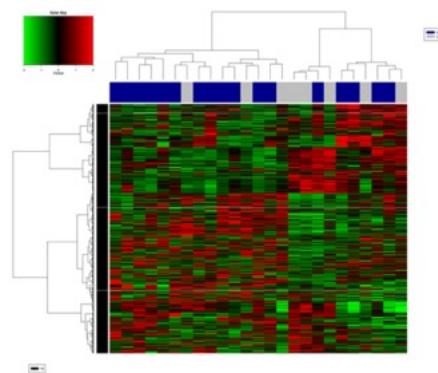
Why you should care about color-blindness

Color-blindness affects a large portion of the population. As many as 8% of males and 0.5% of females have some form of color-blindness, the most common being difficulty in perceiving the difference between the colors red and green. This means that potentially **one out of 12 males and one out of 200 females** who read your paper or walk past your poster can't easily read your figures with certain color combinations.

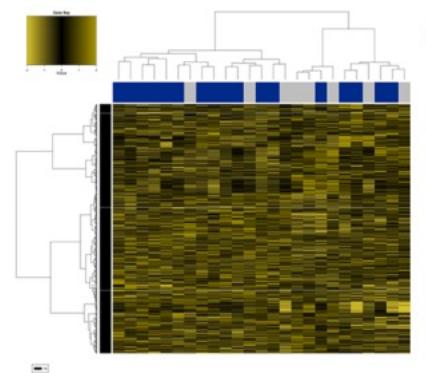
It's time to ditch red and green forever

The red/green color combination is classic in science, most commonly used in heatmaps and fluorescence images. For people with normally-functioning photoreceptors, red and green provide good contrast. However, if a person has a mutation in their red or green cone cells, distinguishing these two colors becomes much more challenging. For example, take a look at what a red/green heatmap might look like to people without functioning red or green cone cells:

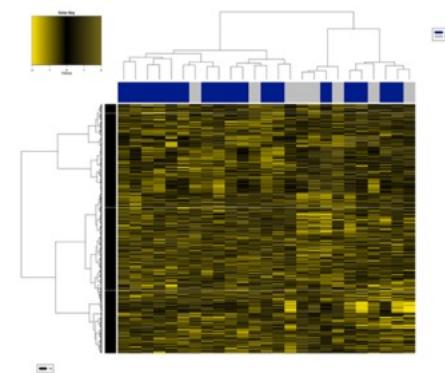
Wild-type photoreceptors

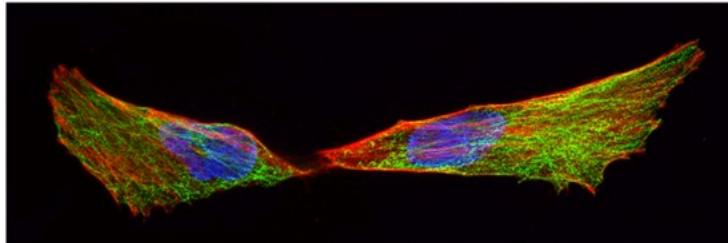


Deutanopia
(no red)

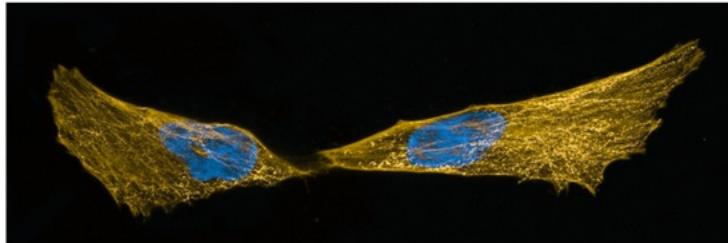


Protanopia
(no green)

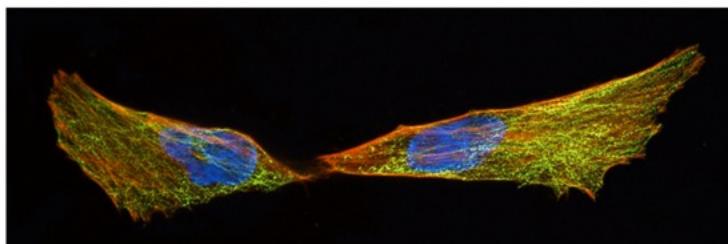




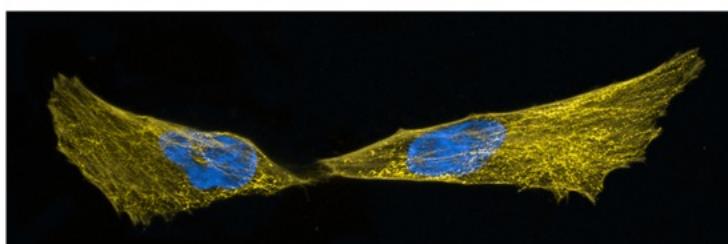
Wild-type photoreceptors



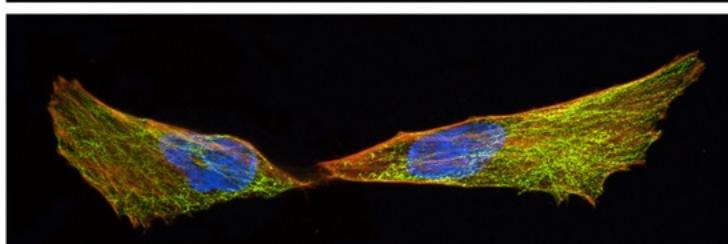
Deutanopia (no green)



Deuteranomaly (reduced green)

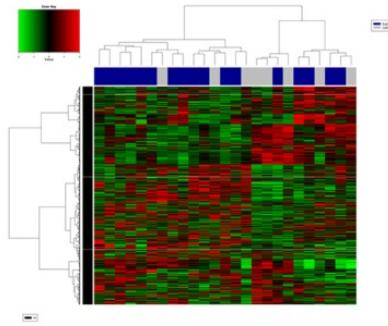


Protanopia (no red)

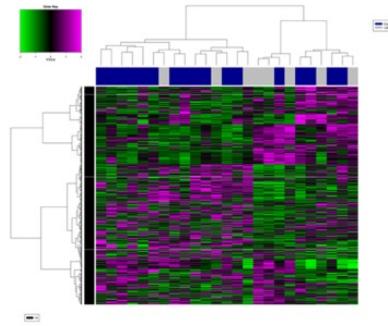


Protanomaly (reduced red)

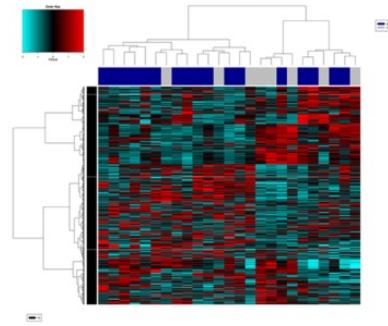
green / red
(don't do this)



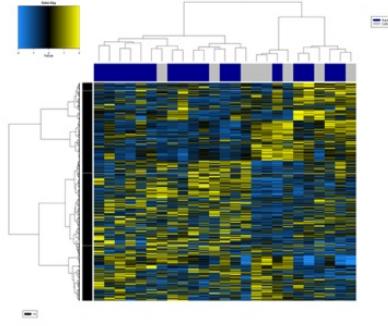
green / magenta



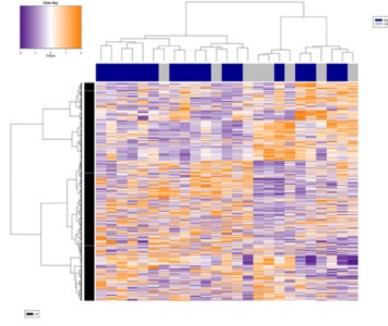
cyan / red



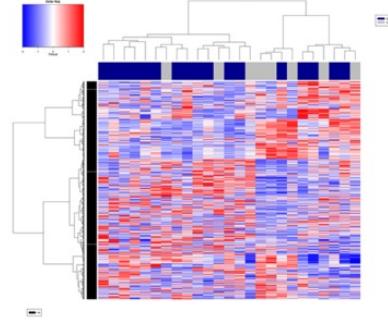
light blue / yellow



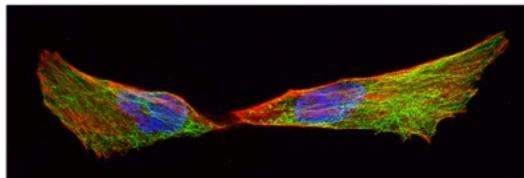
purple / orange



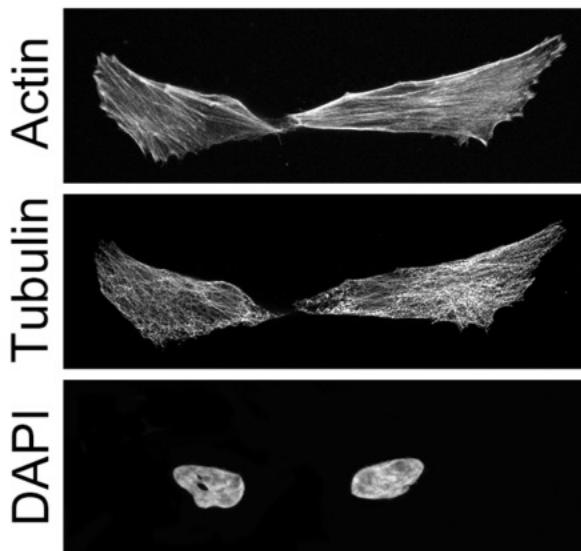
blue / red



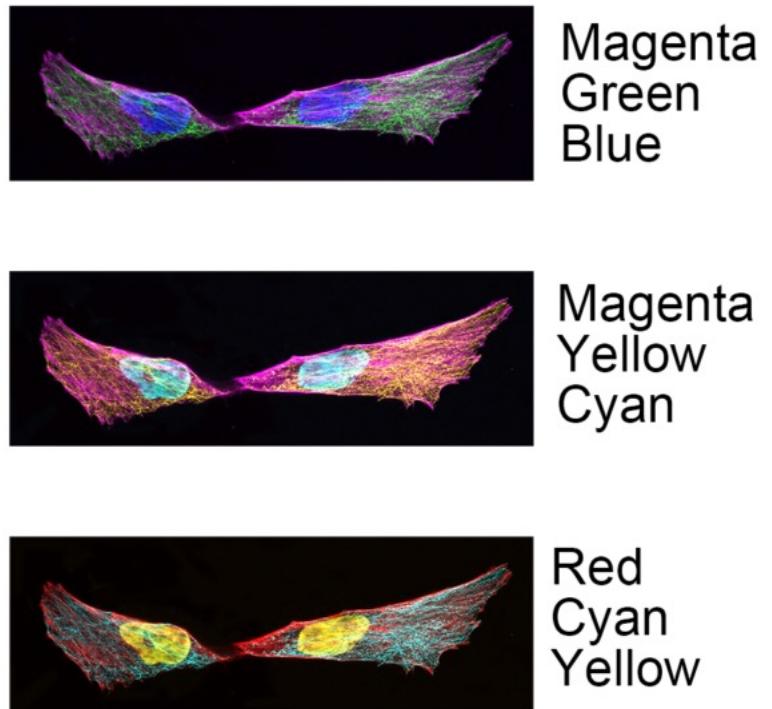
DON'T
Use red and green pseudocoloring
in the same image



DO
Show greyscale images
of each channel



DO
Use colors in merged images that
can still be distinguished by people
with red/green color-blindness



How to make sure your images are accessible for color-blind readers

Many tools are available to proof your images in “color-blind mode”. These programs will change the coloring in your image to simulate common forms of color blindness. In [ImageJ](#) (a commonly used software platform for microscopy analysis), you can go to Image > Color > Dichromacy or Image > Color > Simulate Color Blindness. In Adobe Photoshop CC 2019, you can go to View > Proof Setup > Color Blindness. In addition, [Color Oracle](#) provides a full-screen color-blindness simulator. Using these tools is a great way to check if your data are readable to people with several forms of color-blindness.

How to read red/green images when people forget to include you

If you have color-blindness, I can only imagine the challenge in trying to read scientific data on a daily basis. However, tools do exist to try to re-interpret this data. Assistive software such as [Visolve](#) will transform images in ways to help separate or re-interpret colors in a variety of ways. Apps for mobile devices such as [Color Blind Pal](#) allow you to re-visualize anything through your phone, which may be useful while at poster sessions or conference talks. (*Note: I am not color-impaired, so I can't personally attest to how well these tools work.*)