Ordinary Differential Equations (Ch. 7)

- What is an ODE? It is a differential equation of a single variable.
- We begin with first order, linear ordinary differential equations.

$$\frac{dy}{dt} = f(t)$$

- This is very simple: we can solve it just using ordinary quadrature routines:

$$y = y(t_0) + \int_{t_0}^{t} f(t')dt'$$

where $y(t_0)$ is the initial condition.

Ordinary Differential Equations (Ch. 7)

- Often the problem is more complex, however. Suppose we have:

$$\frac{dy}{dt} = f(t, y), \qquad y(t = 0) = y_0$$

- If f(y,t) is linear in y then the ODE is linear – it doesn't matter if it's nonlinear in t.
- We can't solve this using quadrature schemes, instead we must integrate it step by step!
- Let's discretize the interval in time.

Ordinary Differential Equations (Ch. 7)

- Thus we have the series:

$$t_0, t_1, t_2, \ldots, t_n$$

- with corresponding estimates of the dependent variable:

$$y_0, y_1, y_2, \ldots, y_n$$

- We'll get into how these are made in a bit.
- Often rather than a single equation we have multiple equations are coupled…

Ordinary Differential Equations (Ch. 7)

- Suppose we are examining the populations of foxes and rabbits in a valley. Rabbits reproduce at a rate proportional to their number and get eaten by foxes, thus:

$$\frac{dr}{dt} = 2r - \alpha rf$$

Reproduction rate

Rate of consumption

- Foxes also reproduce if there is enough food (rabbits) and die out without it, thus:

$$\frac{df}{dt} = (\alpha r - 1)f$$

Ordinary Differential Equations

- These comprise a pair of coupled first order nonlinear ODEs!
- In general we have:

$$y_i' = g_1(t, y_1, \ldots, y_n)$$

$$\ldots$$

$$y_n' = g_n(t, y_1, \ldots, y_n)$$

- In the last example n=2, thus:

$$y_1(t) = r(t), \quad y_2(t) = f(t)$$

$$g_1(t, y_1, y_2) = 2y_1 - \alpha y_1 y_2$$

$$g_2(t, y_1, y_2) = -y_2 + \alpha y_1 y_2$$

or $\mathbf{y}' = \mathbf{g}(t, \mathbf{y})$ in vector form!

Ordinary Differential Equations

- We can also write a single n^{th} order ODE as a system of first order ODEs.
- Consider the damped pendulum:

$$2\pi ML(d^2\theta/dt^2) = -Mg \sin\theta - 6\pi\mu a(2\pi L)d\theta/dt$$

- The last term is the resistance due to viscosity of a sphere of radius a moving through a viscous liquid with velocity $(2\pi L)d\theta/dt$.
- We can rewrite this as a pair of first order equations:

$$y_1 = \theta, \; y_2 = d\theta/dt$$

Coupled 1st Order ODEs

- Thus:

$$y_1' = y_2 \quad \text{(by definition)}$$

and $y_2' = -(Mg/2\pi ML)\sin y_1 - 6\pi\mu a(2\pi L/2\pi ML)y_2$

- For an arbitrary nth order ODE we have:

$y_1 = y,\ y_2 = dy/dt, \ldots, y_n = d^{(n-1)}y/dt^{(n-1)}$

- and:

$$y_1' = y_2$$
$$y_2' = y_3$$
$$\ldots$$
$$y'_{n-1} = y_n$$
$$y_n' = f(t,y_1,\ldots,y_n)$$

ODE Stability

- An important aspect of numerical integration is stability. Some equations will be easy to solve, while others may be very difficult.
- Let's look at the single first order ODE:

$$dy/dt = f(y,t)$$

- One solution technique is the explicit Euler method:

$$y^{EM}_{k+1} = y_k + f(t_k,y_k)\, h_k$$

where $h_k = t_{k+1} - t_k$ is the step size in time.

ODE Stability

- This method is equivalent to using the first two terms in a Taylor series for y(t) at t_k and using the linear approximation to estimate $y(t_{k+1})$.
- Methods which use information at t_k to predict y_{k+1} are called <u>explicit</u>.
- Let's see how this integration scheme works for a simple function:

$$dy/dt = y, \quad y(0) = 1$$

ODE Stability

- This has the solution $y = e^t$
- Let's see what the Euler method does to this if $h_k = t_{k+1} - t_k = 0.1$:

	Numerical	Exact	Error
y0=	1	1	0
y_1=1+(1)(0.1)=	1.1	1.1052	5.2e–3
y_2=1.1+(1.1)(0.1)=	1.21	1.221	1.14e–2
y_3=$(1.1)^3$=	1.331	1.3499	1.89e–2
y_{10}=$(1.1)^{10}$=	2.593	2.7183	0.125
y_{100}=$(1.1)^{100}$=	1.38e4	2.20e4	0.82e4

ODE Stability

- So at t=100 the error is nearly a factor of 2!
- This amplification of error occurred because of the differential equation itself. The equation

$$dy/dt = y$$

has the family of solutions

$$y=c\ e^{t}$$

where c must be determined from the initial condition.

ODE Stability

- When you make an error in integration, you are wandering among this family of curves. Thus, if the curves are diverging in time, all errors will be amplified. Such a differential equation is unstable.
- Suppose we have instead that

  $dy/dt = e^t,\ y(0) = 1$

- This has the same solution. What about the numerical error?

ODE Stability

$y_0 = 1$

$y_1 = 1 + e^0 (0.1) = 1.1$

$y_2 = 1.1 + 0.1\, e^{0.1} = 1.2105$

…

$y_{10} = 1 + 0.1 \sum_{1..10} e^{(i-1)/10} = 2.634$

- With error 0.0845, which is about 2/3 the error of the previous equation, but:

$y_{100} = 1 + 0.1 \sum_{1..100} e^{(i-1)/10} = 2.0943e4$

- Which is only off by about 5% rather than a factor of 2!

ODE Stability

- Why? In this case the family of curves is not diverging!

$$y = e^t + c$$

- Even though the solution is the same (for the same initial condition) the behavior is very different. For equations like this, the ODE is called neutrally stable.

ODE Stability

- What if we had the equation:

$$dy/dt = -y$$

- In this case all of the family of solutions converge thus the error tends to be wiped out. Such equations are stable.
- The stability is determined by the Jacobian:

$$J = df/dy$$

- Note that the derivative is with respect to the dependent variable!

ODE Stability

If $J < 0$ the equation is stable

If $J > 0$ it's unstable

If $J = 0$ it's neutrally stable

- We may have an equation which is stable in places and unstable in others. For example:

  $dy/dt = (1-t)\,y \qquad y(0)=1$

  $J>0$ for $t<1$ unstable

  $J<0$ for $t>1$ stable

ODE Stability

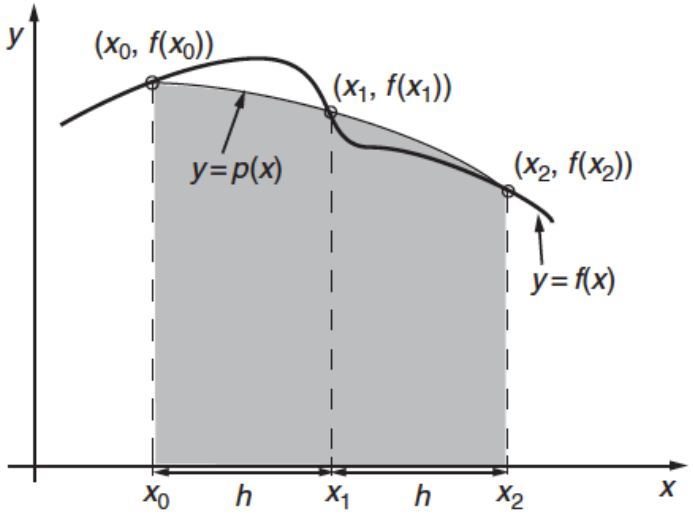
- We have the same for systems of equations. In this case the Jacobian is a matrix.

$$\mathbf{J} = J_{ij} = df_i/dy_j$$

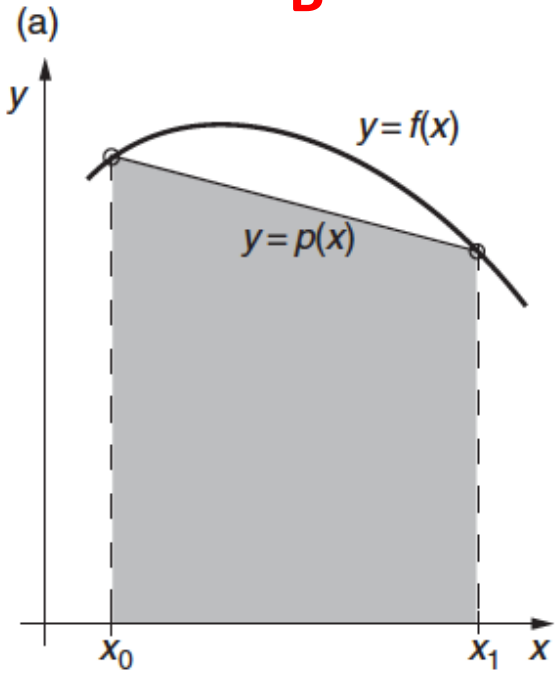
- The stability of a system of equations is related to the eigenvalues of **J**.

Q1: Which diagram depicts Simpson's 1/3 rule?

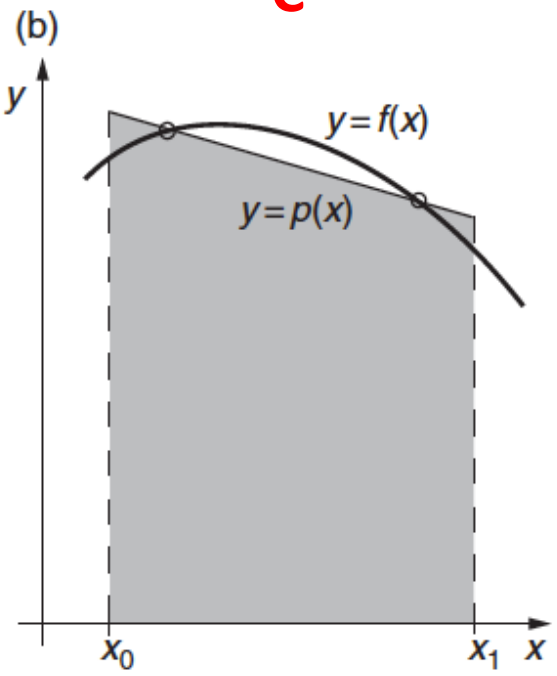
A



B

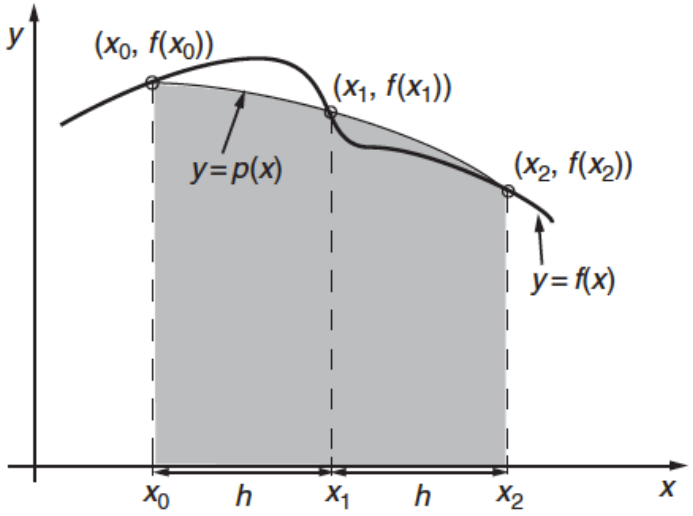


C

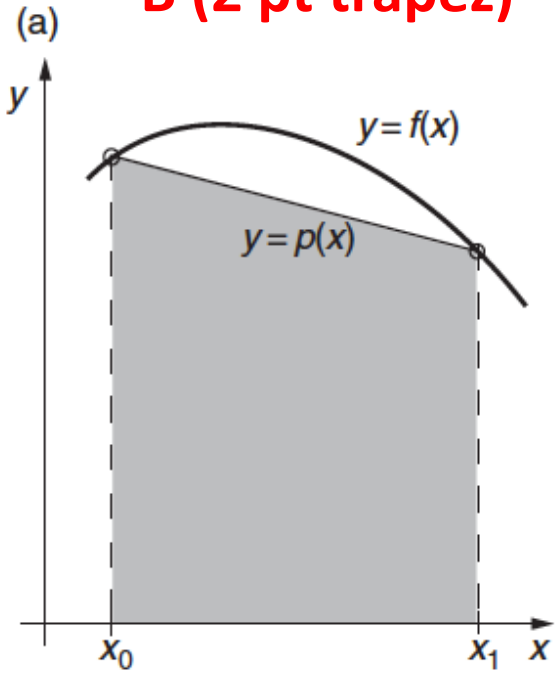


Q2: In general, which quadrature rule is most accurate?

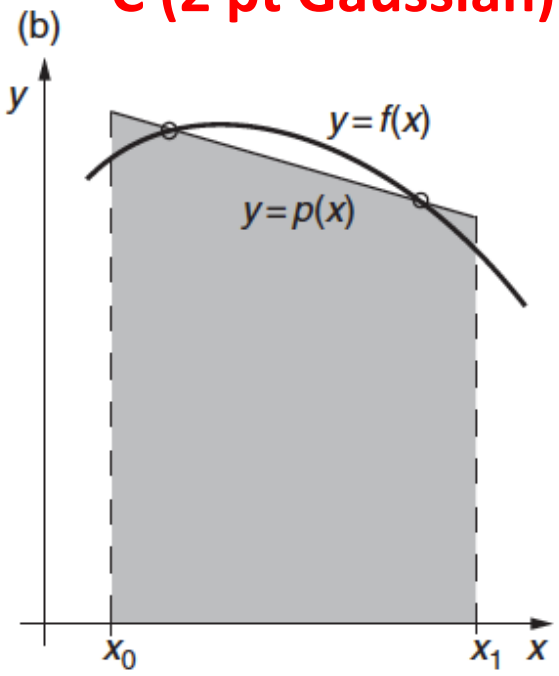
A (3 pt Simpson)



B (2 pt trapez)



C (2 pt Gaussian)



Q3: The six point Gaussian quadrature rule has a node at x=0.

A. True

B. False

Q4: Which quadrature method is NOT well suited for adaptive quadrature schemes?

A. Trapezoidal

B. Simpson's

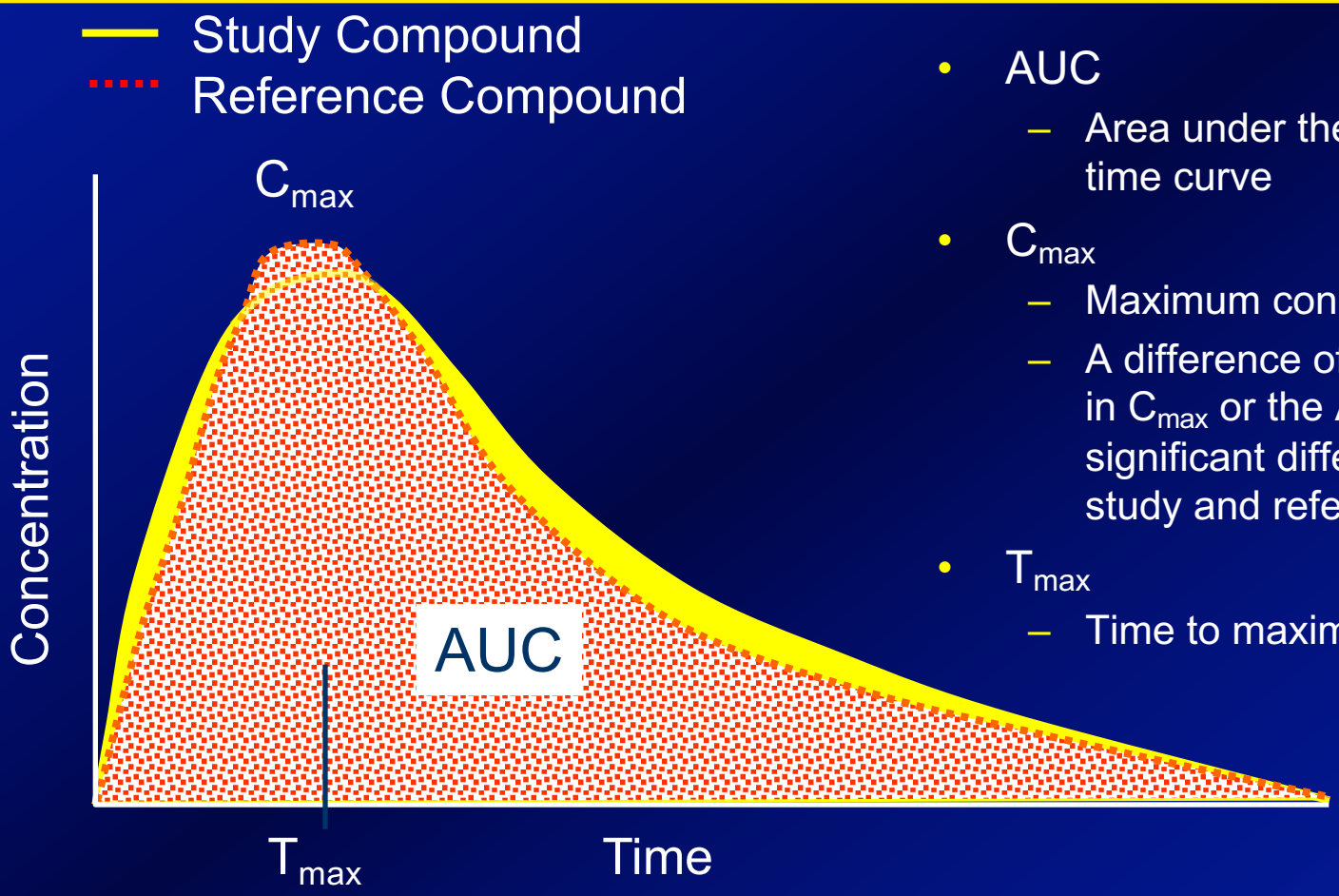
C. Gaussian

FDA Methods to Determine Bioequivalence

- Generic drug manufacturers must demonstrate that a drug is bioequivalent to a reference drug product
- In order of FDA preference, methods used to define bioequivalence
  - Pharmacokinetic studies
  - Pharmacodynamic studies
  - Comparative clinical trials
  - In vitro studies

Food and Drug Administration. Code of Federal Regulations. Title 21, Part 320: Bioavailability and Bioequivalence Requirements. Section 320.24. 2003. Available at: http://www.accessdata.fda.gov. Accessed September 29, 2003.

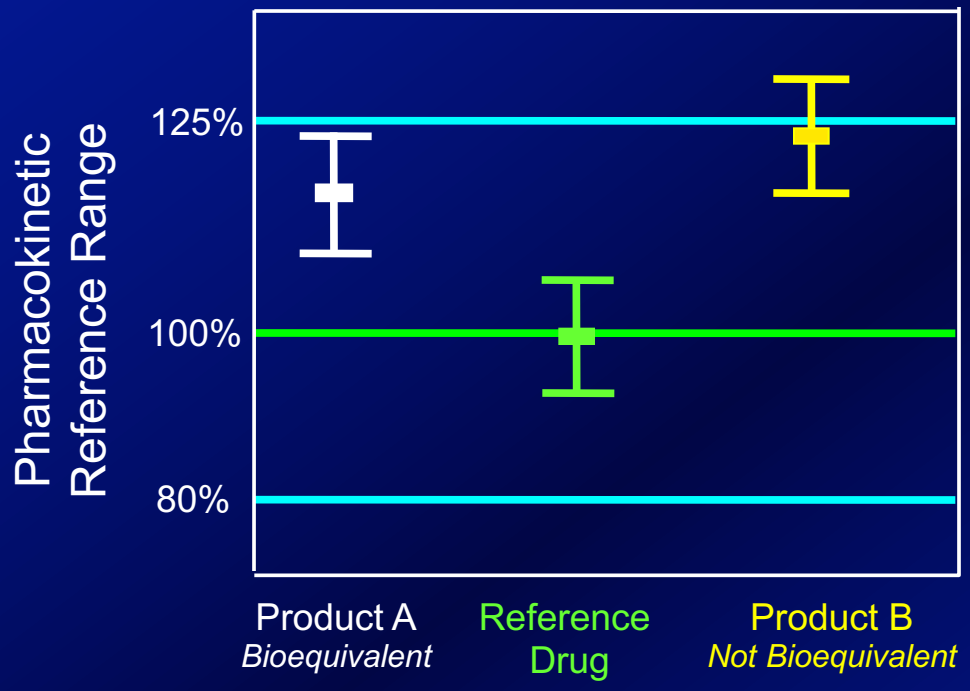
Pharmacokinetic Studies Key Measurements



- AUC
  - Area under the concentration-time curve
- C_{max}
  - Maximum concentration
  - A difference of greater than 20% in C_{max} or the AUC represents a significant difference between the study and reference compounds
- T_{max}
  - Time to maximum concentration

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

FDA Requirements for Bioequivalence



- Product A is bioequivalent to the reference drug; its 90% confidence interval of the AUC falls within 80% to 125% of the reference drug
- Product B is not bioequivalent to the reference drug; its 90% confidence interval of the AUC falls outside of 80% to 125% of the reference drug

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

Pharmacokinetic Studies
Healthy Volunteers Versus Patients

- If 2 drug products perform the same in healthy volunteers, the assumption is made that they will perform the same in patients with the disease, except in the case of some drugs that are potentially toxic

Welage LS, et al. *J Am Pharm Assoc.* 2001;41:856-867.

PLOS BIOLOGY

META-RESEARCH ARTICLE

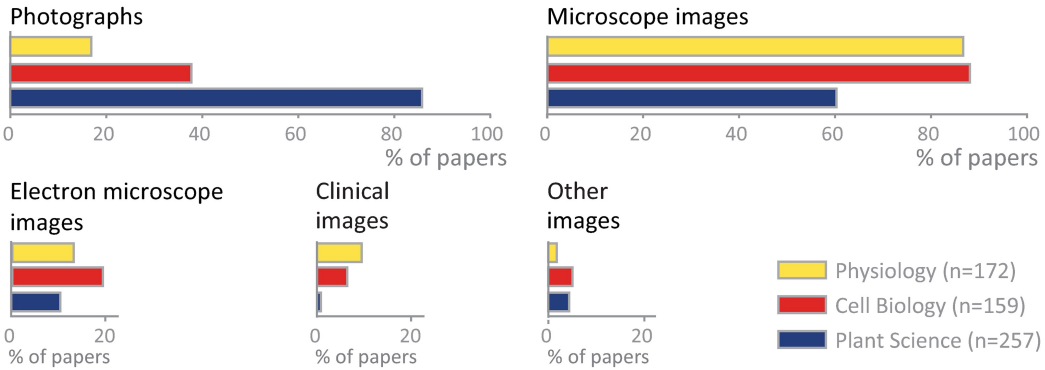
Creating clear and informative image-based figures for scientific publications

Helena Jambor[1‡], Alberto Antonietti[2,3‡], Bradly Alicea[4], Tracy L. Audisio[5], Susann Auer[6], Vivek Bhardwaj[7,8], Steven J. Burgess[9], Iuliia Ferling[10], Małgorzata Anna Gazda[11,12], Luke H. Hoeppner[13,14], Vinodh Ilangovan[15], Hung Lo[16,17], Mischa Olson[18], Salem Yousef Mohamed[19], Sarvenaz Sarabipour[20], Aalok Varma[21], Kaivalya Walavalkar[21], Erin M. Wissink[22], Tracey L. Weissgerber[23]*

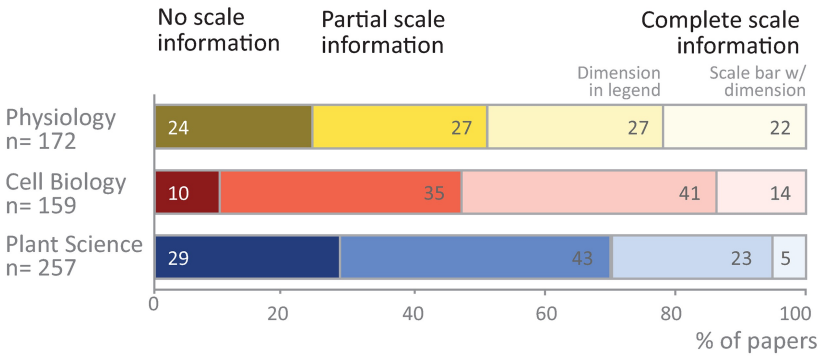
Abstract

Scientists routinely use images to display data. Readers often examine figures first; therefore, it is important that figures are accessible to a broad audience. Many resources discuss fraudulent image manipulation and technical specifications for image acquisition; however, data on the legibility and interpretability of images are scarce. We systematically examined these factors in non-blot images published in the top 15 journals in 3 fields; plant sciences, cell biology, and physiology ($n = 580$ papers). Common problems included missing scale bars, misplaced or poorly marked insets, images or labels that were not accessible to color-blind readers, and insufficient explanations of colors, labels, annotations, or the species and tissue or object depicted in the image. Papers that met all good practice criteria examined for all image-based figures were uncommon (physiology 16%, cell biology 12%, plant sciences 2%). We present detailed descriptions and visual examples to help scientists avoid common pitfalls when publishing images. Our recommendations address image magnification, scale information, insets, annotation, and color and may encourage discussion about quality standards for bioimage publishing.

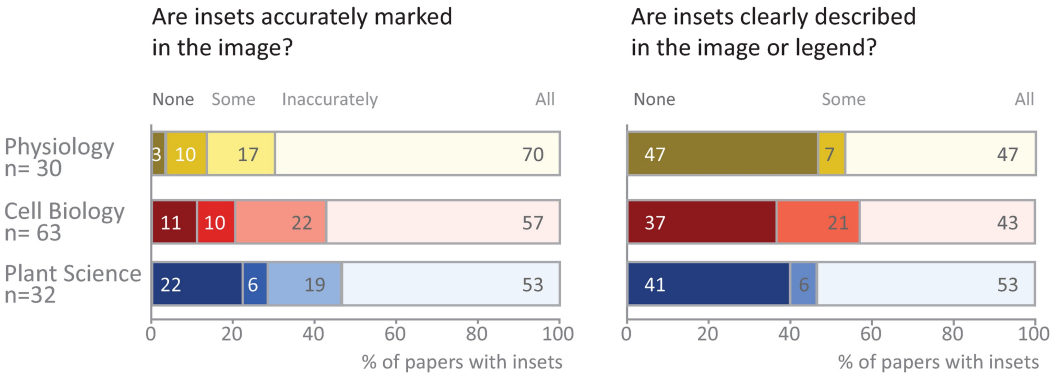
A Percentage of papers with image type



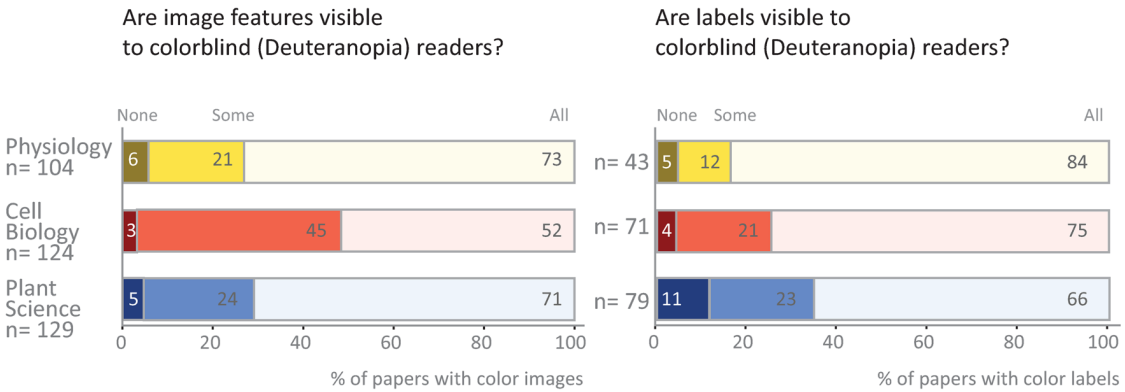
B Reporting of scale information



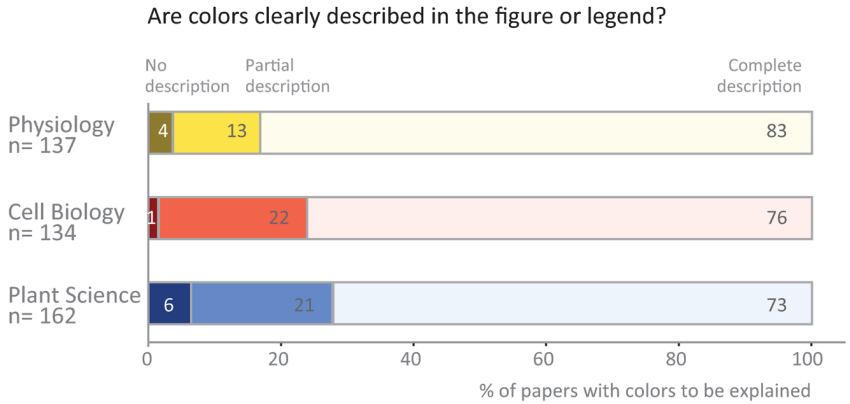
C Reporting of image insets

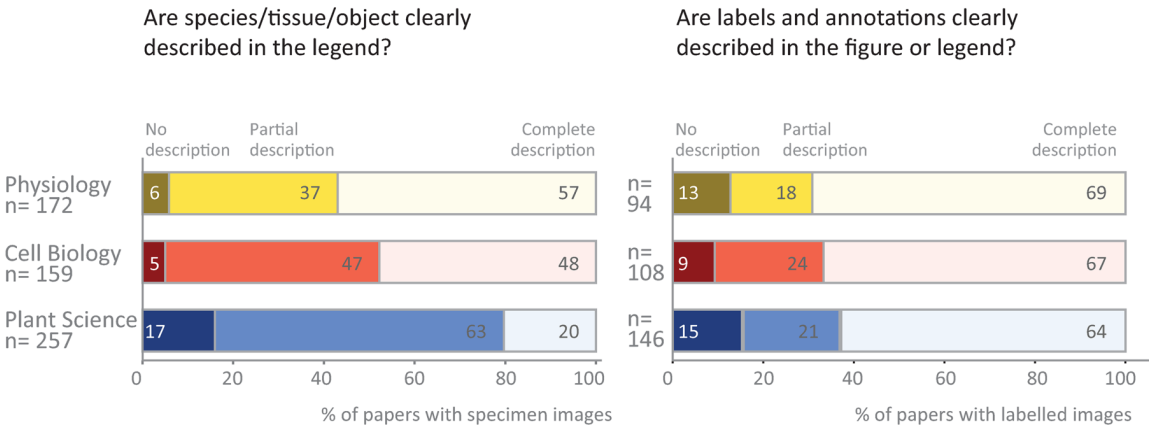


A Colorblind accessibility

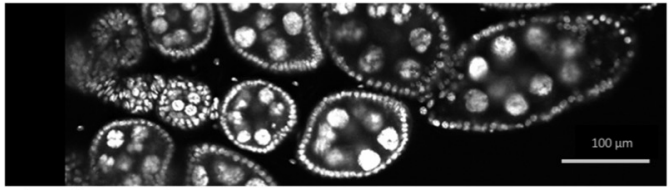


B Explanation in figure legends

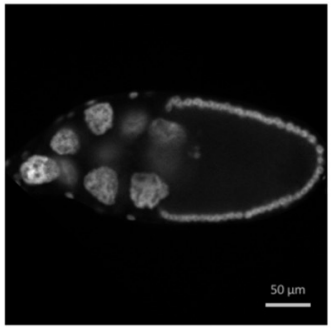




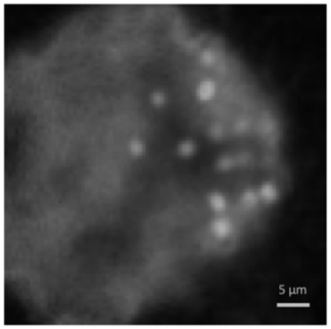
A Magnification/zoom must match message



1. Tissue scale
Drosophila melanogaster Ovary tissue



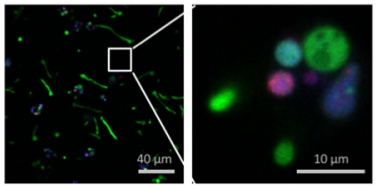
2. Cellular scale
Drosophila melanogaster
Egg chamber with oocyte



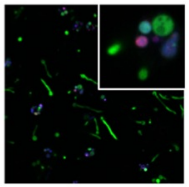
3. Subcellular scale
Drosophila melanogaster,
RNA granules in epithelial cell

B Insets allow readers to see more than one scale

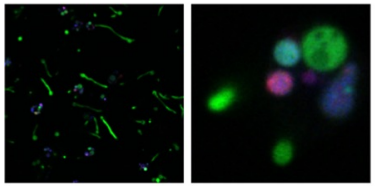
Poor inset examples



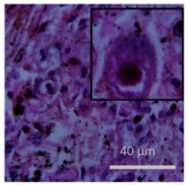
1. Wrongly placed inset
(no cells in marked region)



2. No inset marked,
inset obstructs data

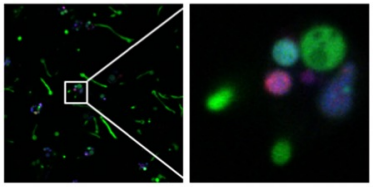


3. Inset origin not marked

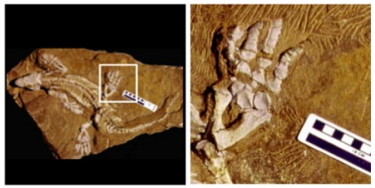


4. No inset marked,
inset obstructs data

Clear examples

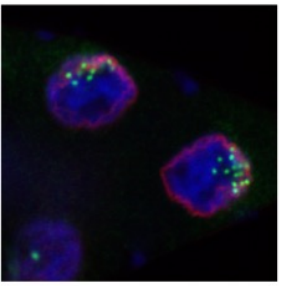


5. Inset indicated

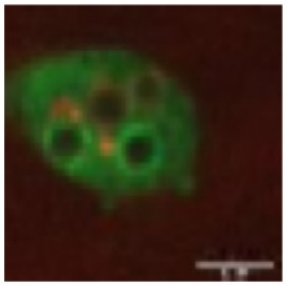


6. Inset indicated

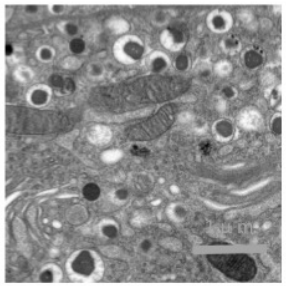
Poor scale bar examples



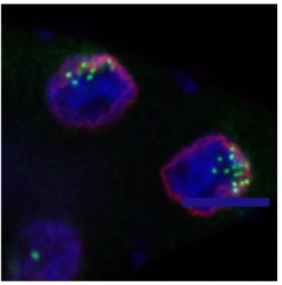
1. No scale bar



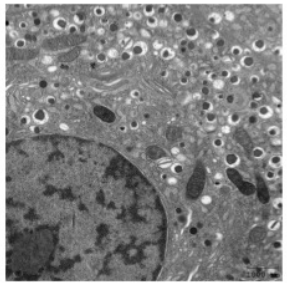
2. Scale bar illegible, poor compression



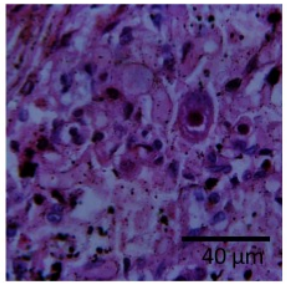
3. Scale bar blends into the background



4. Scale bar in color

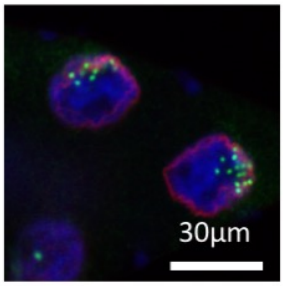


5. Scale bar too small

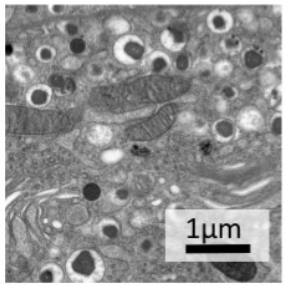


6. Scale bar blends into the background

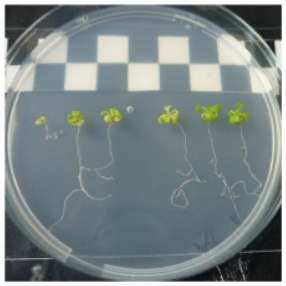
Clear scale bar examples



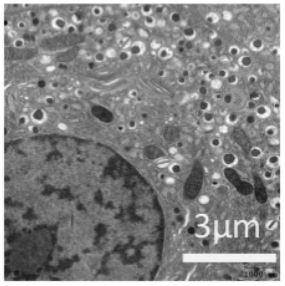
7. Scale bar, good contrast



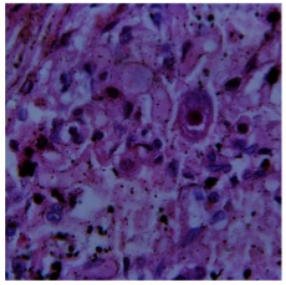
8. White background enhances contrast



9. Ruler as scale bar, Square edge: 1cm

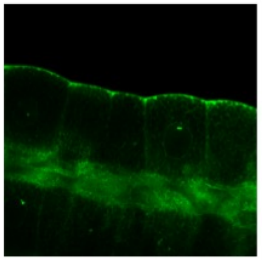
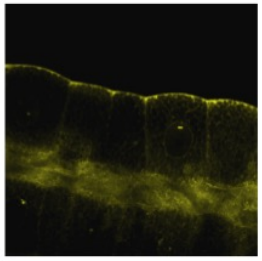
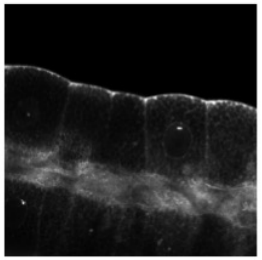
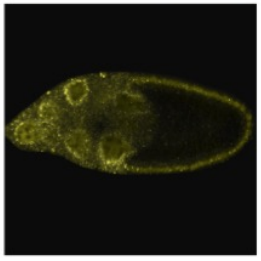
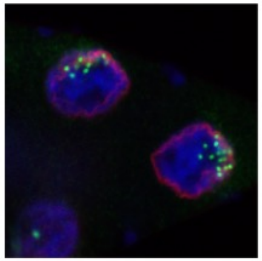
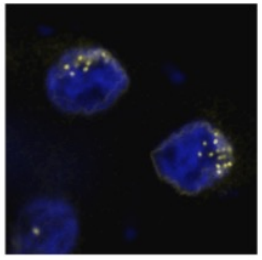
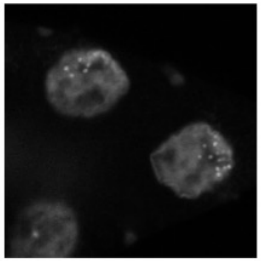
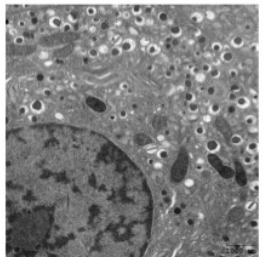
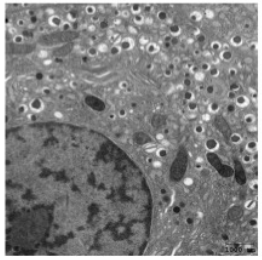
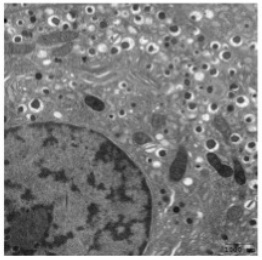


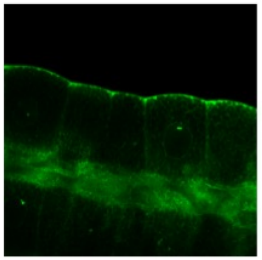
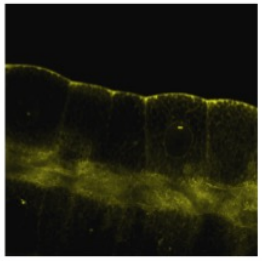
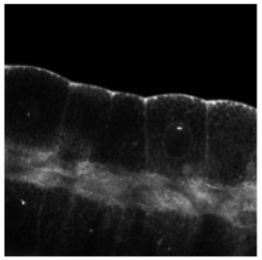
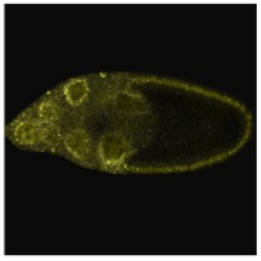
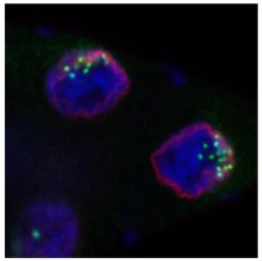
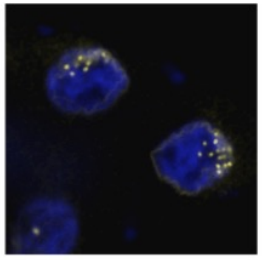
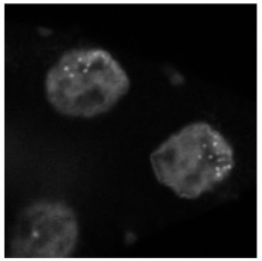
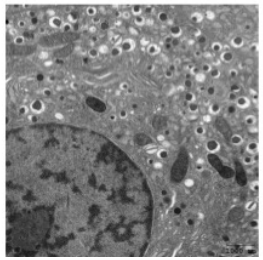
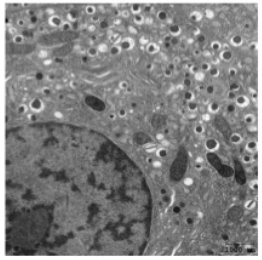
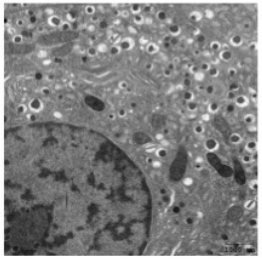
10. Scale bar, good contrast



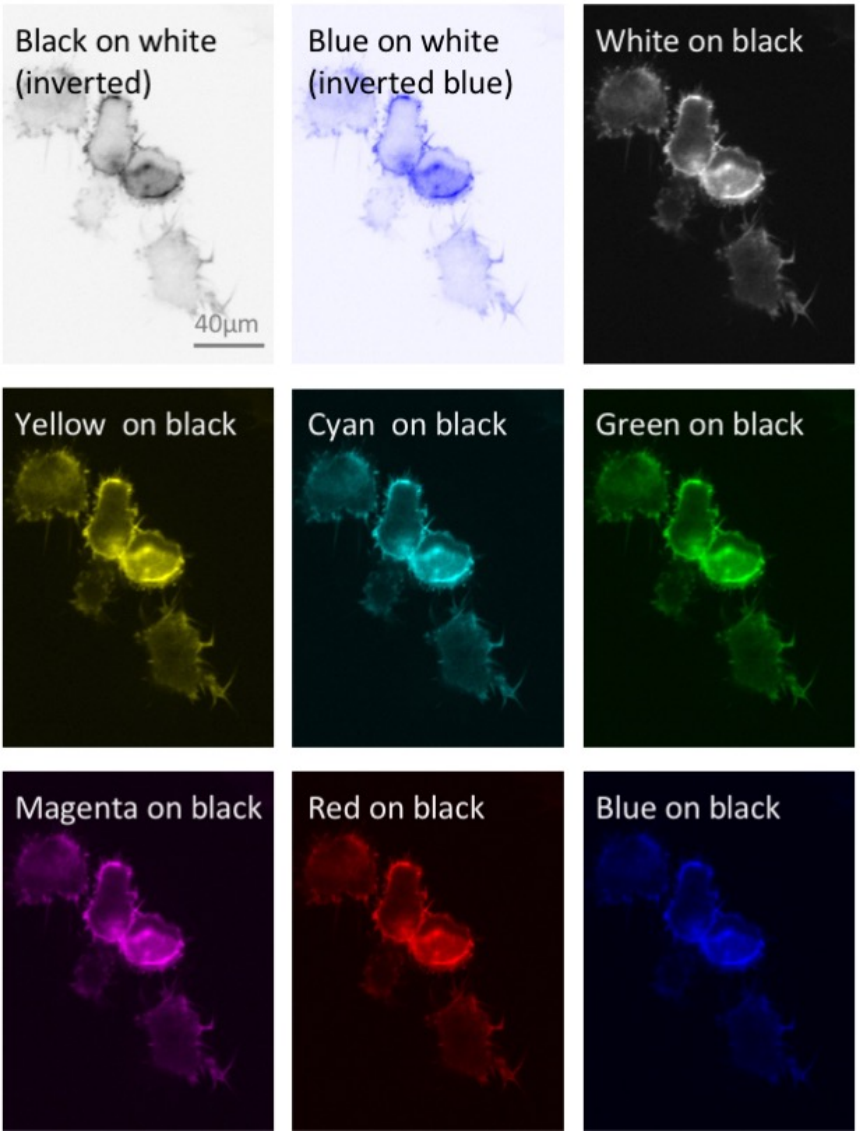
11. Scale bar below image

12. Ruler as scale bar, Square edge: 1cm

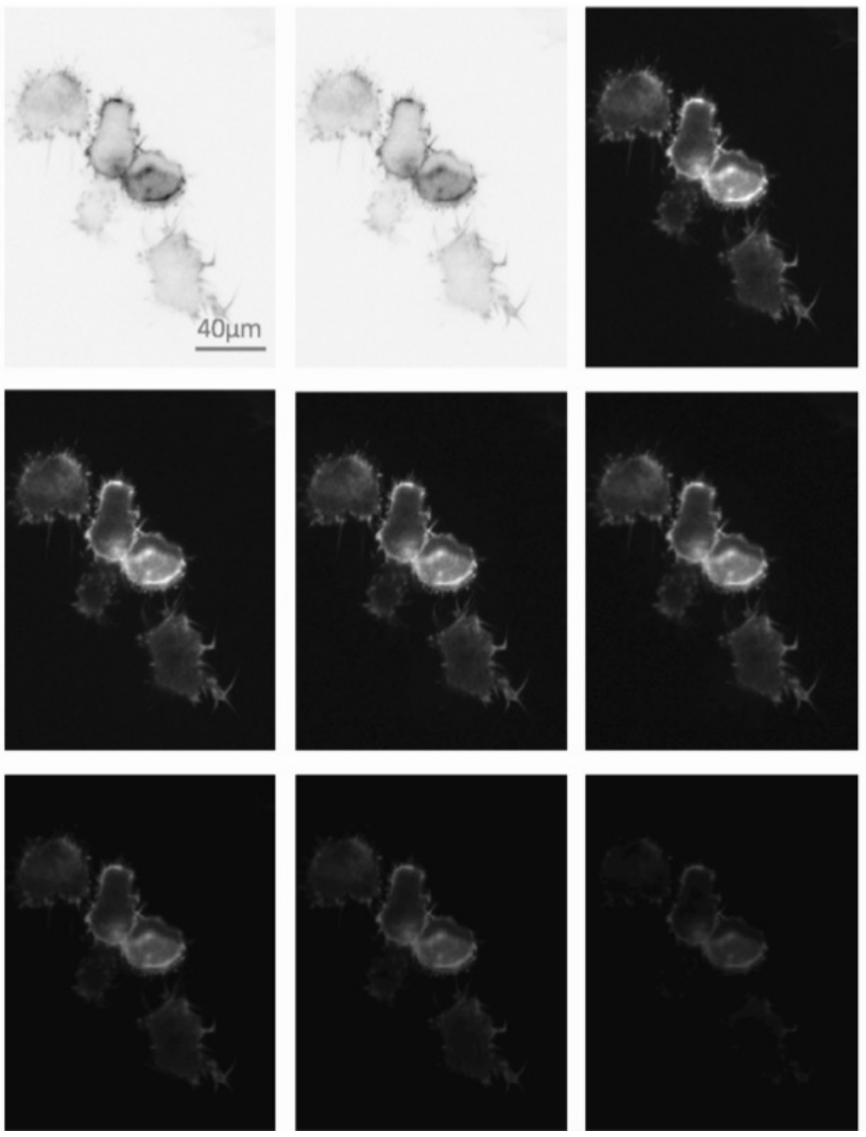
Situation	Example	Visibility tests		Comment	Recommendation
		Colorblind simulation	Grayscale simulation		
Color photo e.g. photograph, tissue staining with dyes.				Color shows natural appearance of subject or staining	Use color. Features may be visible in grayscale, depending on contrast
Microscope image, 1 color				Staining/structure visible in color	Consider using grayscale for higher contrast
Microscope image, 2 colors				Color shows two stains to compare localization within structures	Split channels; show color in two grayscale images side-by-side See also Figure 8
Microscope image, 3 colors				Color shows three stains to compare localization within structures	Show colors or each channel separately in grayscale See also Figure 8
Electron microscope image				Grayscale by default	Use grayscale

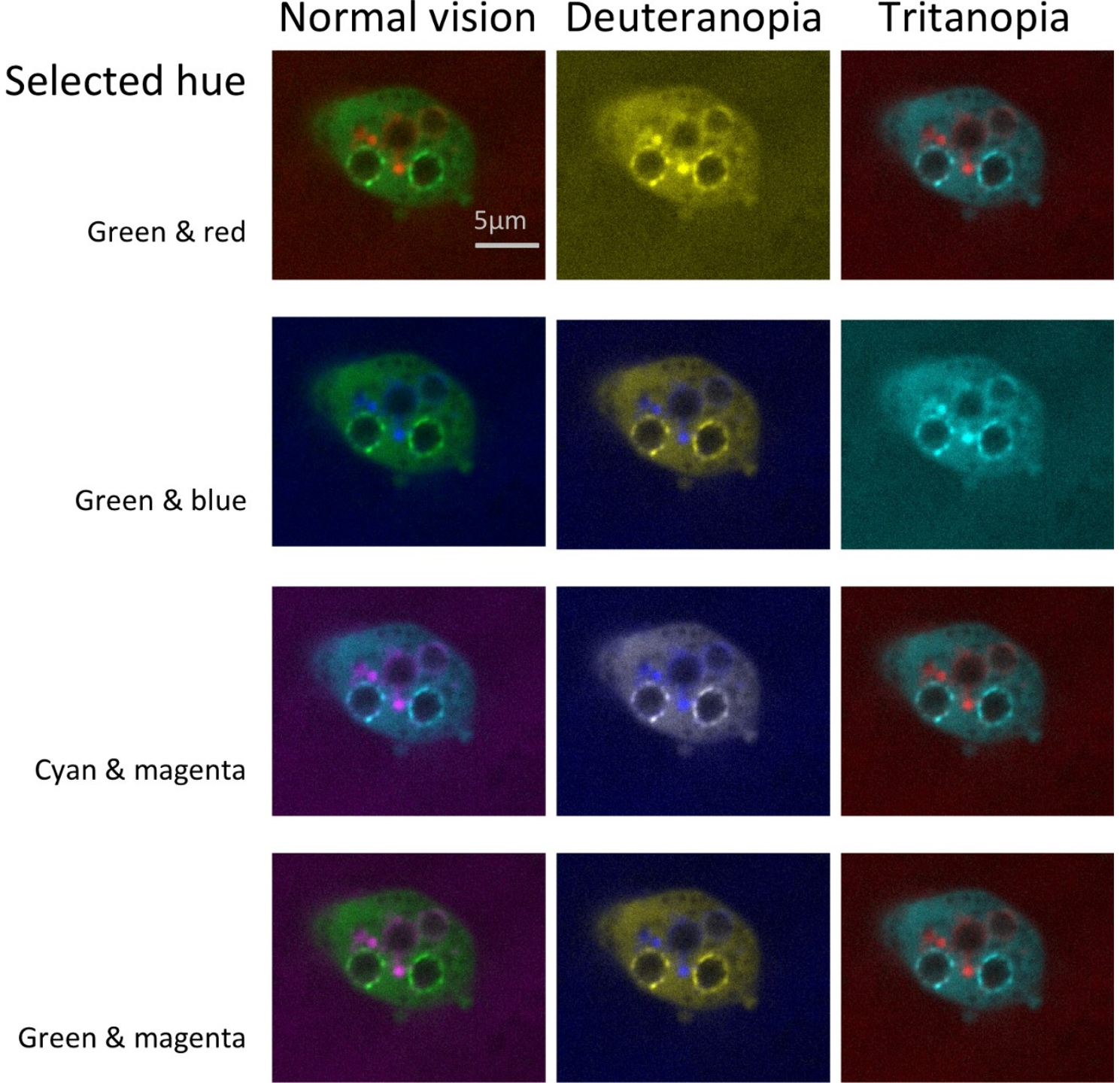
Situation	Example	Visibility tests		Comment	Recommendation
		Colorblind simulation	Grayscale simulation		
Color photo e.g. photograph, tissue staining with dyes.				Color shows natural appearance of subject or staining	Use color. Features may be visible in grayscale, depending on contrast
Microscope image, 1 color				Staining/structure visible in color	Consider using grayscale for higher contrast
Microscope image, 2 colors				Color shows two stains to compare localization within structures	Split channels; show color in two grayscale images side-by-side See also Figure 8
Microscope image, 3 colors				Color shows three stains to compare localization within structures	Show colors or each channel separately in grayscale See also Figure 8
Electron microscope image				Grayscale by default	Use grayscale

Color images



Grayscale test for visibility



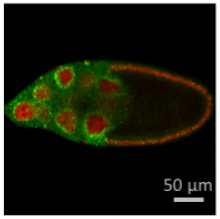

Normal vision
Deuteranopia
Tritanopia
Selected hue
Green & red
5µm
Green & blue
Cyan & magenta
Green & magenta

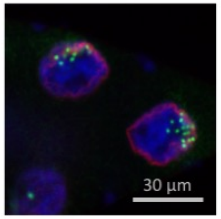
Microscope image, 2 colors

Microscope image, 3 colors

Problem

Key features not visible to a colorblind reader

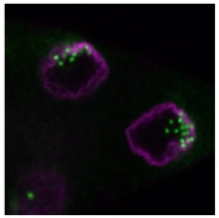


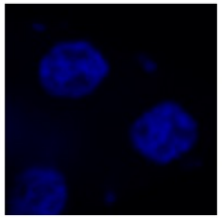


Solutions

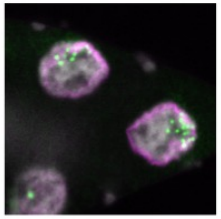
1. **Colorblind safe** hue combination

Change to an accessible hue combination



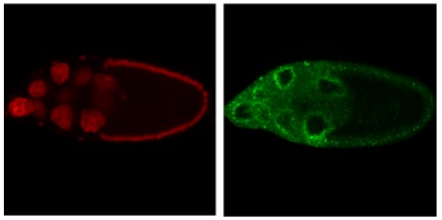


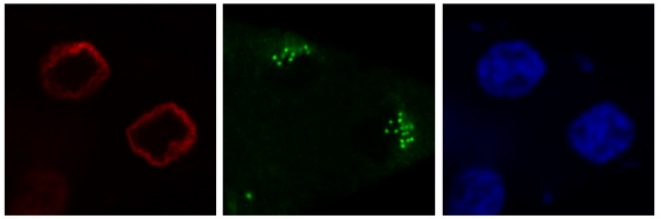
Option 1: Divide channels to two color colorblind safe images. Note: blue channel is suboptimal, consider alternatives (see Fig. 6)



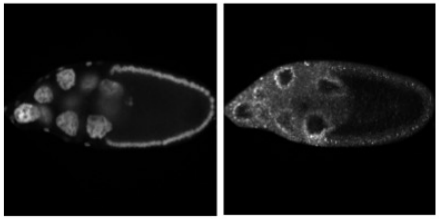
Option 2: Two hues may be combined with grayscale. Depending on the image, this may not be as effective.

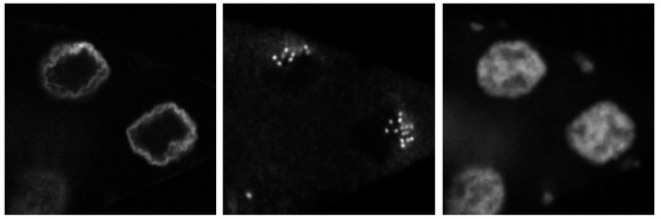
2. Split channels: **colorblind safe**, some colors have low contrast (see Fig. 6)



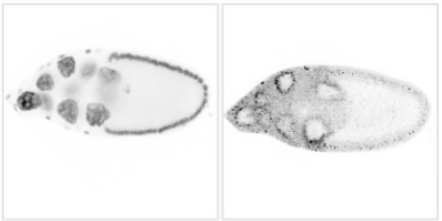


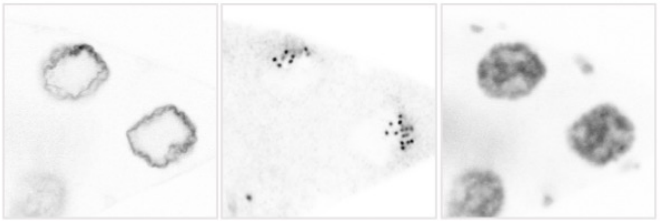
3. Show split channels in grayscale: **colorblind safe, high contrast**





4. Show split channels in inverted grayscale: **colorblind safe, highest contrast**





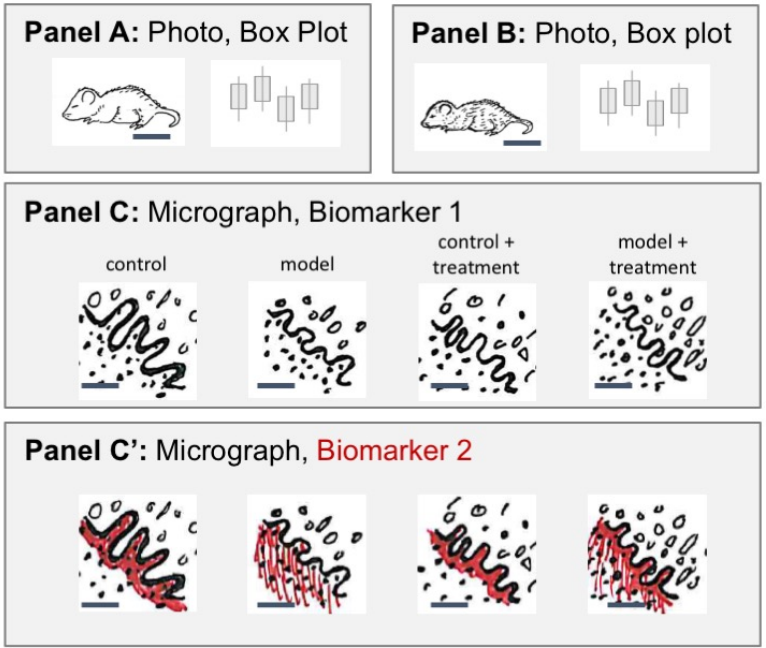
A Organize and plan figures with a "**Figure planning table**"

Example for a study of mouse placenta genetics and test of a treatment.

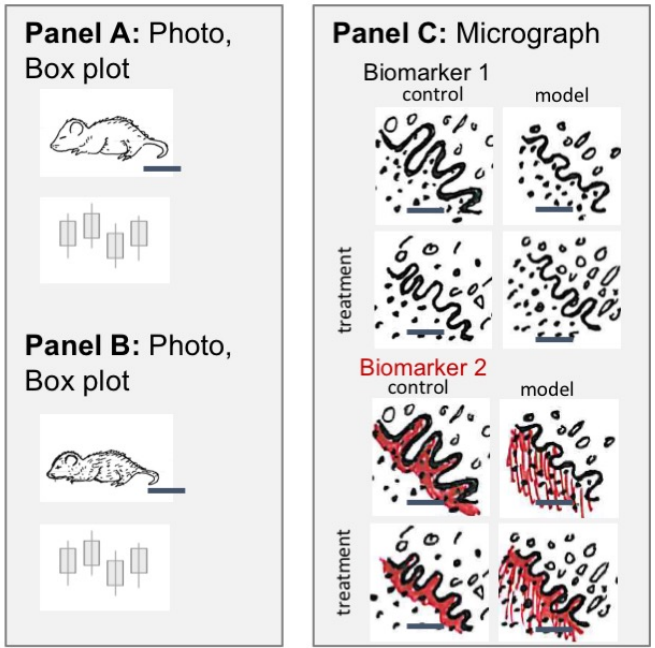
Panel	Panel objective	Visualizations	Experimental groups	Notes
A	Illustrate differences in pup phenotype	Photograph, chart	1. Control group + placebo 2. Animal model + placebo 3. Control group + treatment 4. Animal model + treatment	Photo with scale (ruler for pups) Box plot: fetal weight
B	Illustrate differences in placenta phenotype	Photograph, chart	See above	Photo with scale (ruler) Box plot: placental weight
C	Illustrate histological differences in placenta e.g. staining for two biomarkers	Micrograph	See above	One image per group; separate rows for each biomarker

B Organize panels into "**Figure layout sketch**", exemplary for Figure planning table in A

Layout in rows

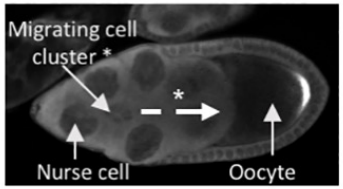


Layout in columns

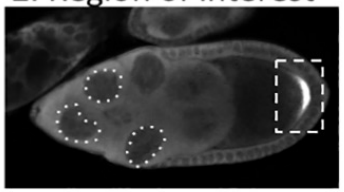


Annotation strategies

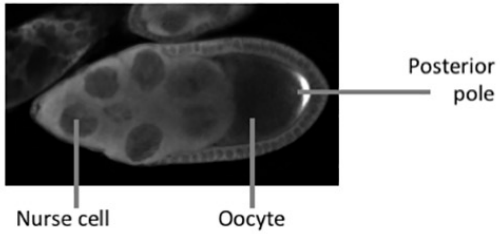
1. Arrows



2. Region of interest



3. Lines



4. Letter code, symbols

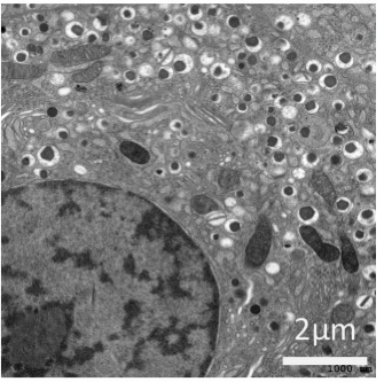
A – nurse cell nuclei
B – migrating cell cluster
C – posterior pole of oocyte
D – oocyte nucleus
∗ – somatic cell layer

	Use	Caution	Tips
1. Arrows	Points to structure May indicate direction of movement (e.g. *)	Do not concurrently use arrows for pointing to structure and indicating movement (example *) Arrowheads alone often have no clear direction	Avoid crossing arrows Align arrows
2. Region of interest	Delineates entire structure	May obstruct image features (especially when fill color is used)	Careful when saving: dashed lines may be too thin
3. Lines	Direct labeling of structure at line end	Label may be outside of image to not obstruct image features	Avoid crossing lines Align lines
4. Letter code, symbol	Labels many features clearly where lines and arrows would confuse	Legend is critical, requires large space. Labels may obscure image features	Choose suitable font e.g. sans serif

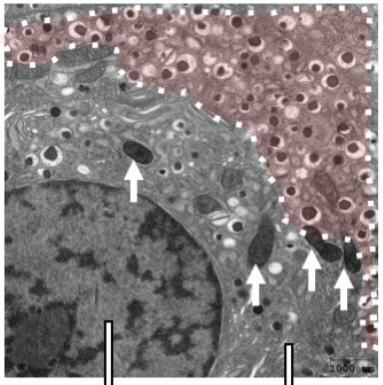
Feature to be Explained	Annotation
Size	Scale bar with dimensions
Direction of movement	Arrow with tail
Draw attention to:	
• Points of interest	Symbol (arrowhead, star, etc.)
• Regions of interest: black and white image	Highlight in color if this does not obscure important features within the region OR Outline with boxes or circles
• Regions of interest: Color image	Outline with boxes or circles
• Layers	Labeled brackets beside the image for layers that are visually identifiable across the entire image OR A line on the image for wavy layers that may be difficult to identify
Define features within an image	Labels

https://doi.org/10.1371/journal.pbio.3001161.t001

1. No annotation



2. Some annotation

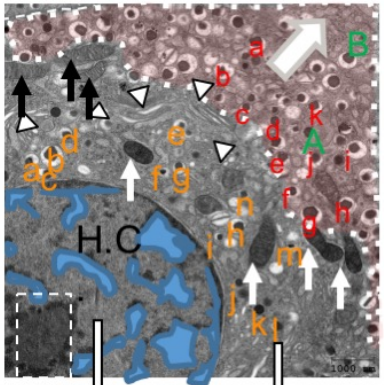


Nucleus Cytoplasm

Peripheral insulin secretory granules

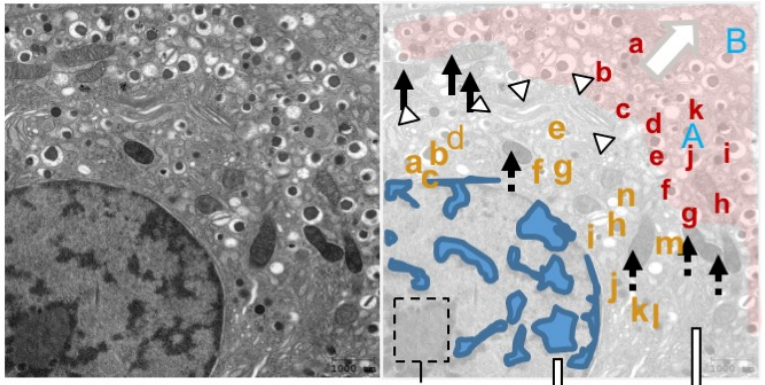
Mitochondrion

3. Excessive labels



N: Nucleus
C: Cytoplasm
H.C.: Heterochromatin
blue shape: Euchromatin
arrowhead: Golgi
white arrow: Mitochondrion
black arrow: light mitochondrion
pale red shape: Peripheral insulin secretory granules
white fat arrow: Cell periphery
dashed rectangle: Nucleolus
red letters: Individual insulin secretory granules
green capital letters: Lysosomes
orange letters: Central insulin secretory granules

4. Solution for many annotations



Euchromatin

Peripheral area insulin granules

Golgi

Plasma membrane

Mitochondria

Mitochondria (light)

A,B: lysosomes

a-k: peripheral insulin granules

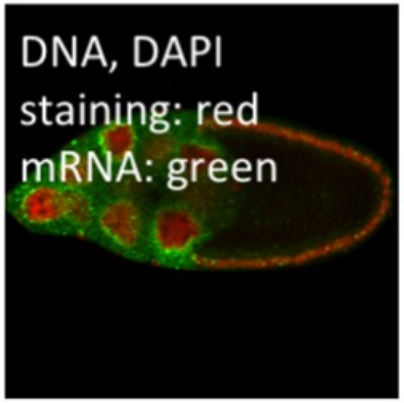
a-n: central insulin granules

Poor color annotation

1. No color annotation

2. Color annotation not colorblind safe

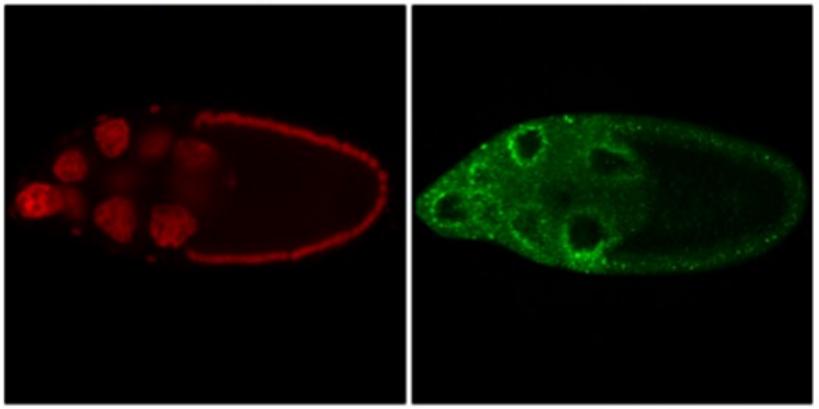
3. Illegible and/or incomplete annotation



4. Annotation covers image content

Clear color annotation

5. Colorblind safe annotation



6. Colorblind image and annotation (split color channels). Note: red has low contrast on black background, see Fig. 6.

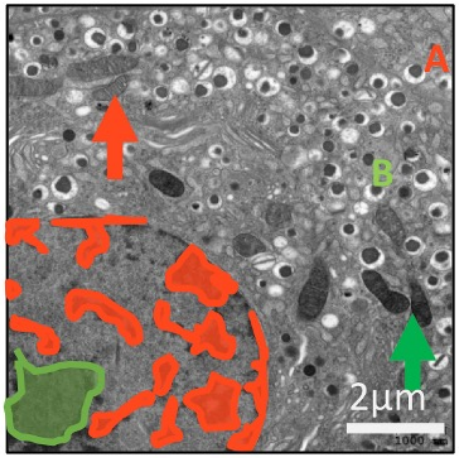
7. Name colors when text must be in grayscale

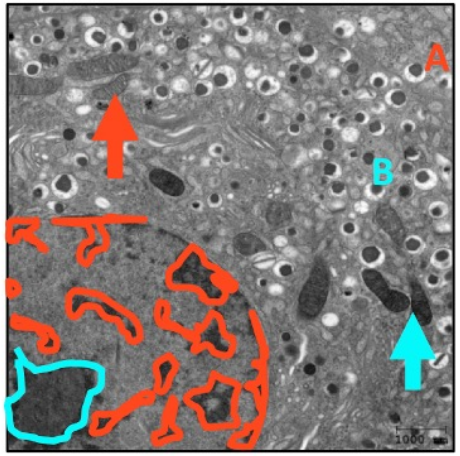
1. Colored annotation, not colorblind safe

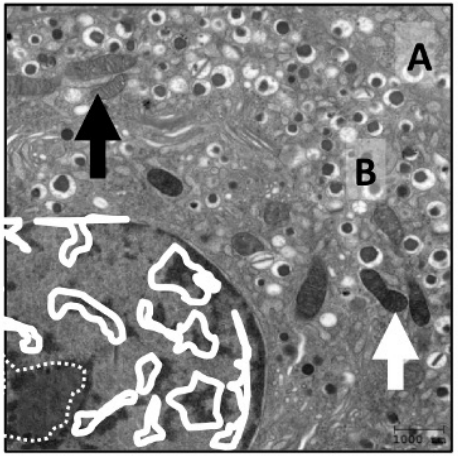
2. Colored annotation, colorblind safe

3. Grayscale annotation

Example







Visibility test

Colorblind vision render