HDYDI Series WS 2023

Can mathematics unlock nature's secrets?

Mehrta [Balzarotti Lab] / **Chris** [Menche Lab]

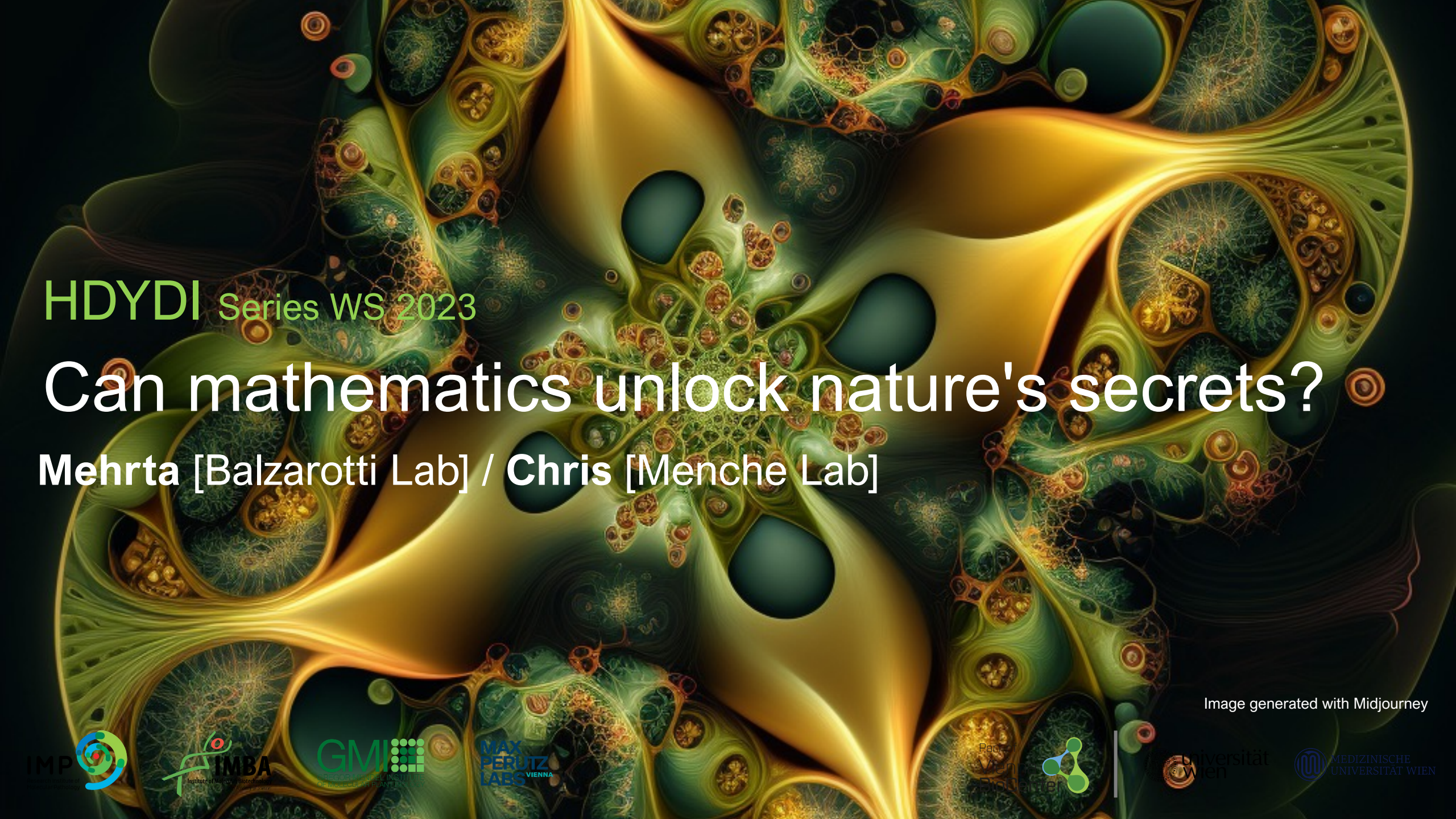


Image generated with Midjourney

Overview of today's HDYDI

We will introduce three projects – from the perspective of a biomedical engineer and a applied mathematician -

where mathematical modeling was part of a process to understand biology

 # 1 – On Population genetics models

 # 2 – On Cell population density

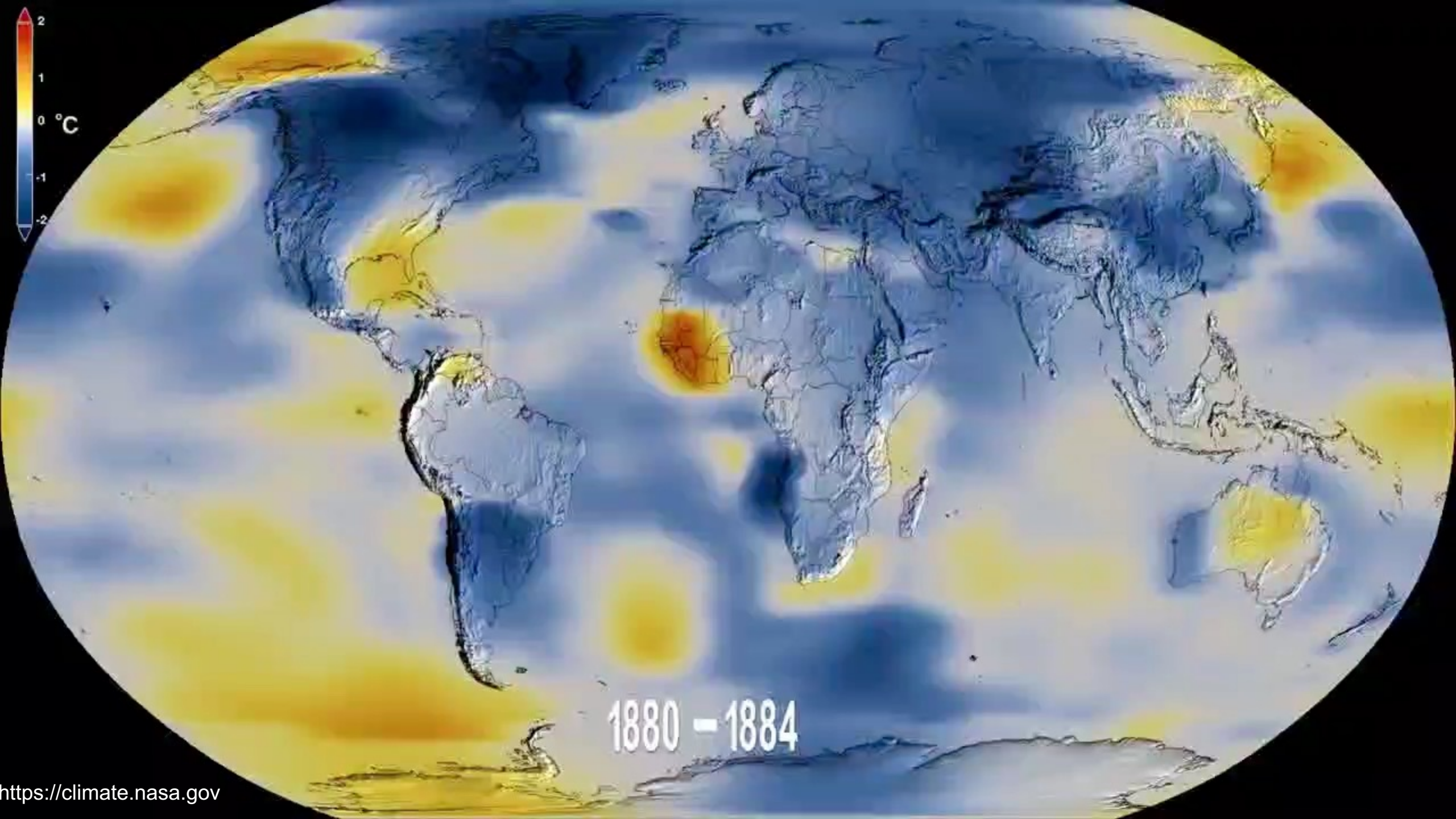
 # 3 – How modeling light behavior **can benefits biology**

Please jump in whenever you have

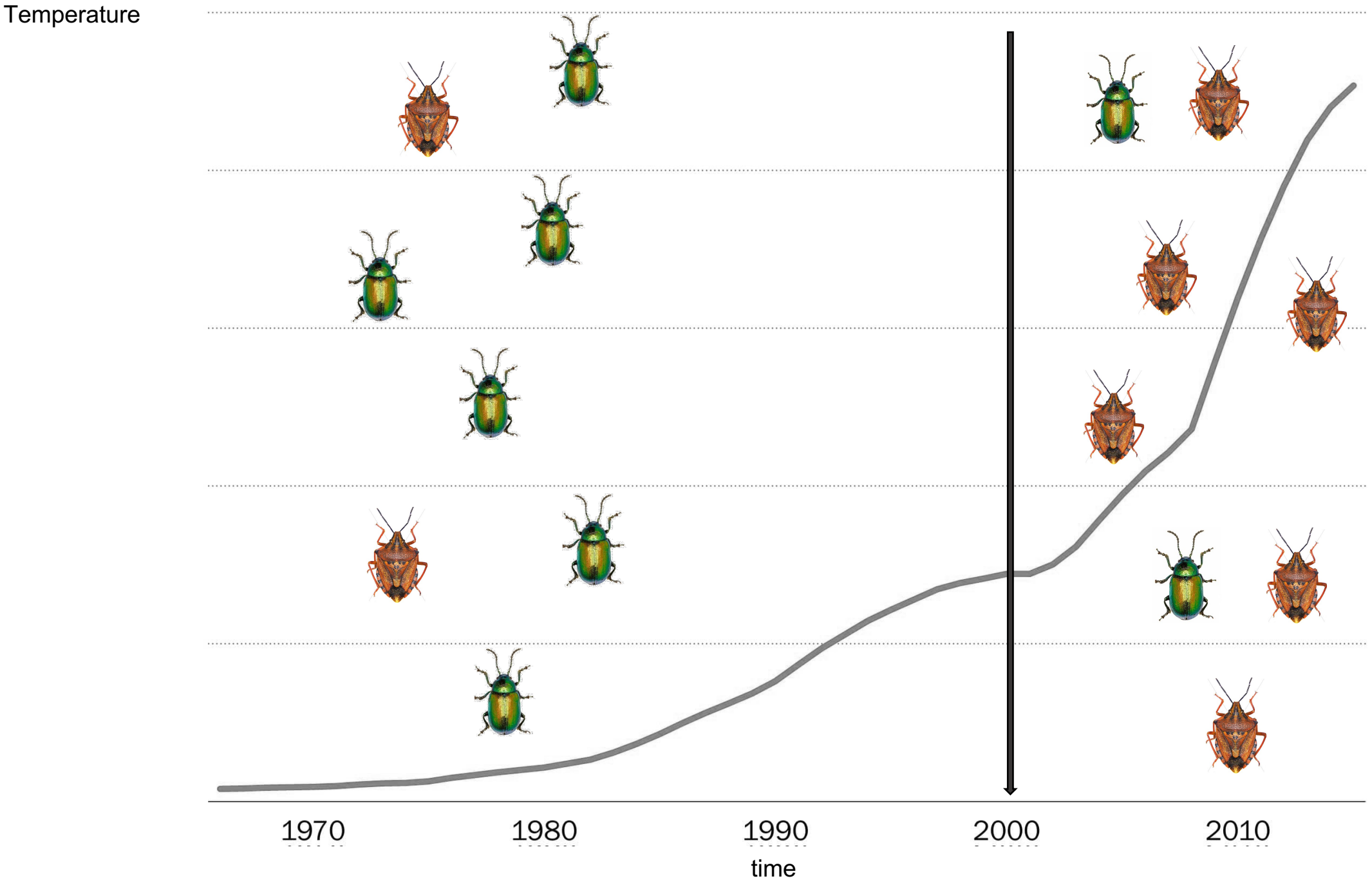
questions or comments - anytime!

1 – Polygenic adaptation of a binary trait

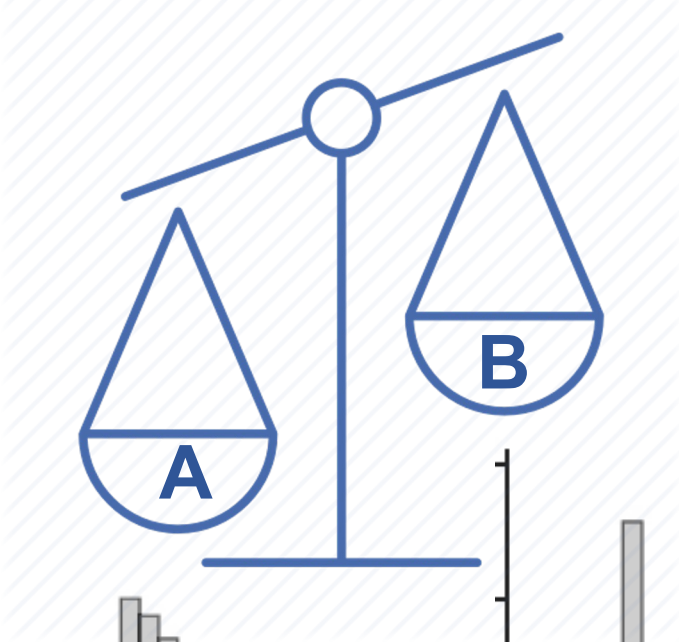
Image generated with Midjourney



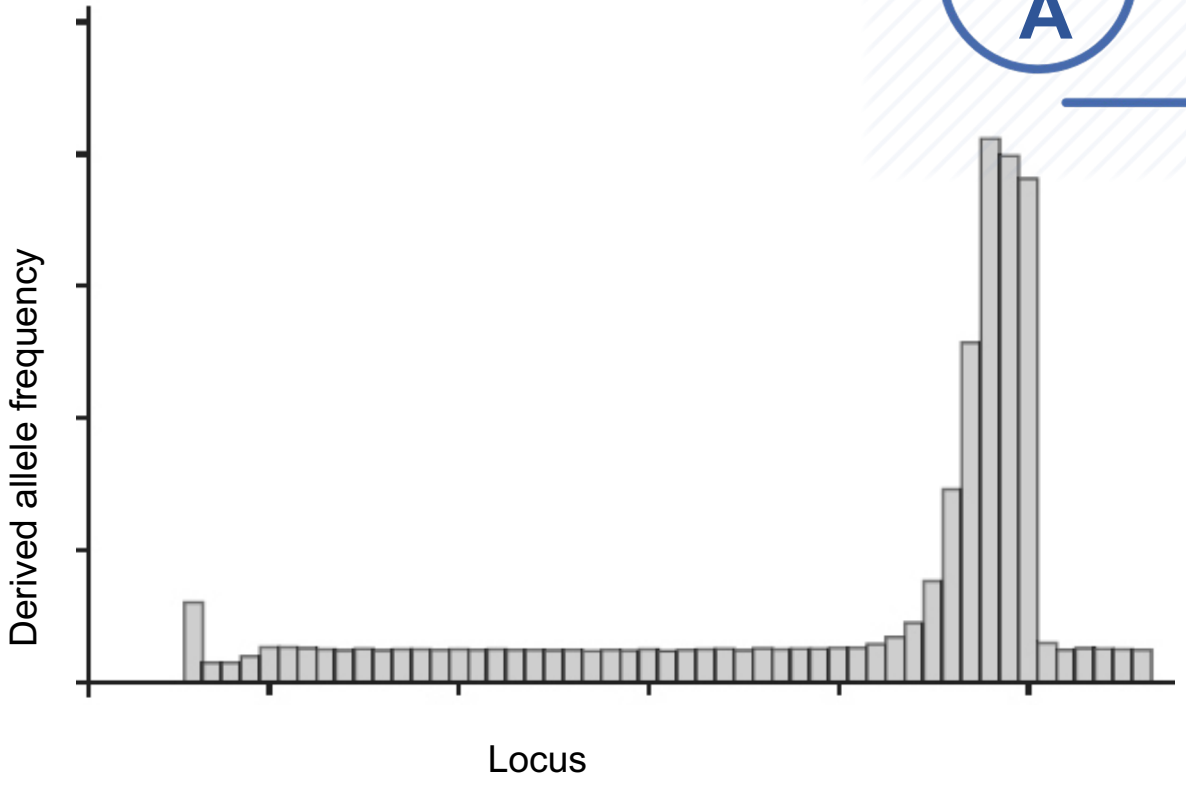
https://climate.nasa.gov

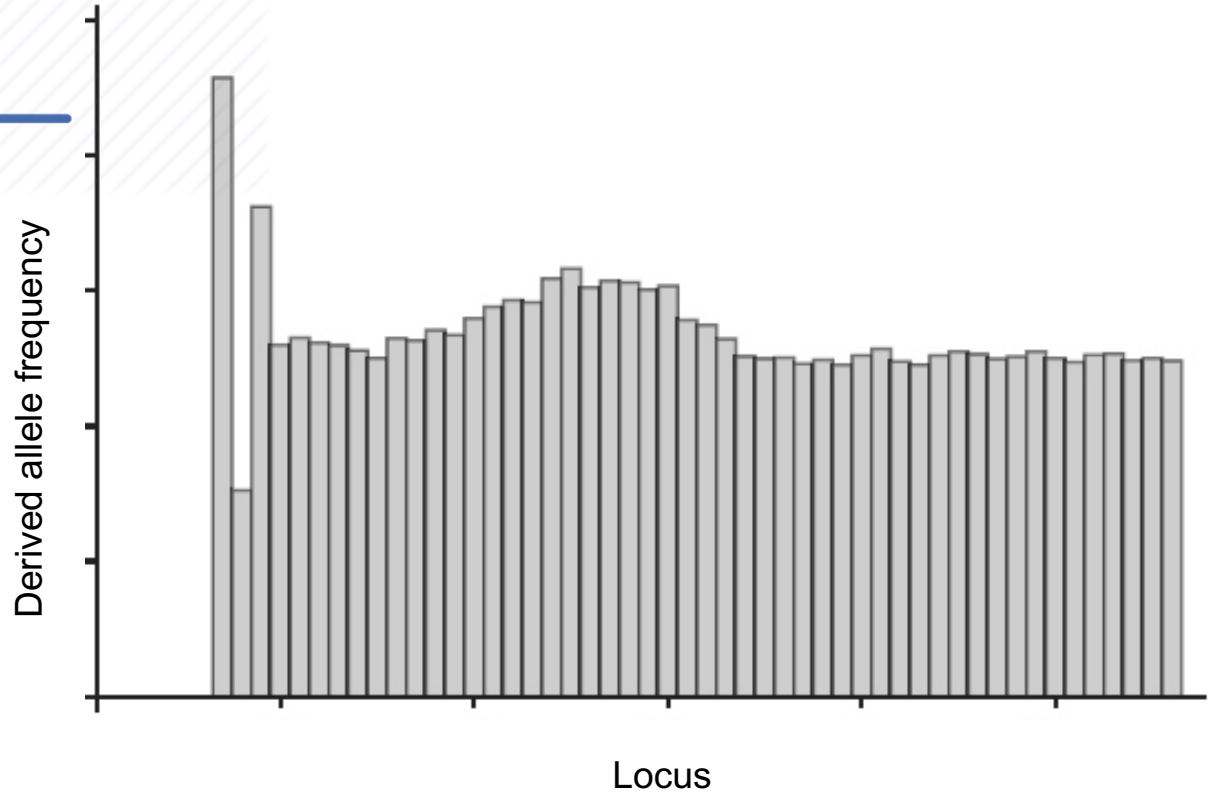

Temperature
1970
1980
1990
2000
2010
time

A) Selective sweep

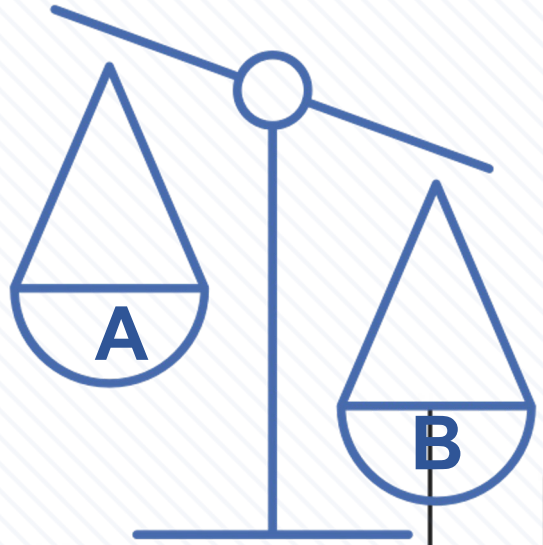


B)Polygenic adaptation

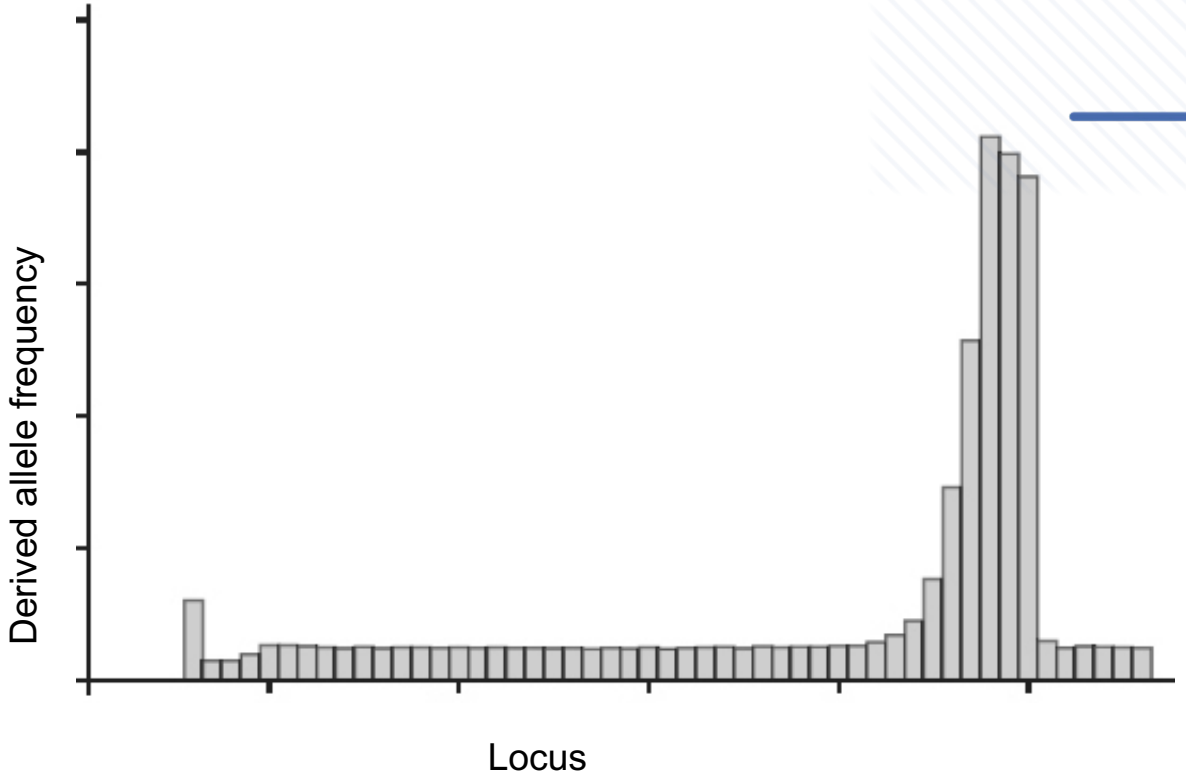


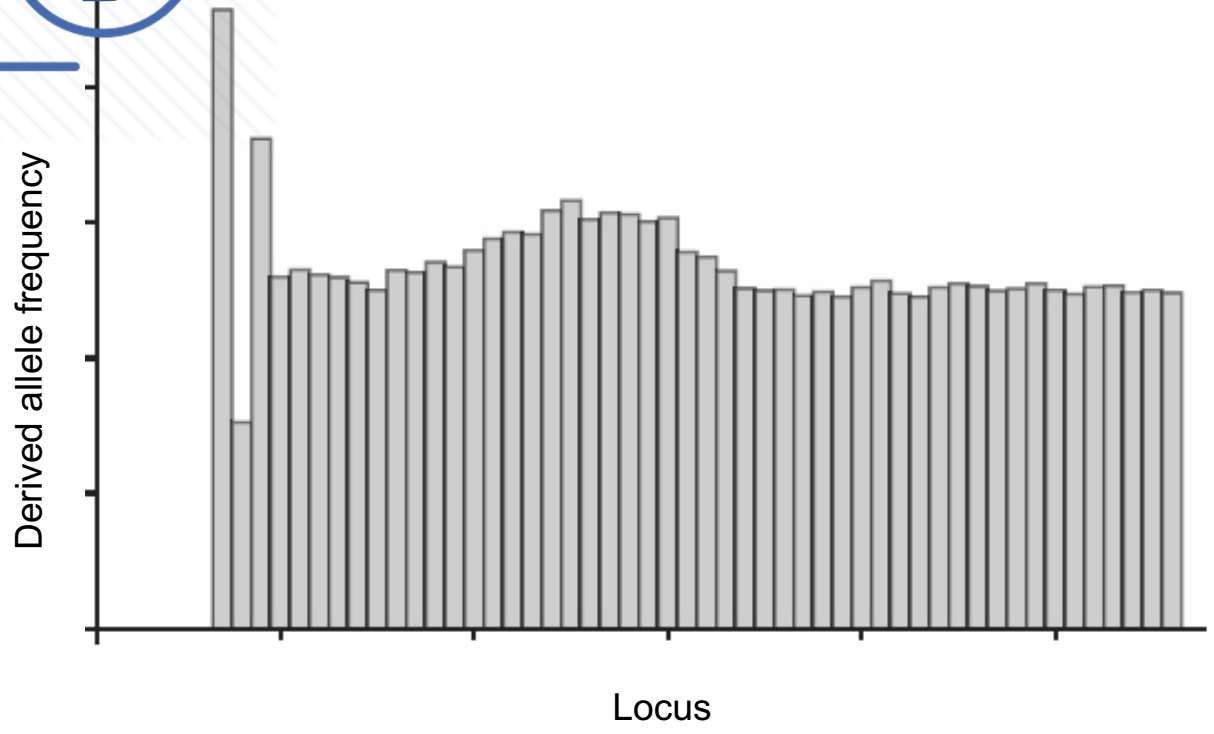


A) Selective sweep



B)Polygenic adaptation





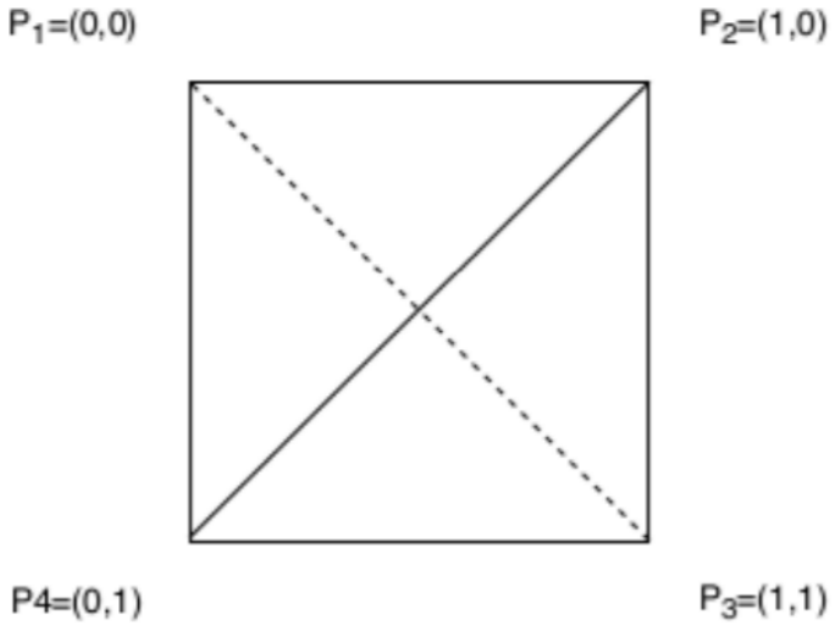
Mehrta Shirzadian

Joachim Hermisson

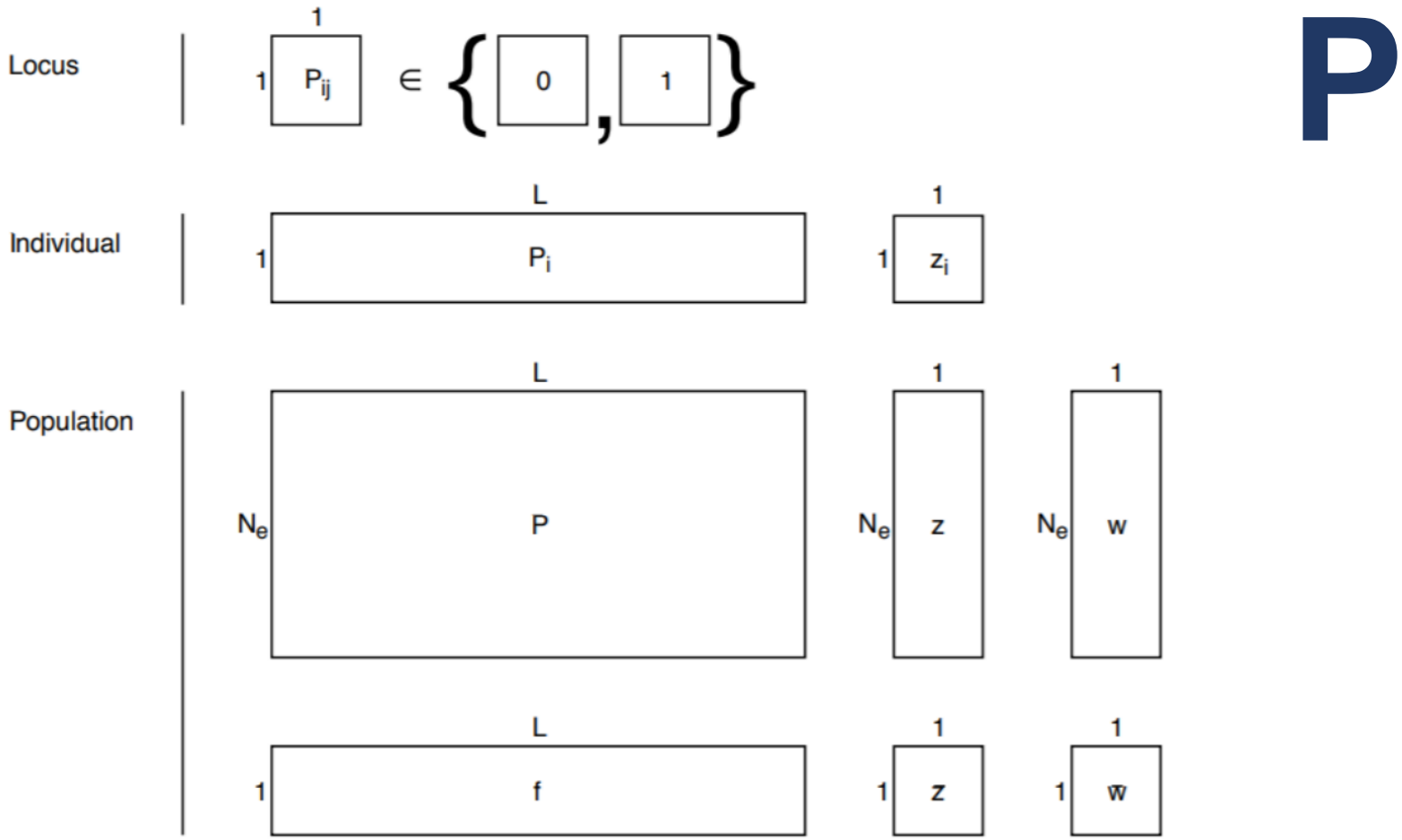
Polygenic adaptation under directional selection

Introduction

Imagine an individual with 2 bi-allelic loci:



Introduction



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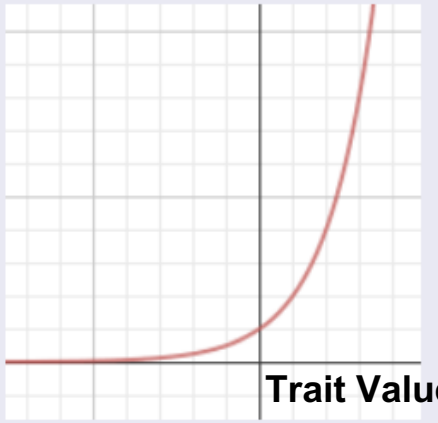
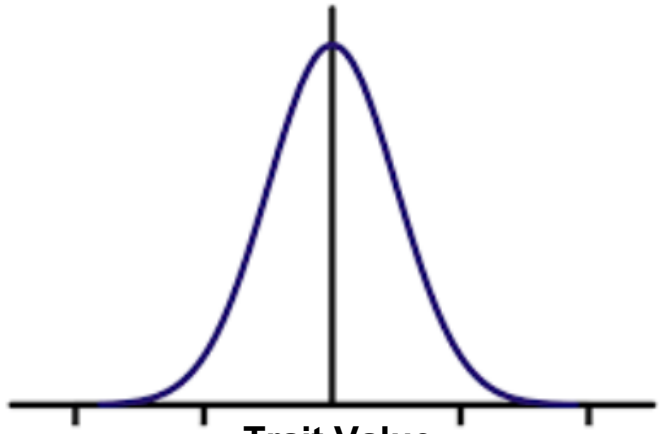
Genotype : mutation, selection, recombination, genetic drifts, migration

Directional selection



$$\dot{p_{A_i}} = p_{A_i}(1 - p_{A_i}).\sigma\gamma_i$$

Stabilizing selection

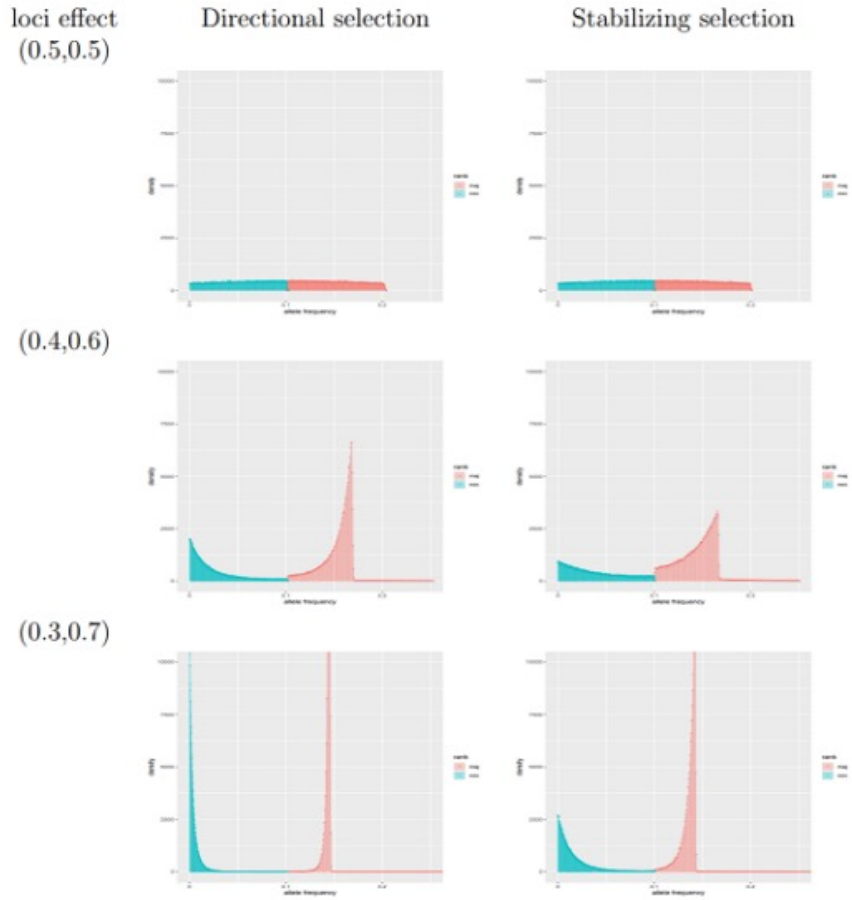


$$\dot{p}_{A_i} = p_{A_i}(1 - p_{A_i})\sigma\gamma_i\,(z_{opt} - \bar{z})$$

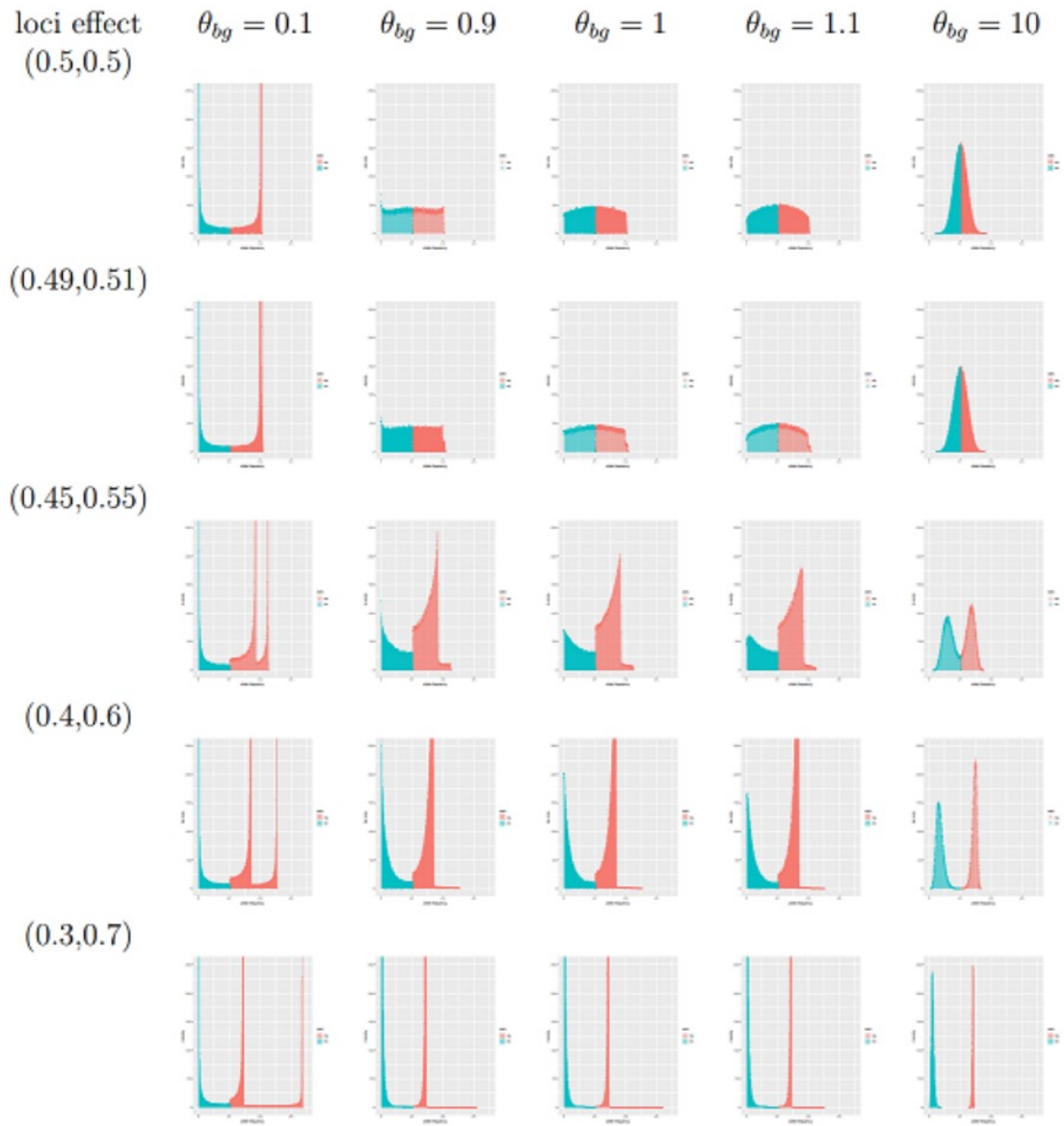
Simulation

```
1
2  void Genaraiton::Reproduction( gsl_rng *rng){
3
4
5      ZMean=0;
6          for (int i=0; i<numloci; i++){
7
8            ZMean = ZMean + (popArray[i]/(double)N)*LociWeights[i];
9
10         }
11
12         for (int l= 0; l<numloci;l++){
13
14            popArrayWeightsBeforeMut[0]=(N-popArray[l])/(double)N;
15
16            double fitness=exp(LociWeights[l]*sigma);
17
18
19     //*** add mutation to weights***
20
21             popArrayWeights[0] = popArrayWeightsBeforeMut[0]
22             *(1-mu_locus)+popArrayWeightsBeforeMut[1]
23             *mu_locus*BackMutFac;
24
25             popArrayWeights[1] = popArrayWeightsBeforeMut[1]
```

Results(Different locus effect, $\theta_{bg} = 1$, Directional vs. Stabilizing)



Results(Different locus effect, Directional selection)



2 – Modeling cell population density

Image generated with Midjourney

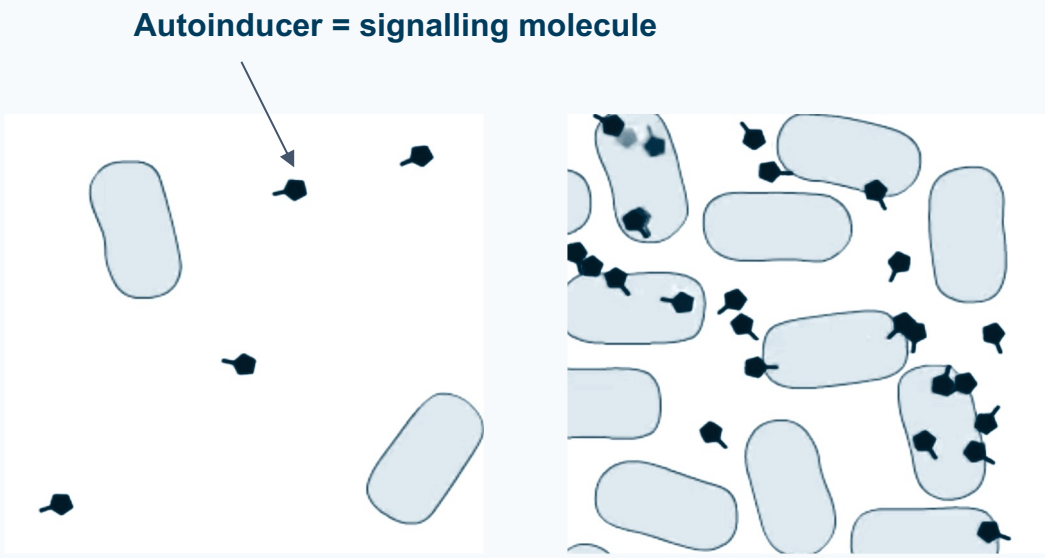
But first: BIOLOGY | How do cell populations control local densities?

Quorum Sensing

- **a chemical form of communication** in a decentralized system
  e.g. bacteria, insects, …

- autoinducers mediate cell-cell signaling in bacteria
- and **regulate bacteria group behavior**

- bacteria communicate through (species spec.) **autoinducers**
  → can sense density
  → can also sense if mono- or polyspecies community



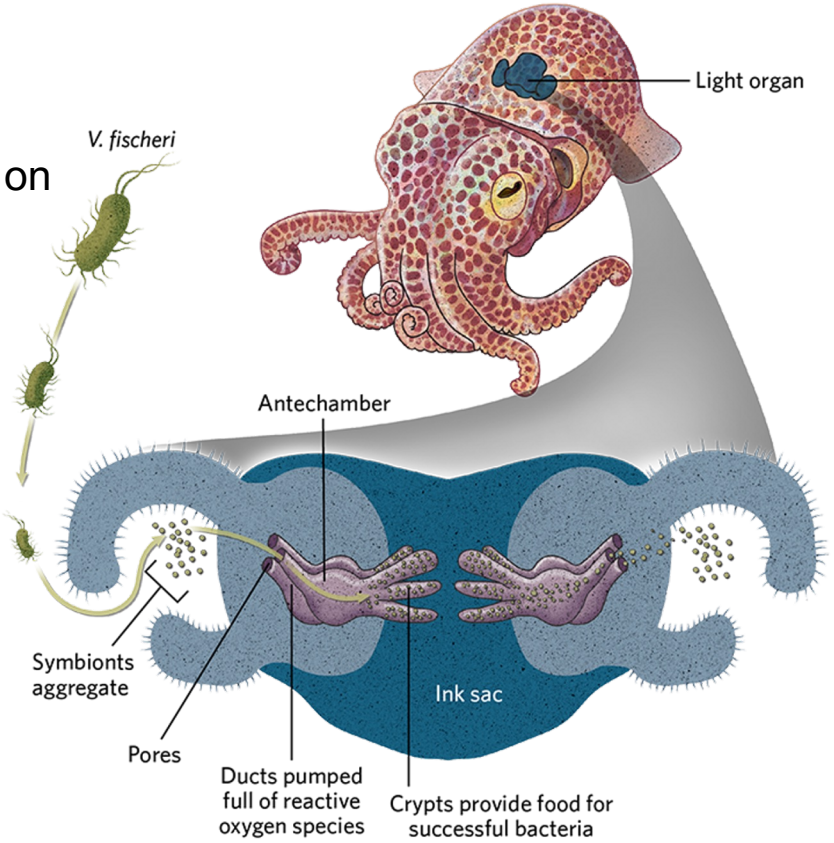
https://scholar.princeton.edu/basslerlab/research
https://openspace.infohio.org/courseware/module/347/student/?task=2

Quorum sensing | Population behavior in diverse contexts

Example - in nature: **Hawaiian bobtail squid**

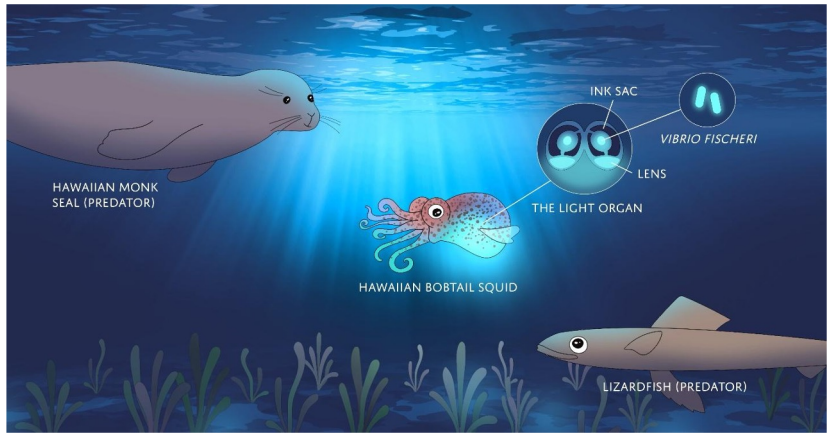
- bacteria in ink sack (light organ) of squid produce light (**bioluminescence**)

→ when high in population density, gene expression for producing light is switched on



A safety mechanism to be invisible to predators:

to “hide” the squid to have no shadow on sea floor

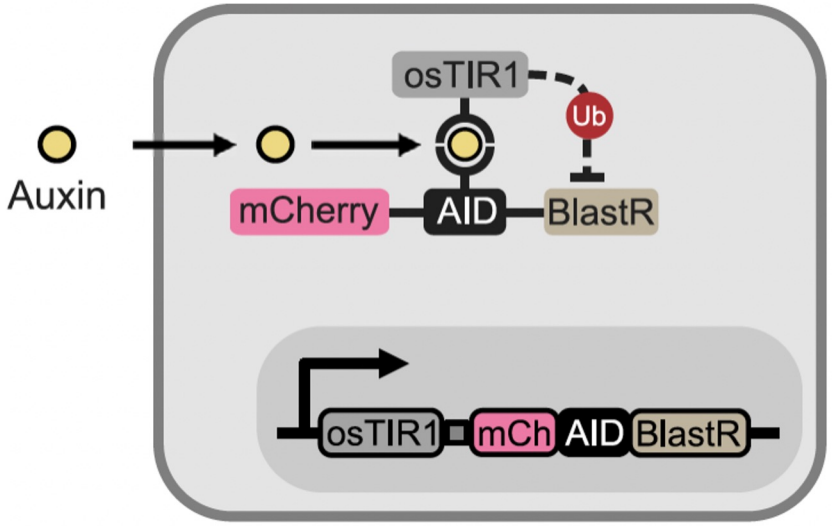


Xavier K., Bacterial interspecies quorum sensing in the mammalian gut microbiota, C R Biol, 2018

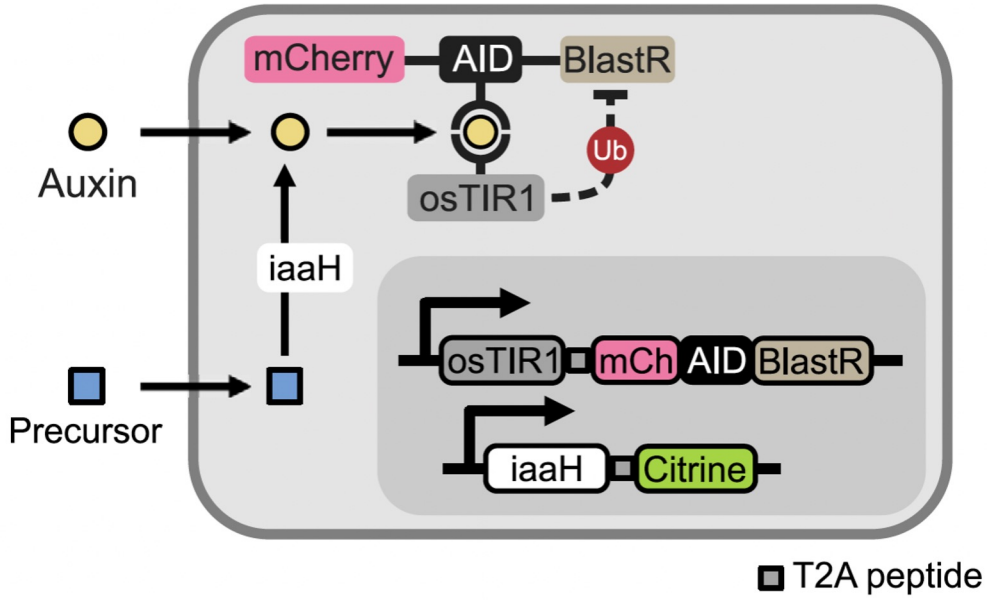
https://www.the-scientist.com/features/symbiotic-organs-extreme-intimacy-with-the-microbial-world-70493

Engineering cell line to sense/respond and produce own signal

Auxin **Receiver** Cells



Auxin Sender-Receiver Cells



Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

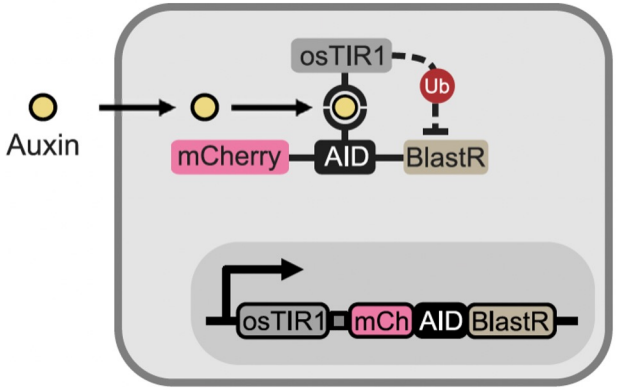
Quorum sensing | Population behavior in diverse contexts

Example - a synthetic concept: **Communication system in mammalian cells**

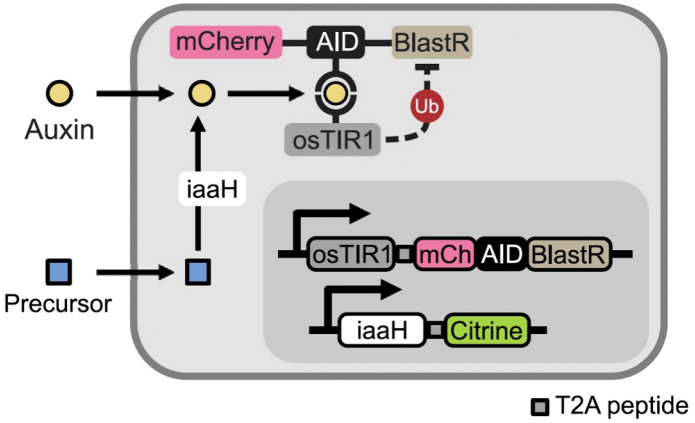
- Defining Characteristics of an ideal model system
  - + avoid undesired interactions (with non-engineered cells) – private communication channel
  - + permit external control and operate in broad variety of cell types

A Signal Molecule

A cell type to receive signal



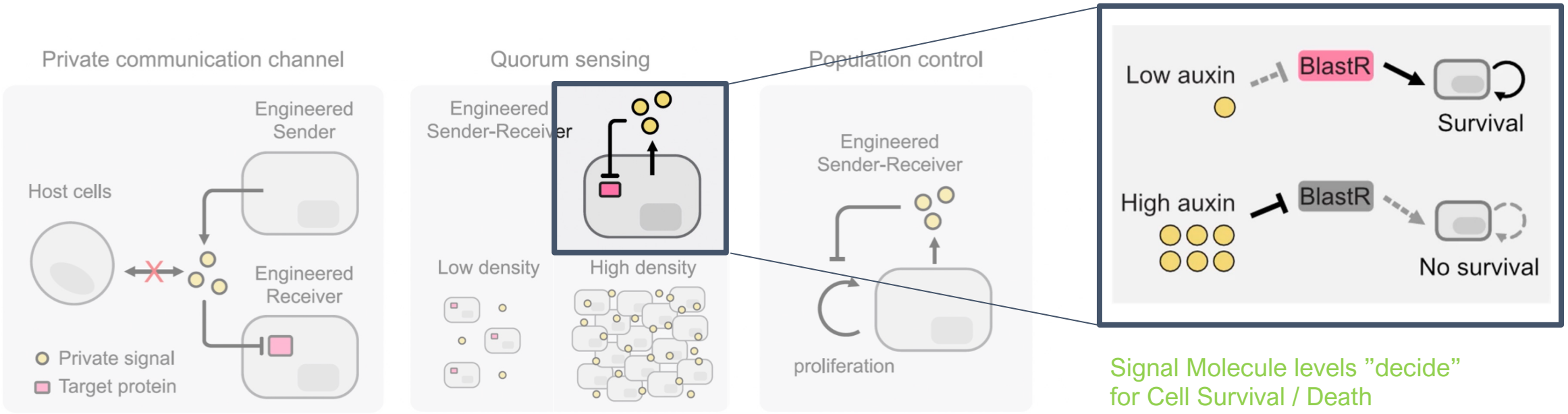
A cell type to produce more signal



Auxin → Blastidin Resistance is inhibited → Cell not surviving in Environment

Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

A Communication Channel in Mammalian Cells



Signal Molecule levels ”decide” for Cell Survival / Death

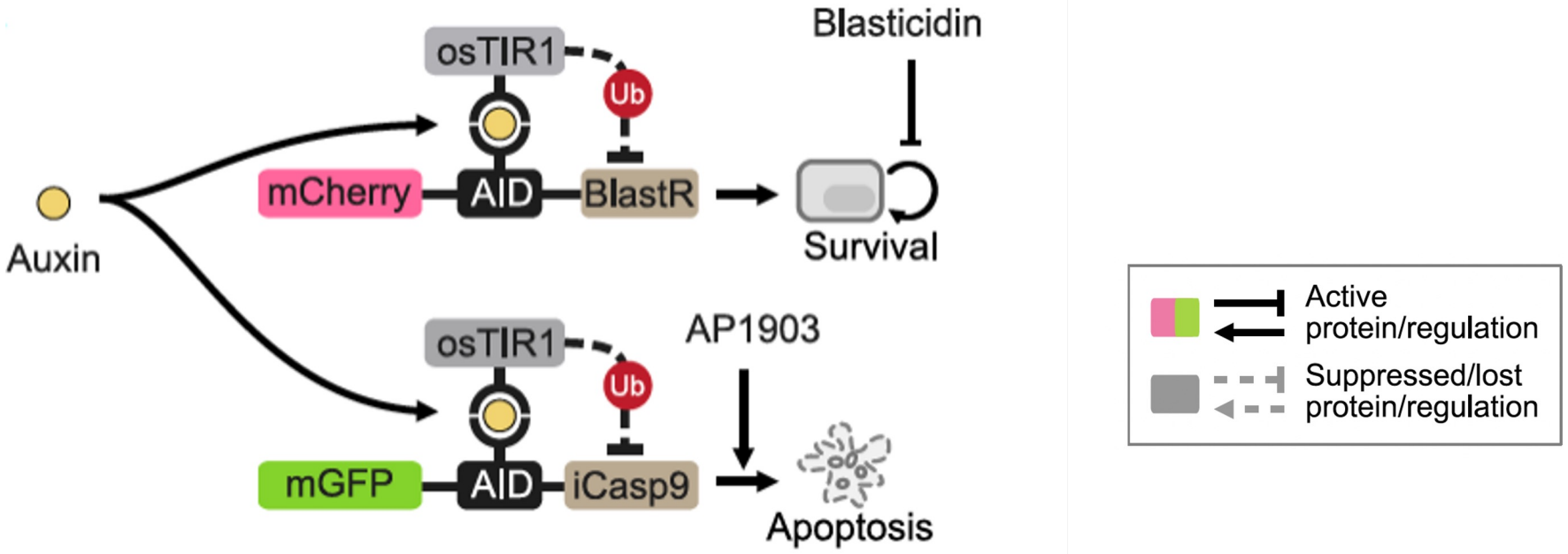
Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

Concept against cheater mutations escaping the control mechanism

The “Paradaux” Circuit: A Concept against cheater mutations

→ signal induces **proliferation <u>and</u> death** of same target cell population

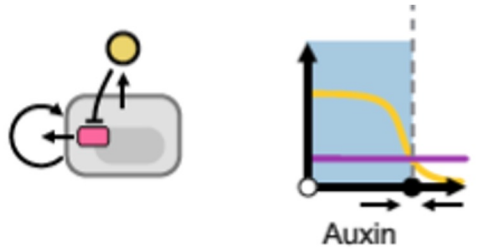
→ with the goal to control cell population



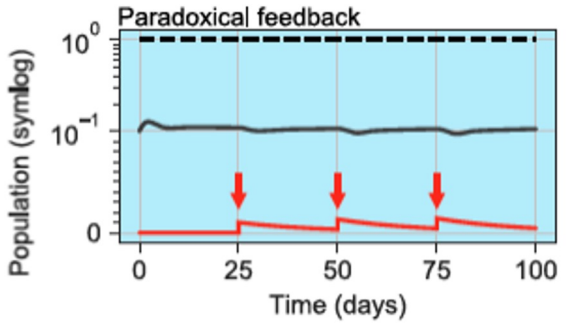
Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

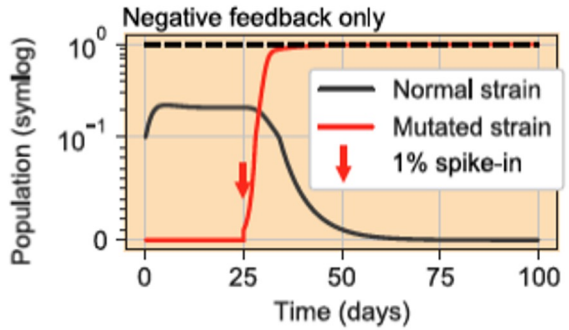
Observing population density - the “paradaux” vs. the negative feedback

Negative Feedback

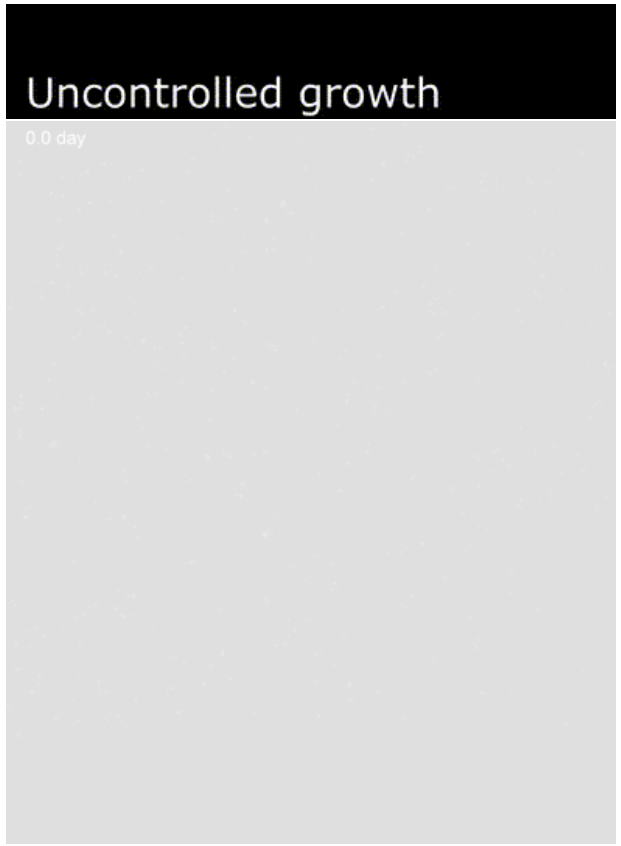


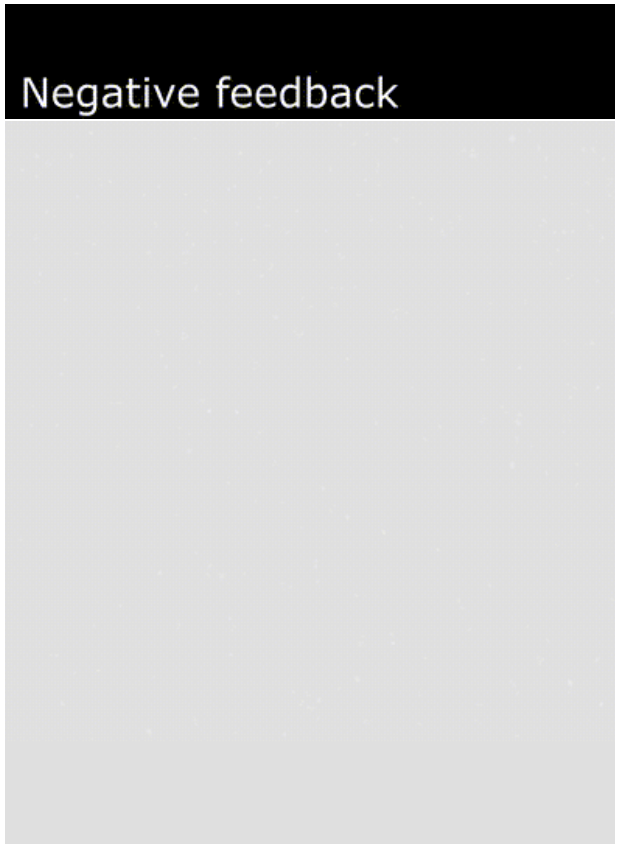
no mutations





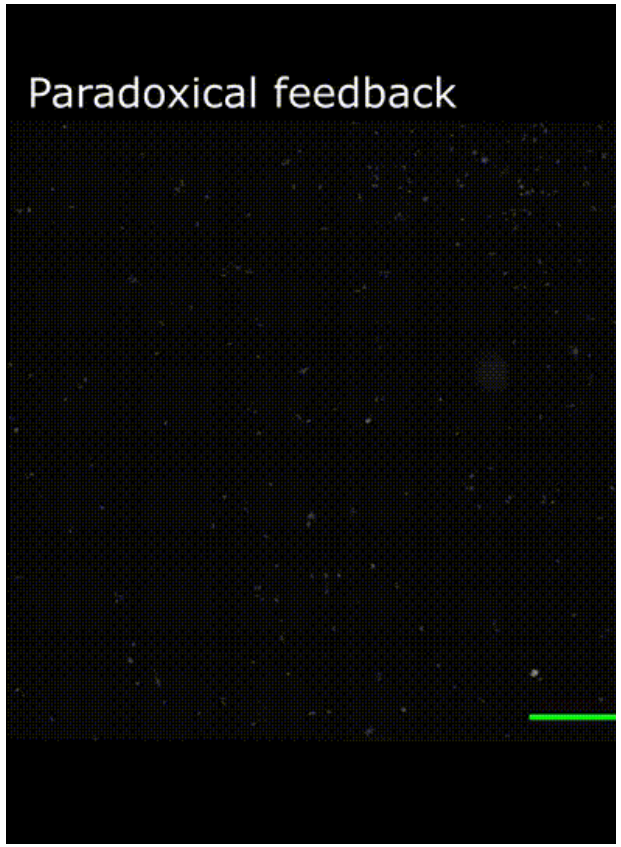
Regulating circuit via levels of blasticidin and AP1903





Blasticidin only

after ~1-2 oscillatory cycles
uncontrolled growth after 20-30 day



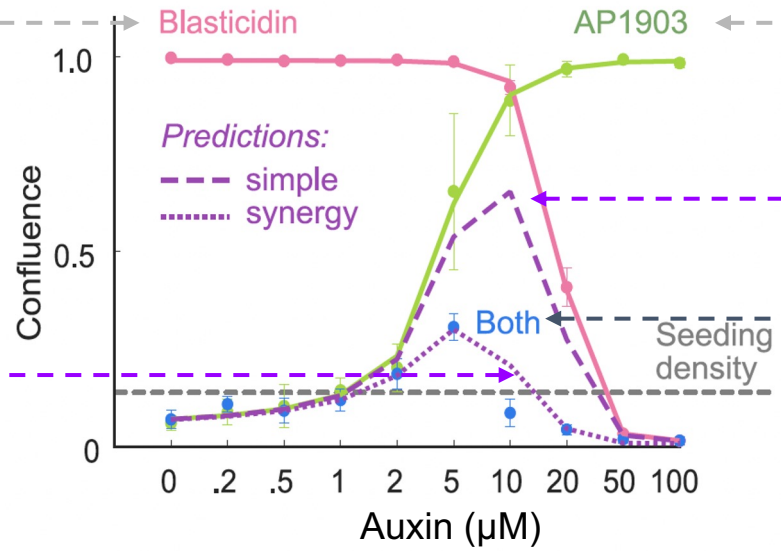
Blasticidin + AP1903

oscillatory cycles
remain after 32 days

Which parameters govern the paradoxical circuit (“Paradaux”)

Individual circuits

presence of blasticidin
→ decreasing cell population



presence of AP1903
→ increasing cell population

overestimated actual growth rates

Paradoxical circuit

presence of both
→ biphasic survival curve

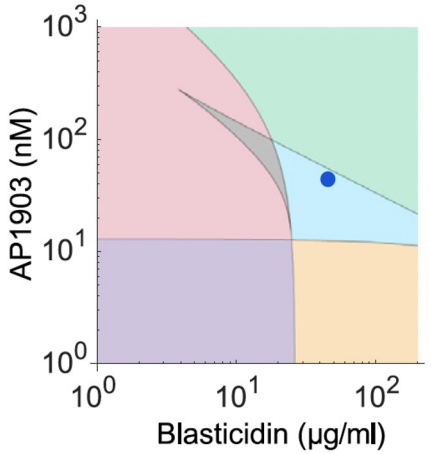
adding synergistic correction
(due to combined effect of both circuit paths)

Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

Identifying 5 behavioral patterns based on circuit driving molecules

Cell proliferation only
beyond min. A concentration

Uncontrolled growth
in low range of B, AP



Negative net growth
high range of B, AP

Paradoxical Circuit
population regulation

Negative Feedback
leading to population decay

Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

How to start | What do we want to understand?

+ *How **AP1903 and Blasticidin govern behavior patterns** ?*

+ *Which **other factors** contribute to that ?*

+ *Can we reach **behavior control** (i.e. **oscillating effect** of cell density) ?*

DISCLAIMER: We can not cover the full complexity of nature – but we can partially learn about a system's behavior through approximations

What do we know / What can we approximate

1) **extracellular auxin concentration** (shared by all cells) → approximating *A over time*

$$\frac{dA}{dt} = \lambda_A \cdot N - \delta_A \cdot A$$

Auxin concentration shared by all cells
assuming that A is produced by a **constant reproduction** and eliminated by **dilution** due to media changes

2) **cell population size** → approximating *N over time*

$$\frac{dN}{dt} = R_g(B, I, A) \cdot N \cdot (1 - N^{\nu})$$

Describing **cell population size** with
a cellular growth Rate $\boldsymbol{R_g}$
(combining auxin-dependent effects on blasticidin, iCasp9)

N .. cell population size
B .. Blasticidin
A .. Auxin
I .. iCasp9
λ .. production rates
δ .. elimination rates
v .. logistic growth coefficient

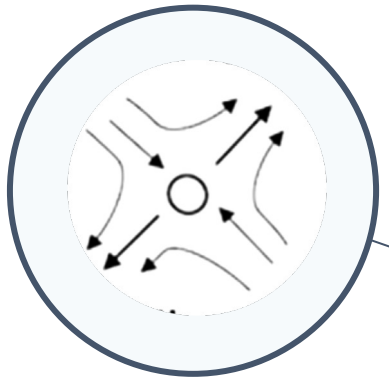
Approximating Phase Spaces to understand system dynamics

- Phase space → each parameter involved = 1 axes/dimension
- fixed points = where derivatives are 0

Calculate Fixed Points:

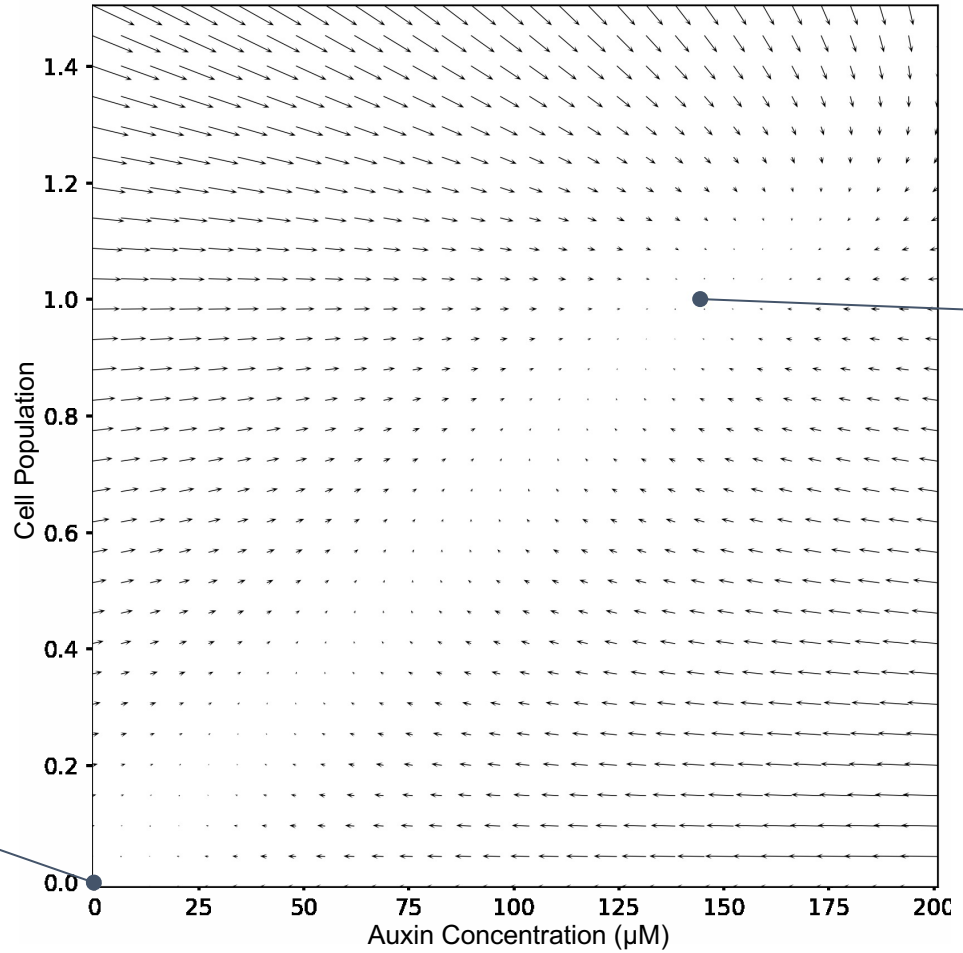
$$0 = R_g \cdot N \cdot (1 - N^{\upsilon}) \longrightarrow N = 0 \quad \longrightarrow N = 1$$

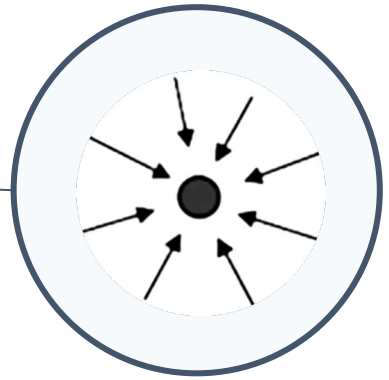
$$0 = \lambda_a \cdot N - \delta_a \cdot A \longrightarrow = \frac{4.18}{0.0289} \cdot 0 = 0 \quad \longrightarrow = \frac{4.18}{0.0289} \cdot 1 = 144$$



“saddle point”

$P1(0, 0)$





stable fixed point

$P2(144, 1)$

The cellular growth rate R_g | ”behind the scenes”

$$\frac{dN}{dt} = R_g(B, I, A) \cdot N \cdot (1 - N^{\nu})$$

$$R_g(B, I, A) = (\alpha + \beta) \cdot G(B, A) - \beta - \beta_C \cdot D(I, A)$$

$$G(B, A) = \frac{(\kappa_A A + 1)^{n_1} + \left(\frac{P_R}{\delta}\right)^{n_1}}{(\kappa_A A + 1)^{n_1} (\kappa_B B + 1) + \left(\frac{P_R}{\delta}\right)^{n_1}}$$

$$D(I, A) = \frac{\kappa_I I \cdot \left(\frac{P_C}{\delta}\right)^{n_2}}{\kappa_I I \cdot \left(\frac{P_C}{\delta}\right)^{n_2} + (\kappa_A A + 1)^{n_2}}$$

Note: We do assume quite a few things... to make it simpler for modeling
such as that blasticidin and iCasp9 involving processes are at equilibrium

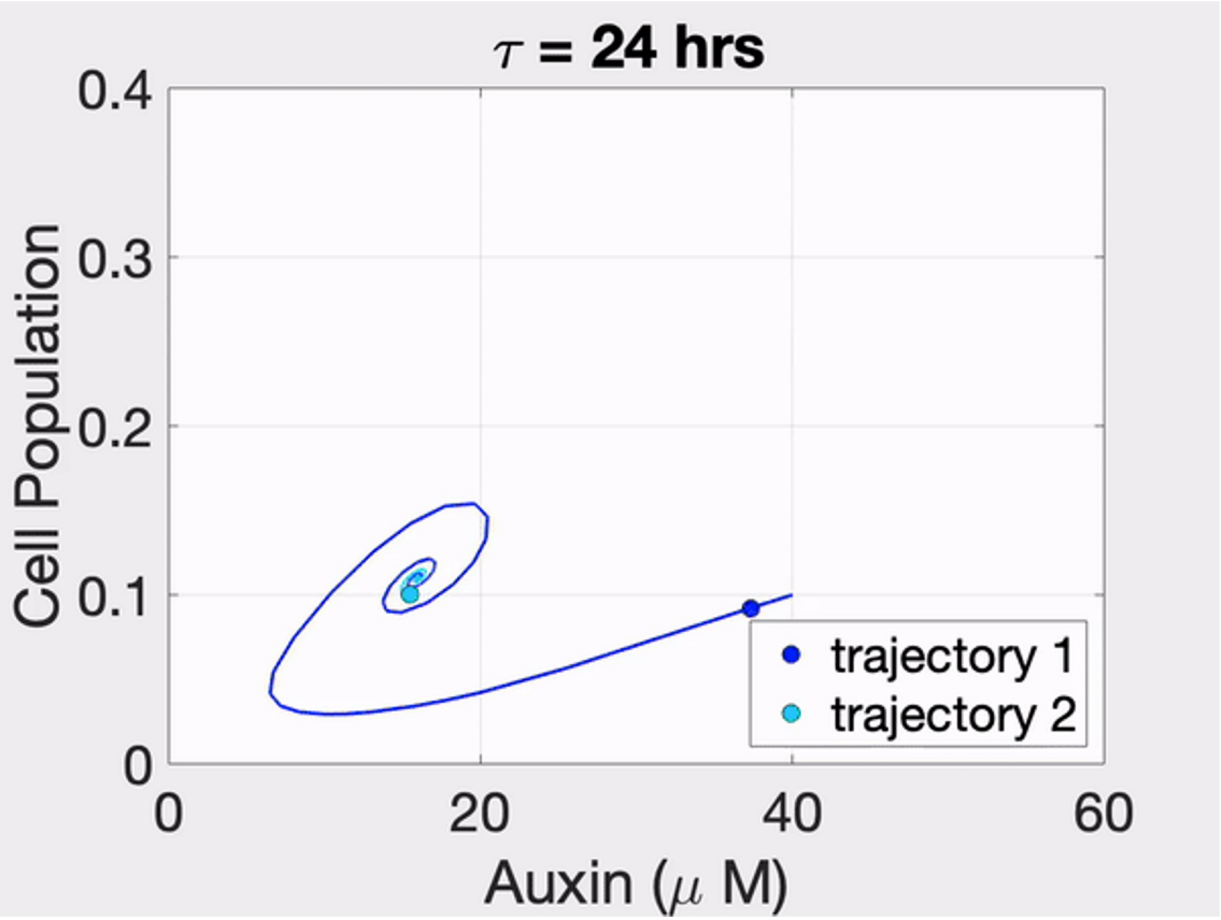
alpha = natural cell proliferation rate
beta = max net growth (B)
$beta_C$ = max death rate (I)

What do we learn from the model ?

- we can reach an **oscillating effect**
- and even run into a **limit cycle**

→ this means we have reached

a state of controlled system's behavior



Ma, Y. et al., Synthetic mammalian signaling circuits for robust cell population control, Cell, 2022

Two approaches for One Goal | Experiments + Simulations

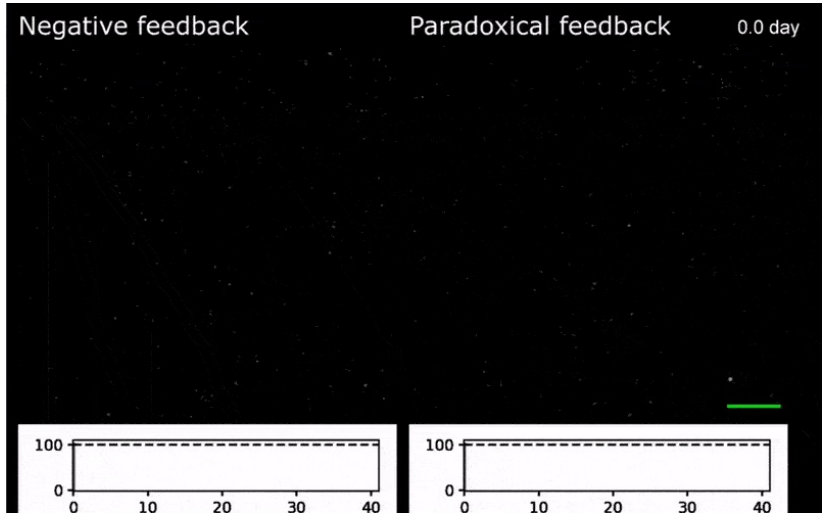
Observations from Experiments:

- negative vs. paradoxical circuit
- to create oscillatory behavior *in vitro*

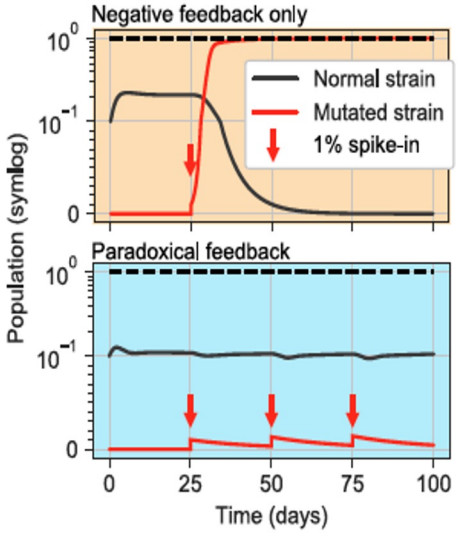
Simulations – an *in silico* Model:

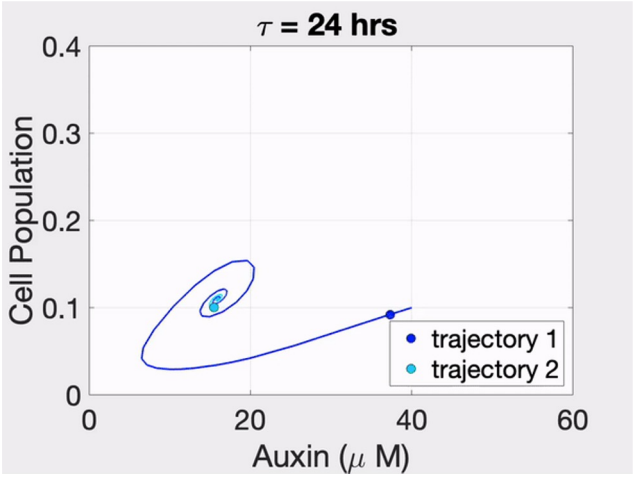
- to learn more about factors governing the behavior
- to recreate oscillation = control of system's behavior (over time period)

Private Cell-Communication Channel + Paradoxical circuit for population density regulation



A mathematical (simplified) model to estimate parameter interplay and understanding system's behavior





3 – How modeling light behavior can benefits biology?

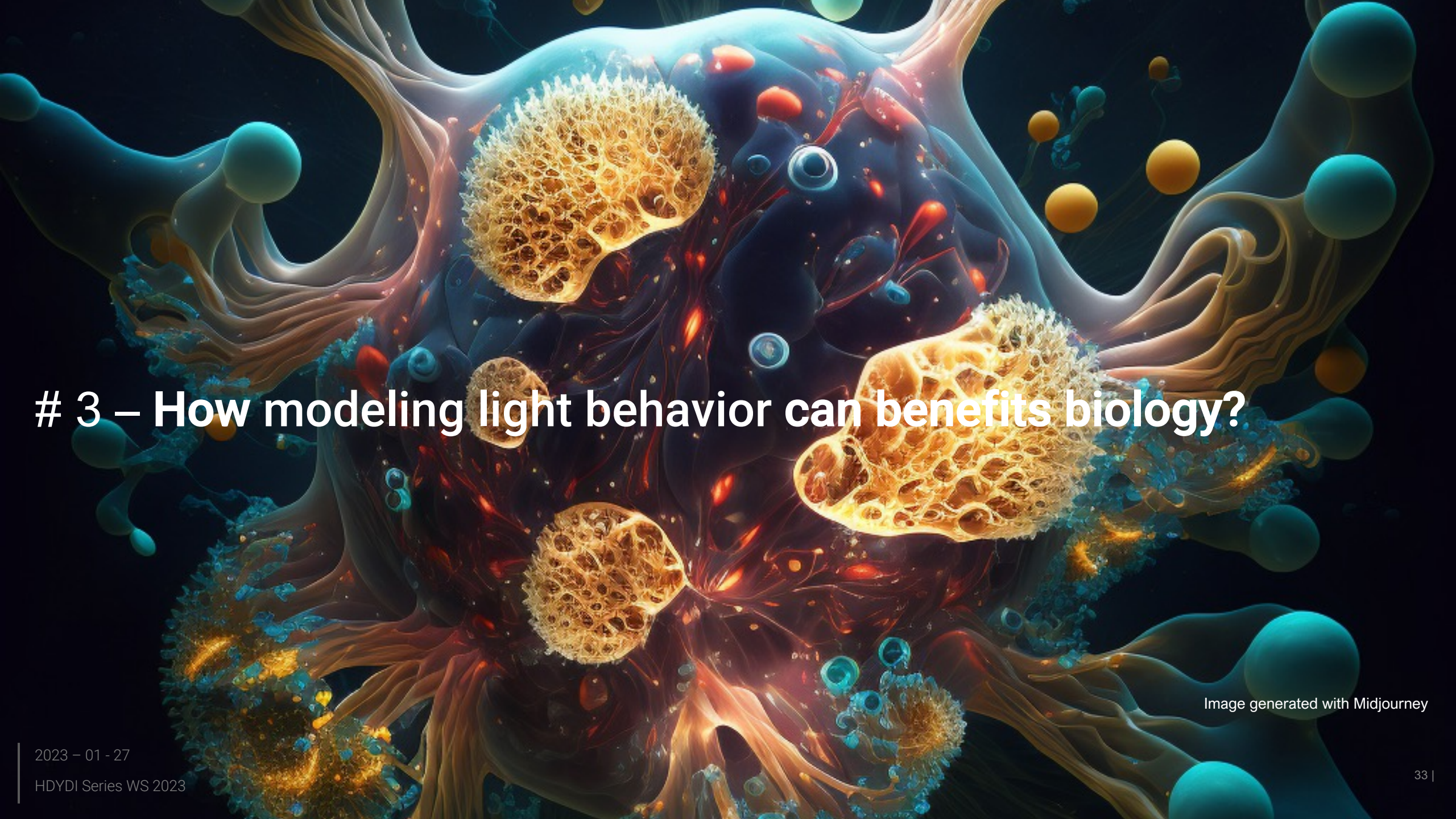
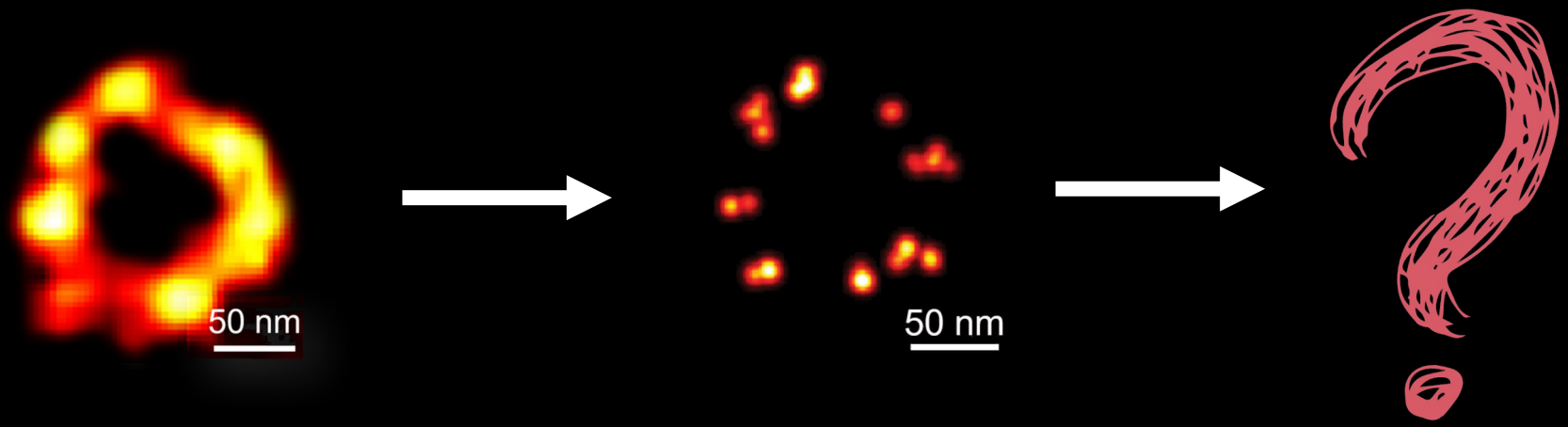
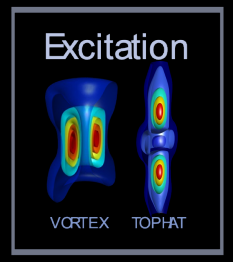
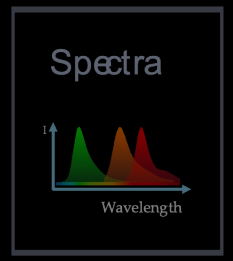
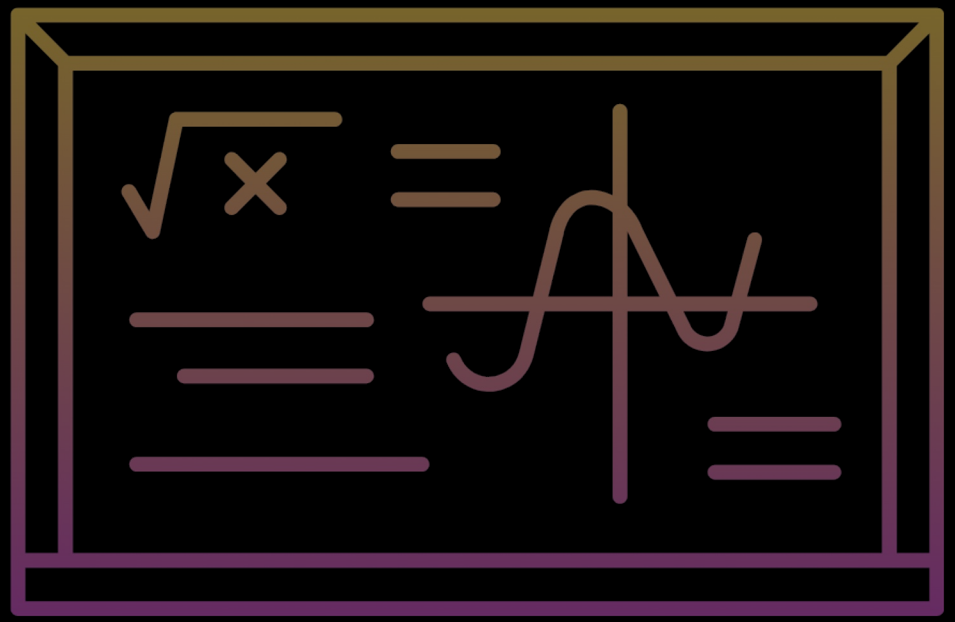


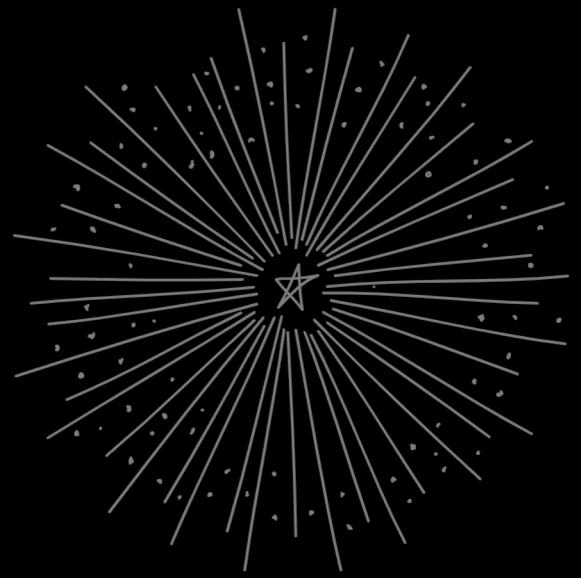
Image generated with Midjourney


50 nm
50 nm

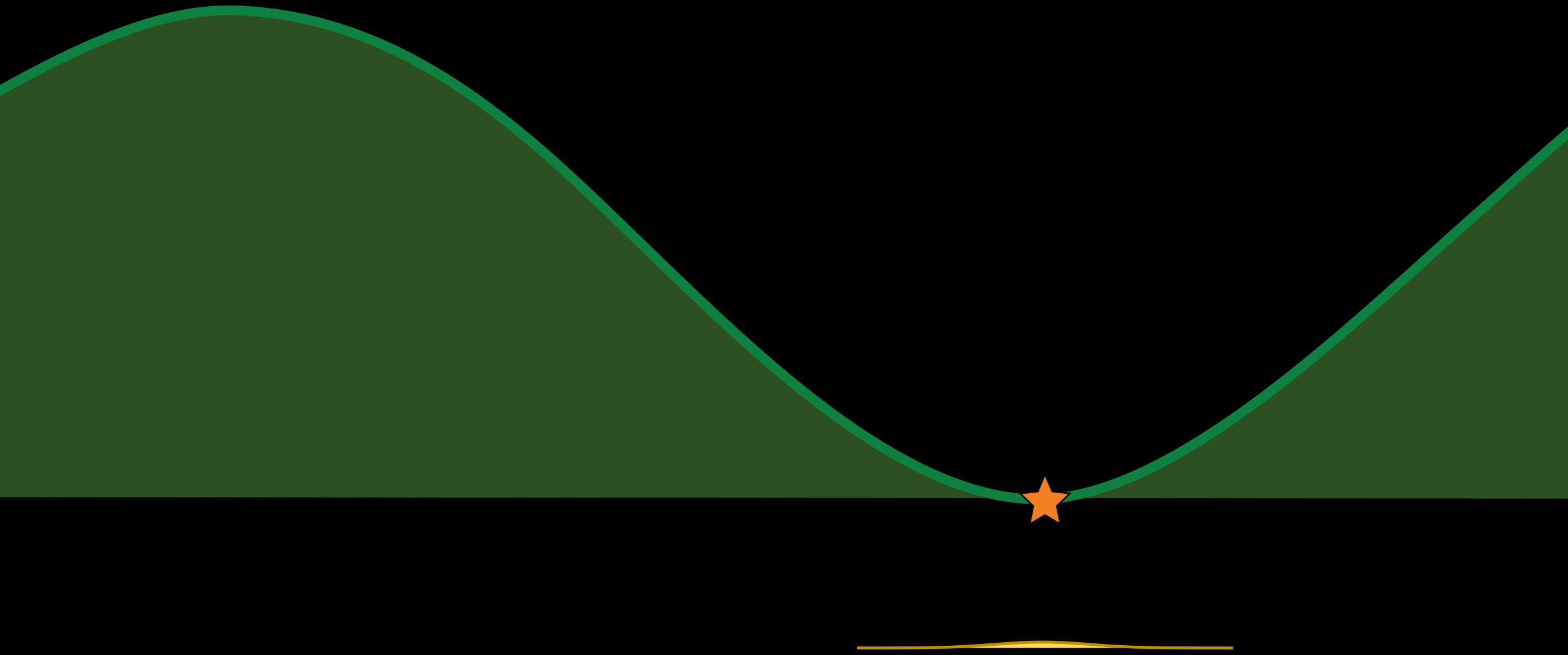


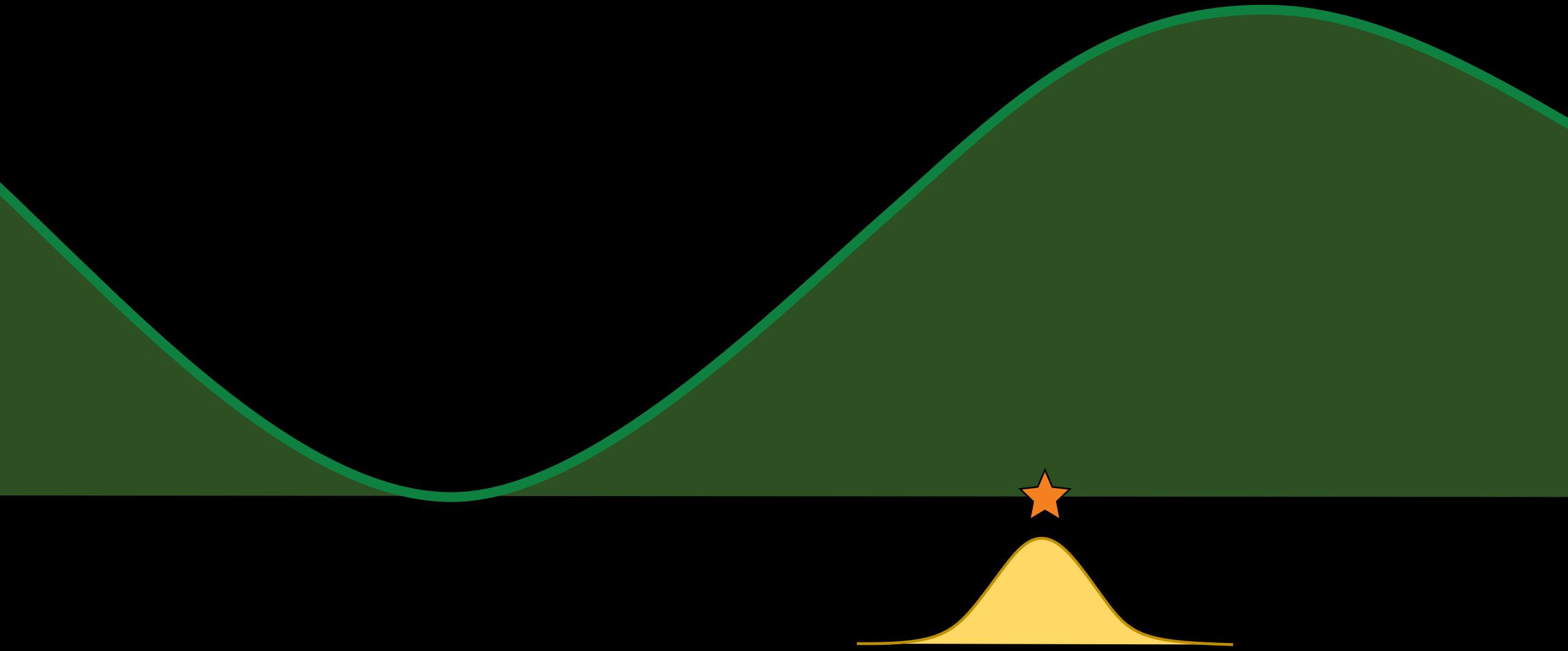


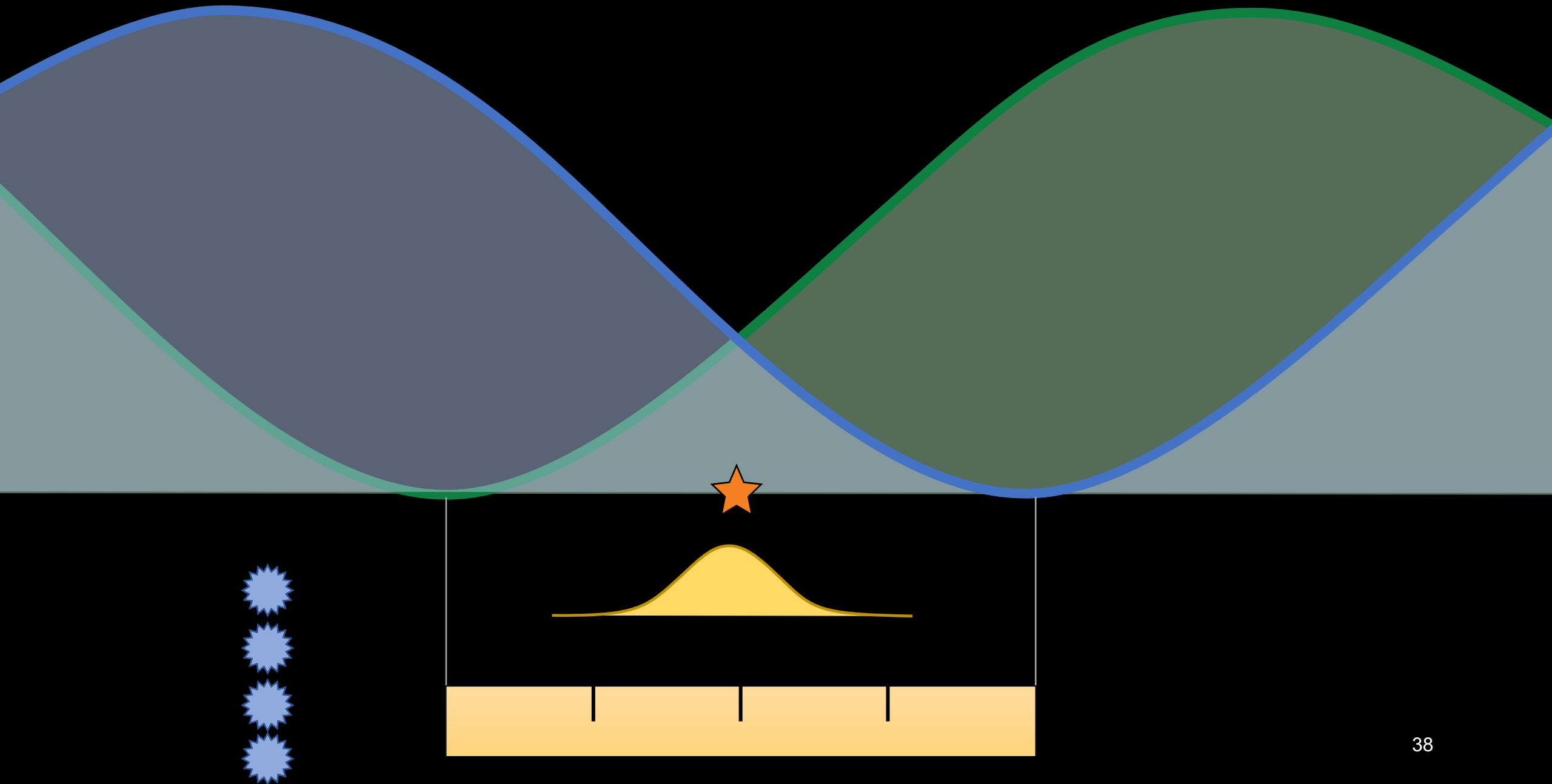


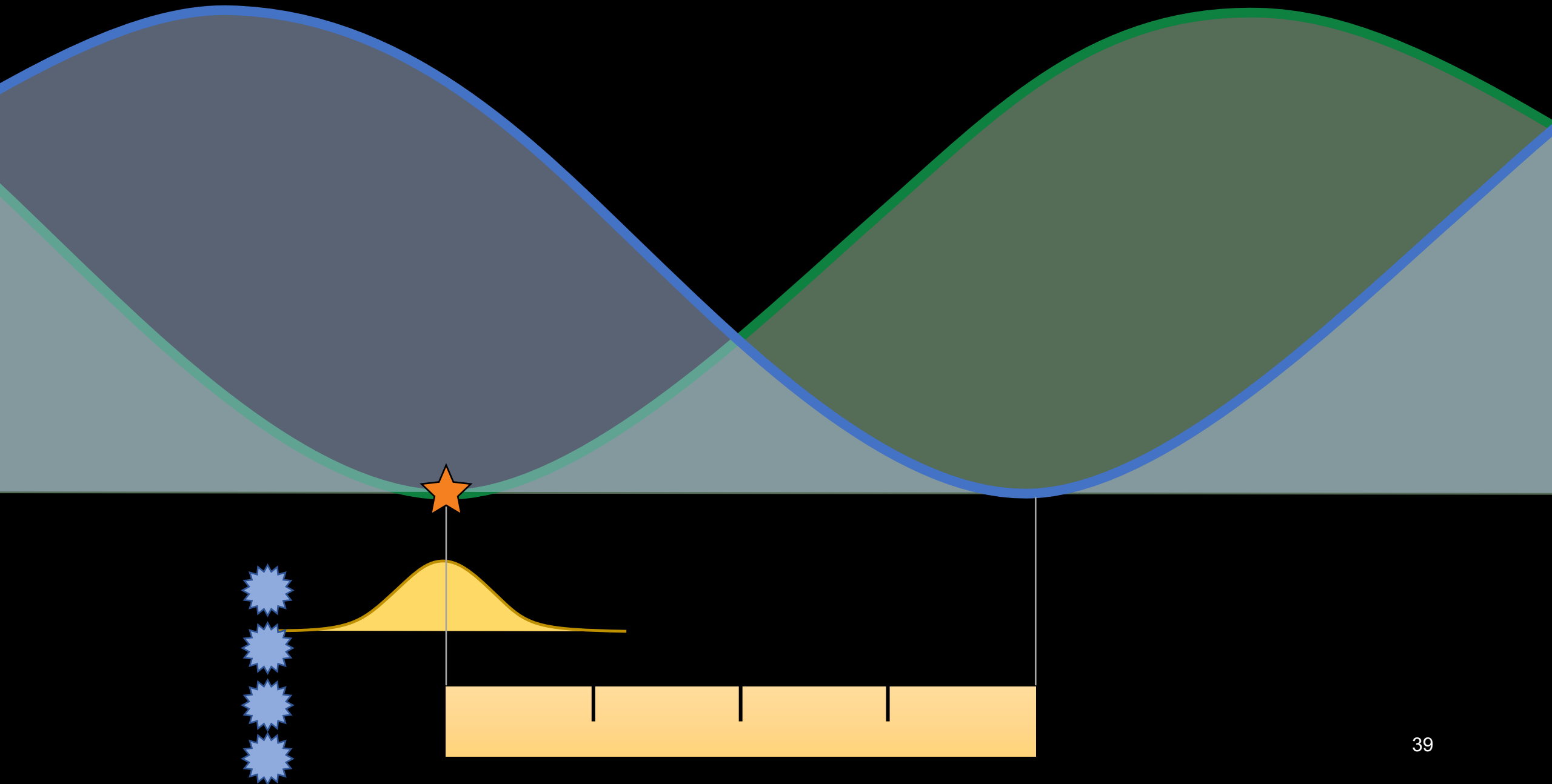


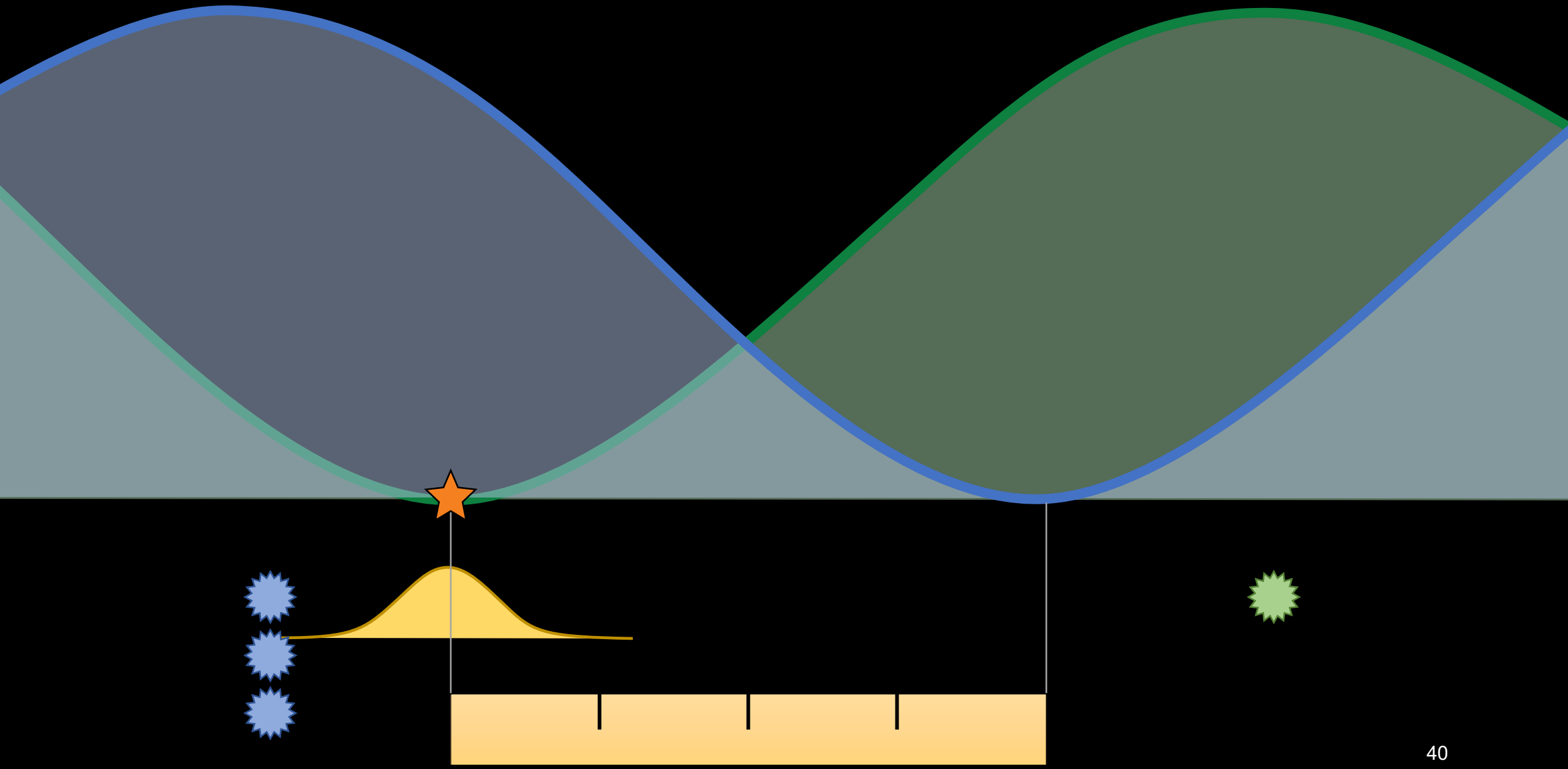
$$P_{ijt} = \frac{SBR}{1+SBR} \cdot \frac{\lambda_{S_{ij}} q_t}{\Sigma_{ijt} \lambda_{S_{ij}} q_t} + \frac{1}{1+SBR} \cdot \frac{\lambda_{B_{ij}} q_t^b}{\Sigma_{ijt} \lambda_{B_{ij}} q_t^b} \text{a}$$

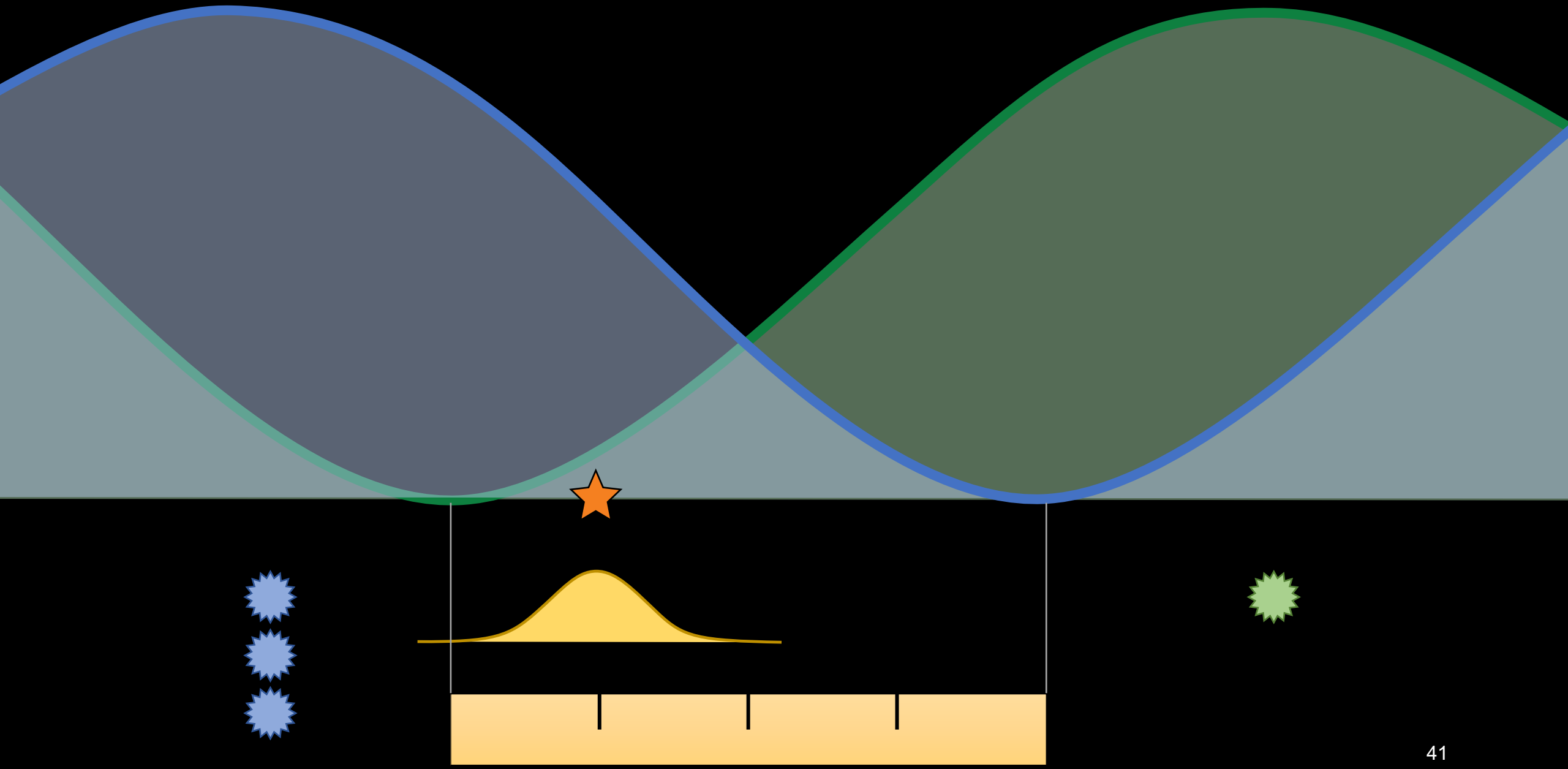


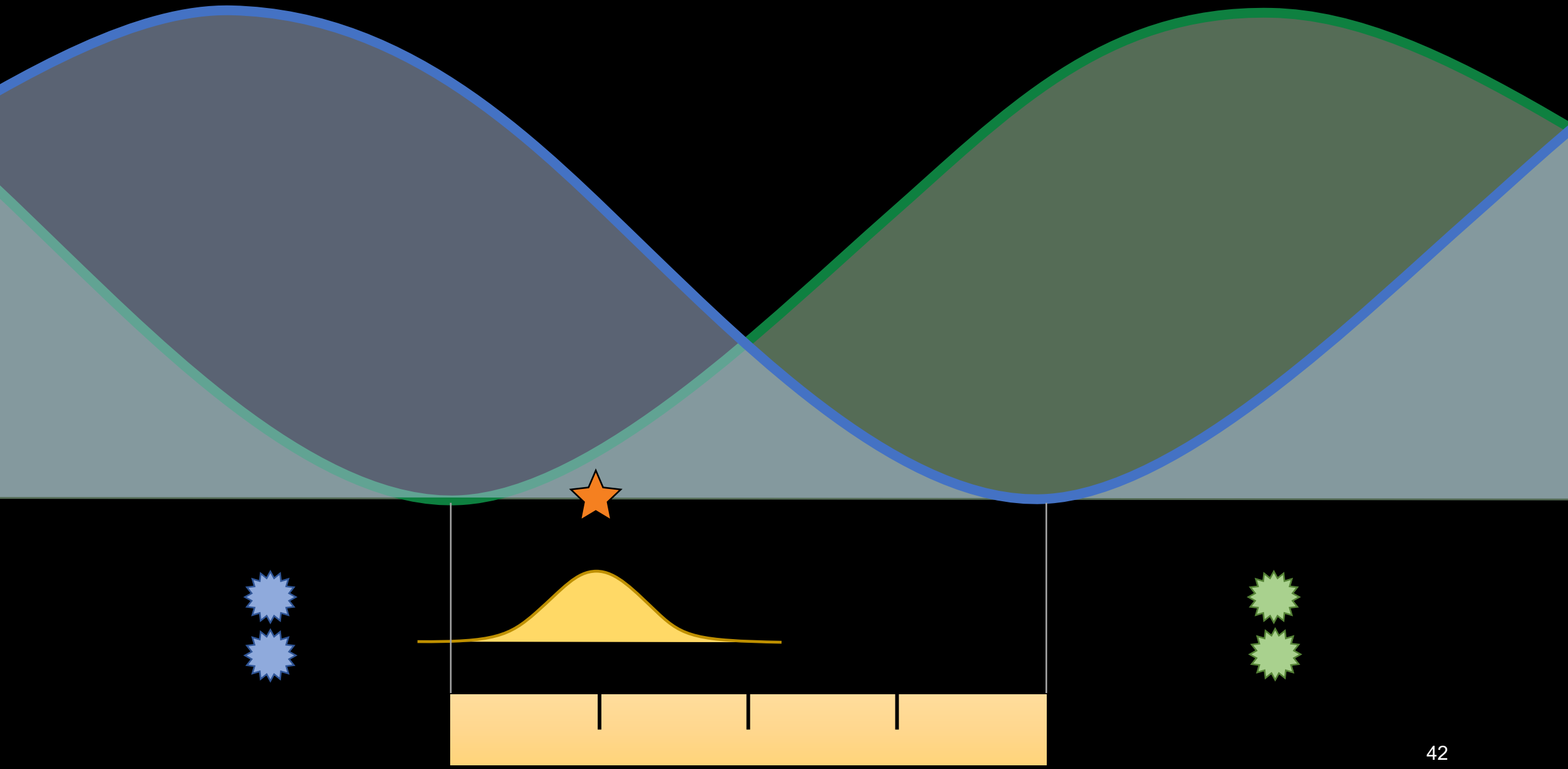


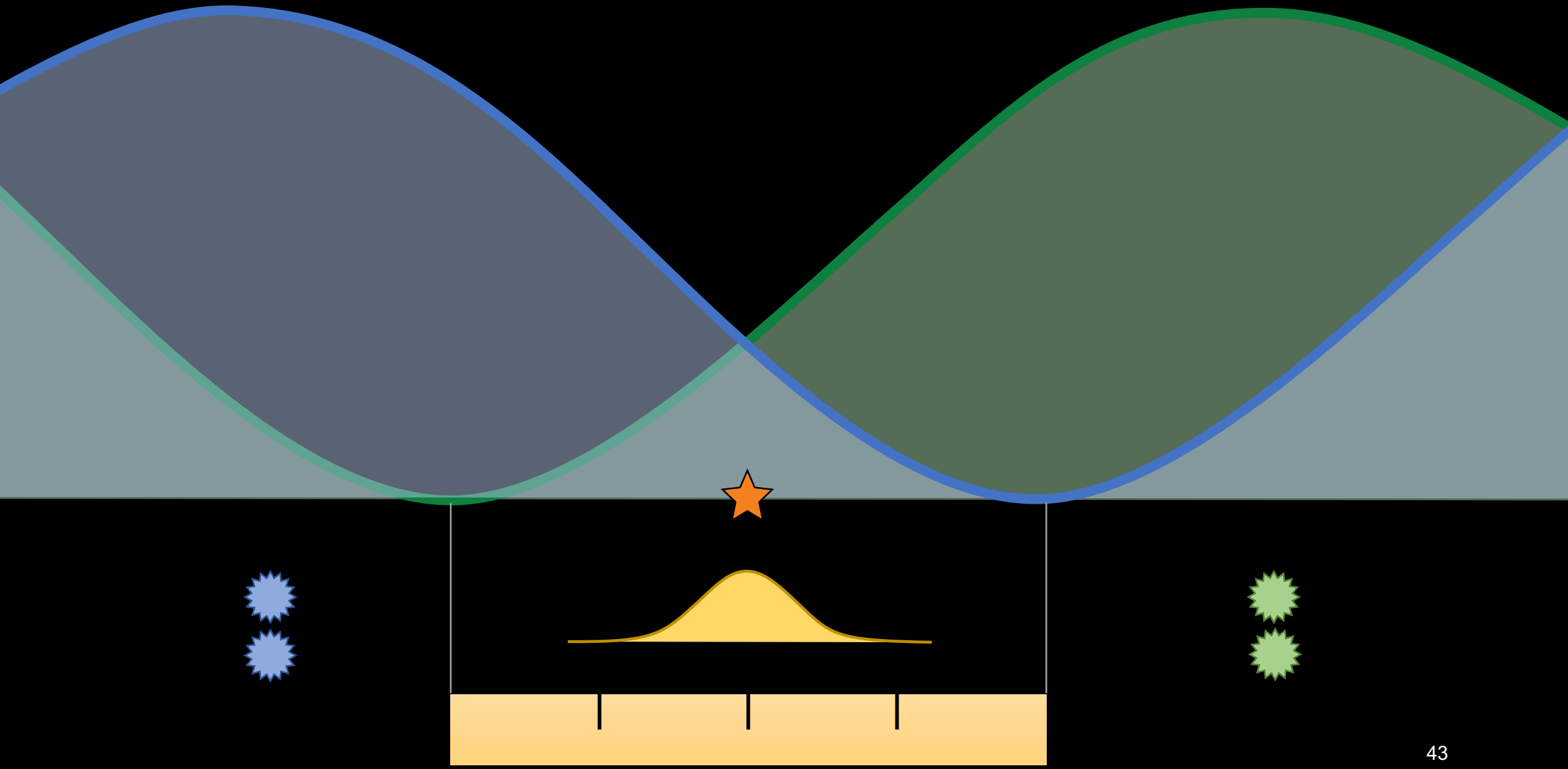


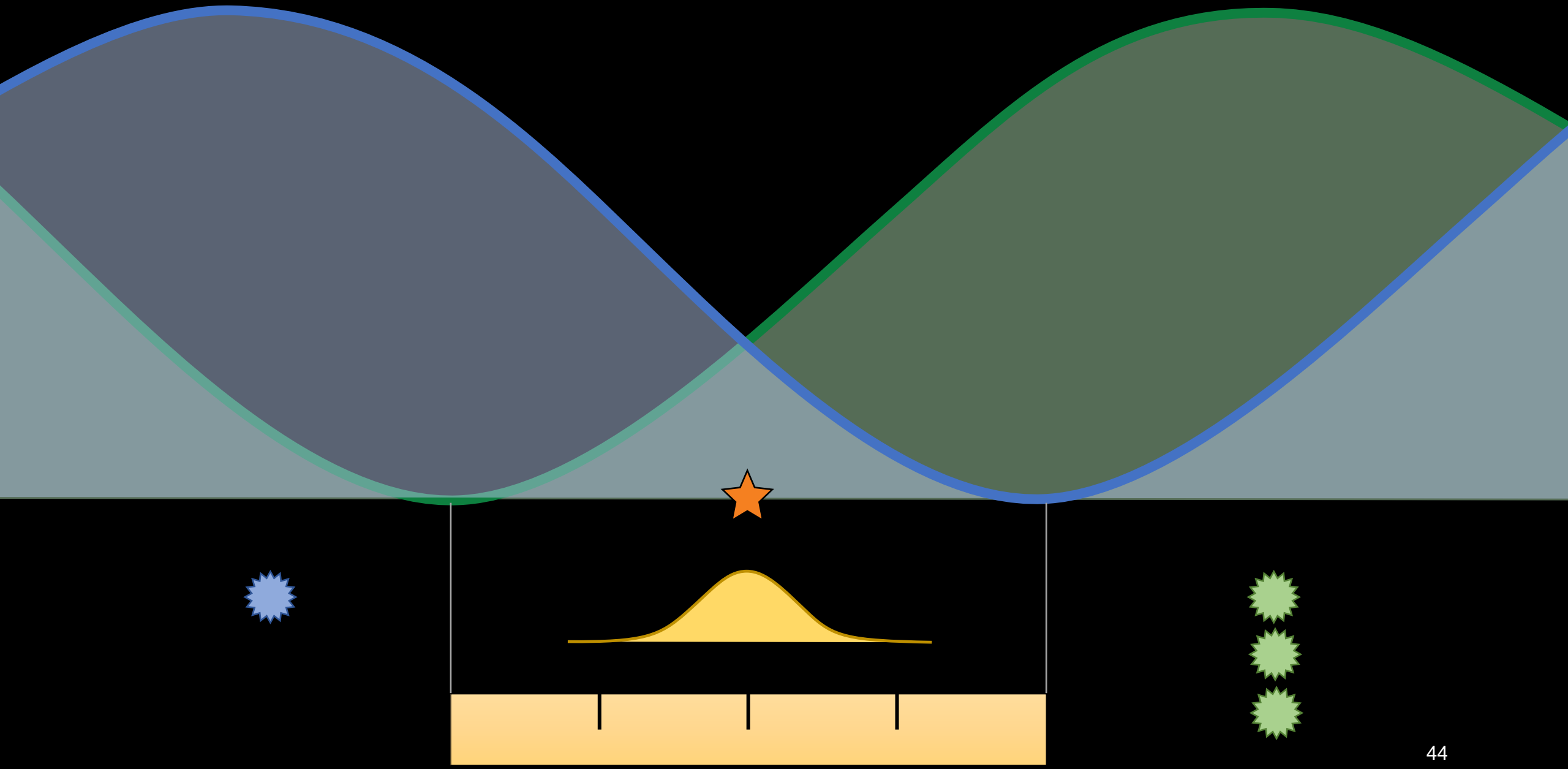


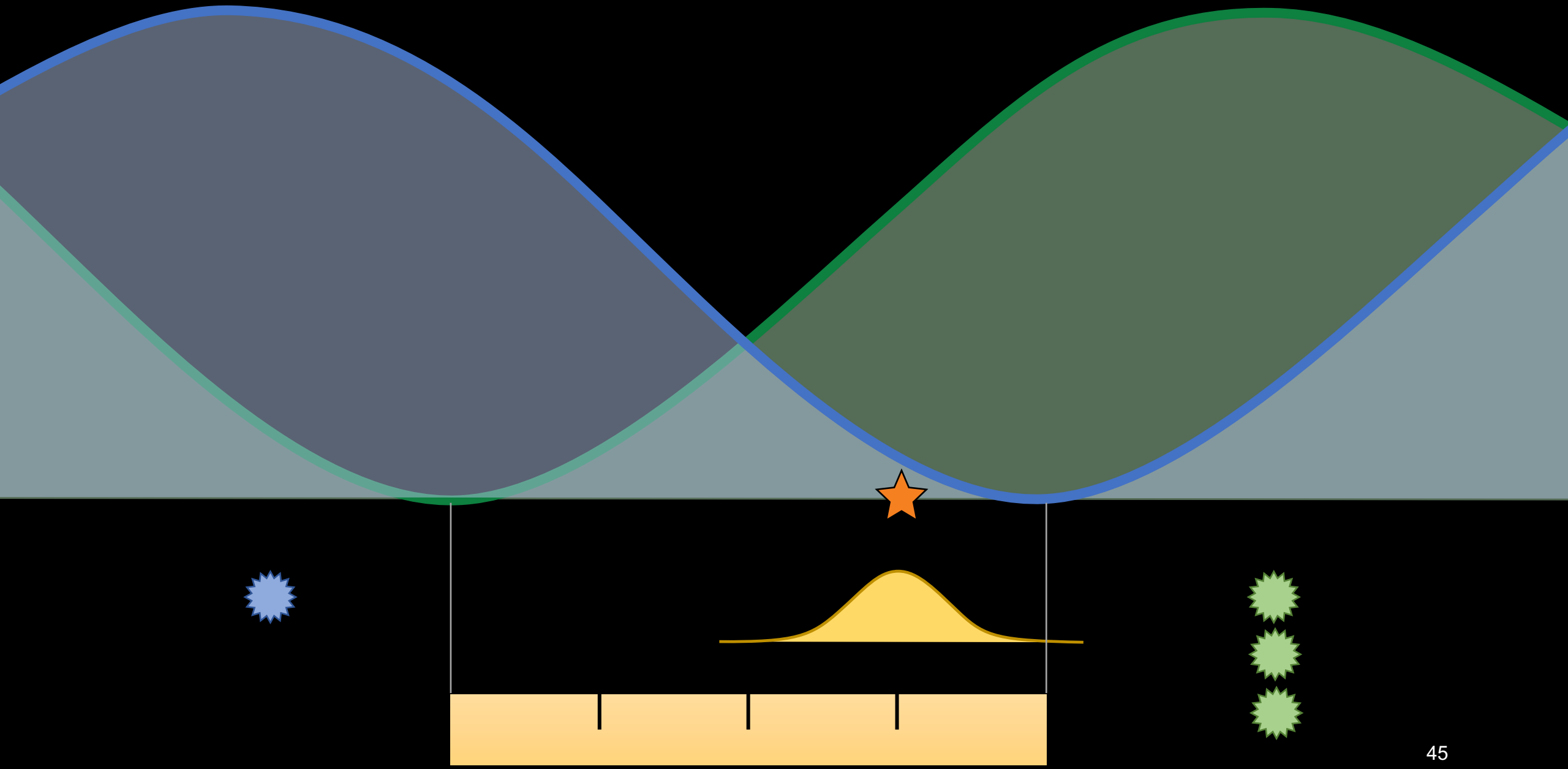


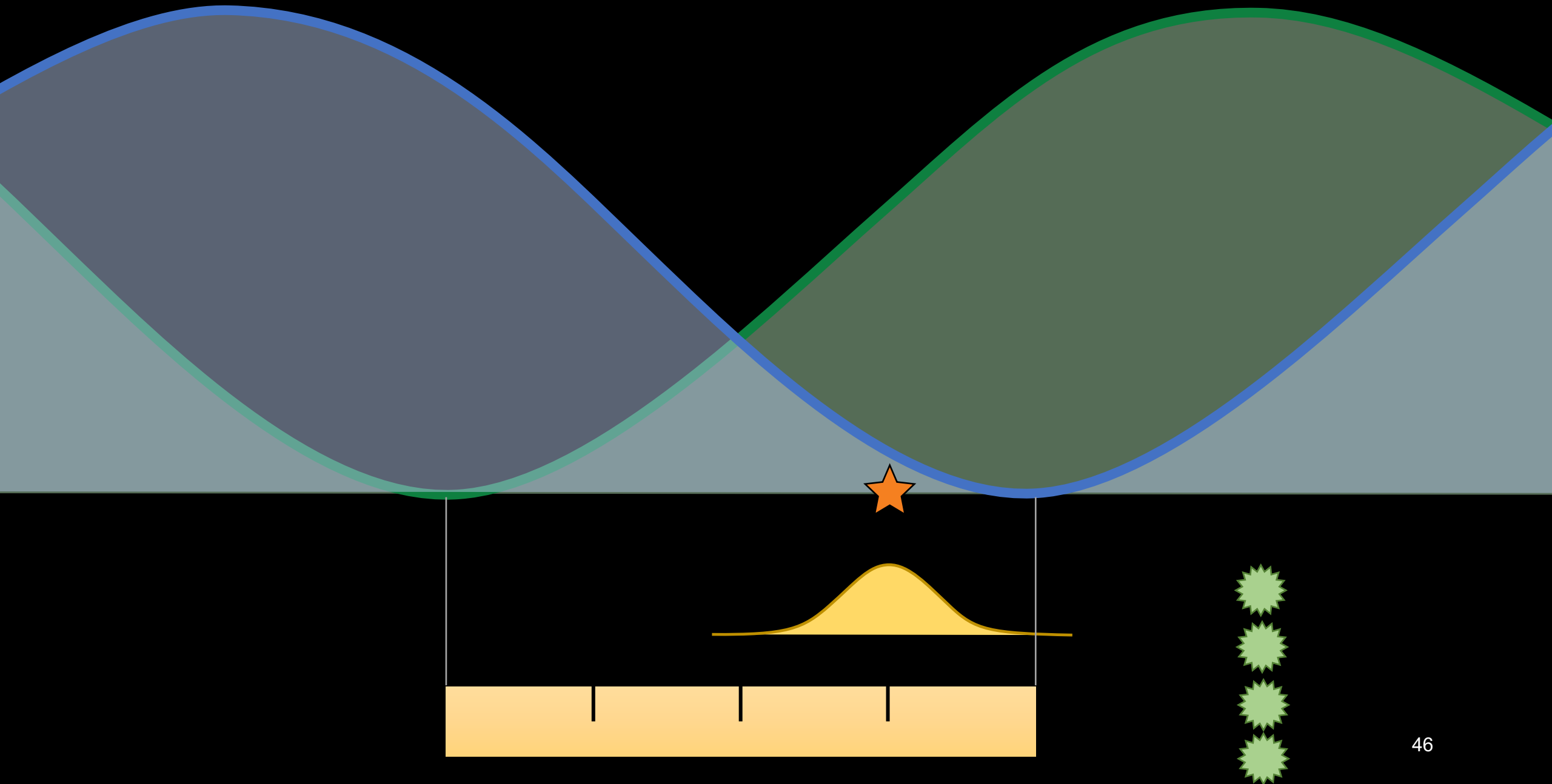


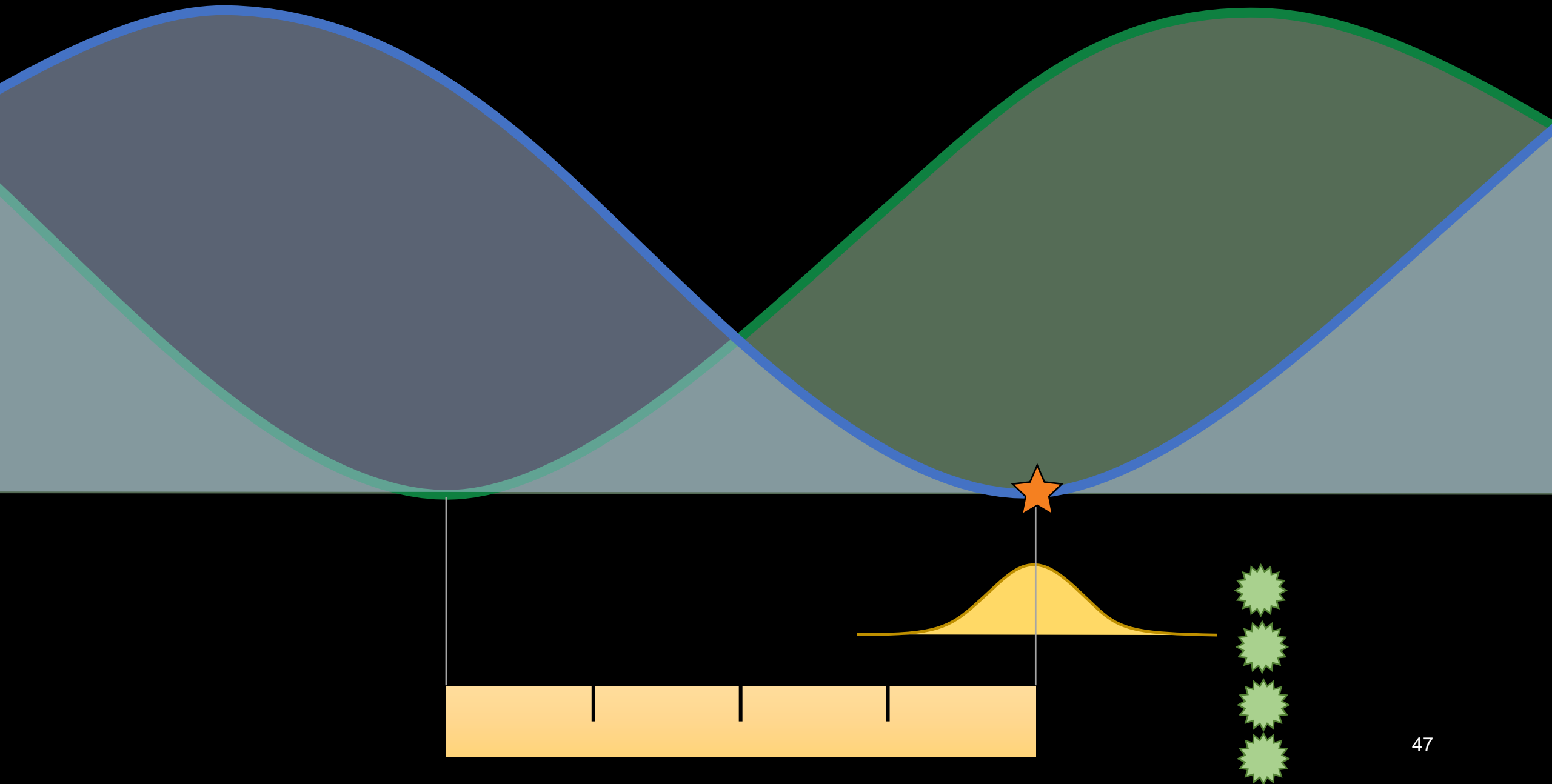


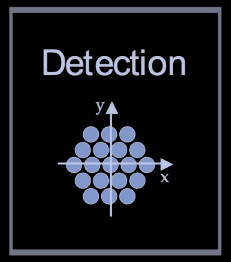












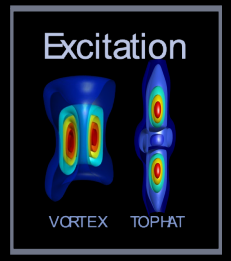
APD1

APD2

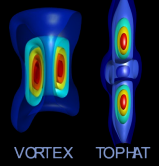
APD3

$$p_{ij}(\vec{r}) = \frac{SBR(\vec{r})}{1+SBR(\vec{r})} * p_{ij}^{(0)}(\vec{r}) + \frac{1}{1+SBR(\vec{r})} * \frac{\lambda_{Bij}}{\Sigma_{ij}\lambda_{Bij}}$$

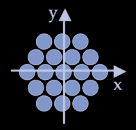
	V0	V1	V2	V3
APD1	0.05	0.1	0.15	0.2
APD2	0.01	0.15	0.05	0.04
APD3	0.01	0.05	0.04	0.15



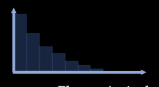
Excitation



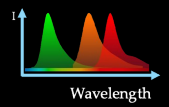
Detection

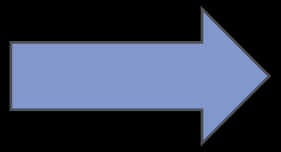


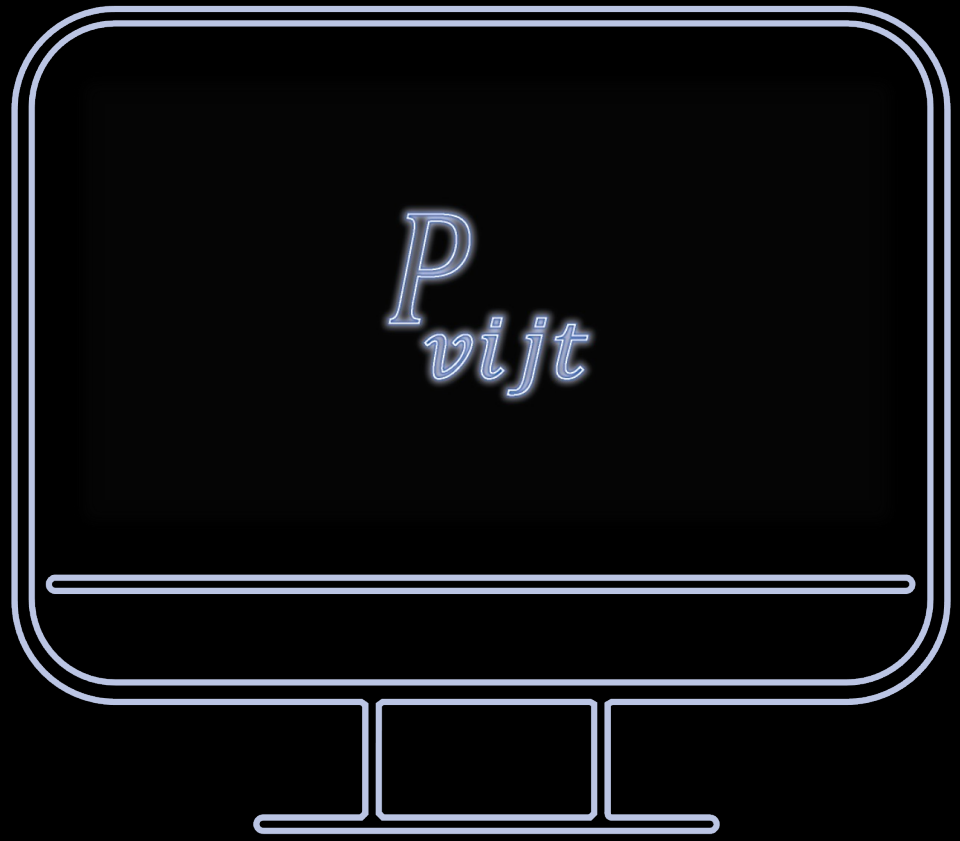
Lifetime

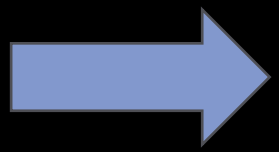


Spectra







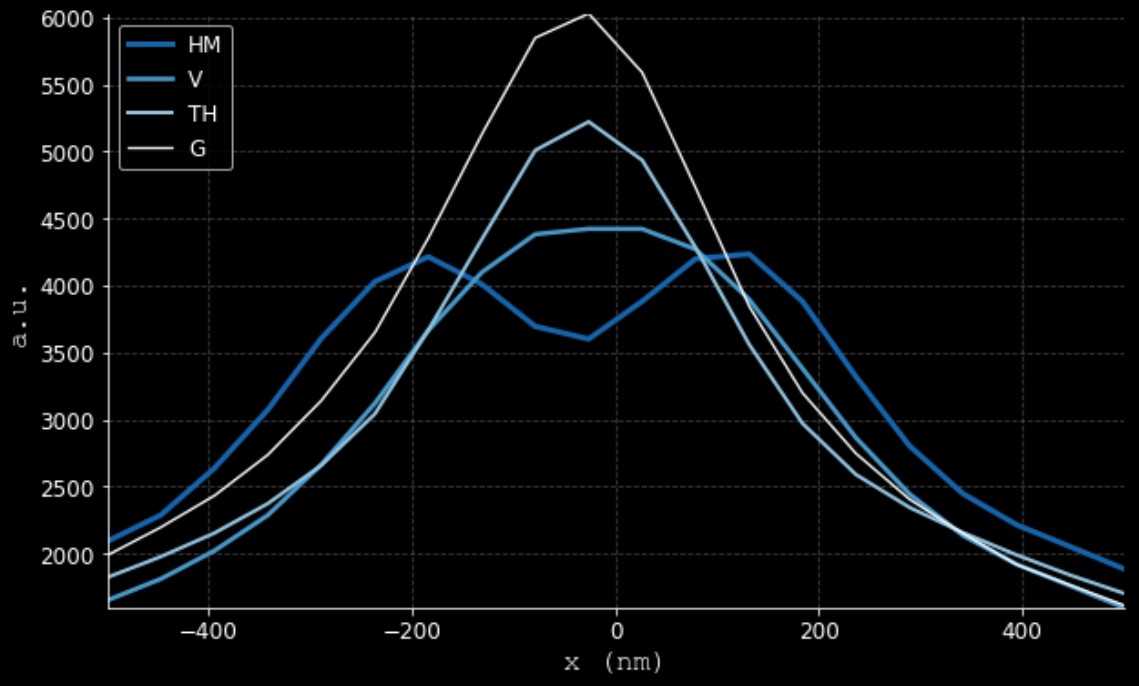


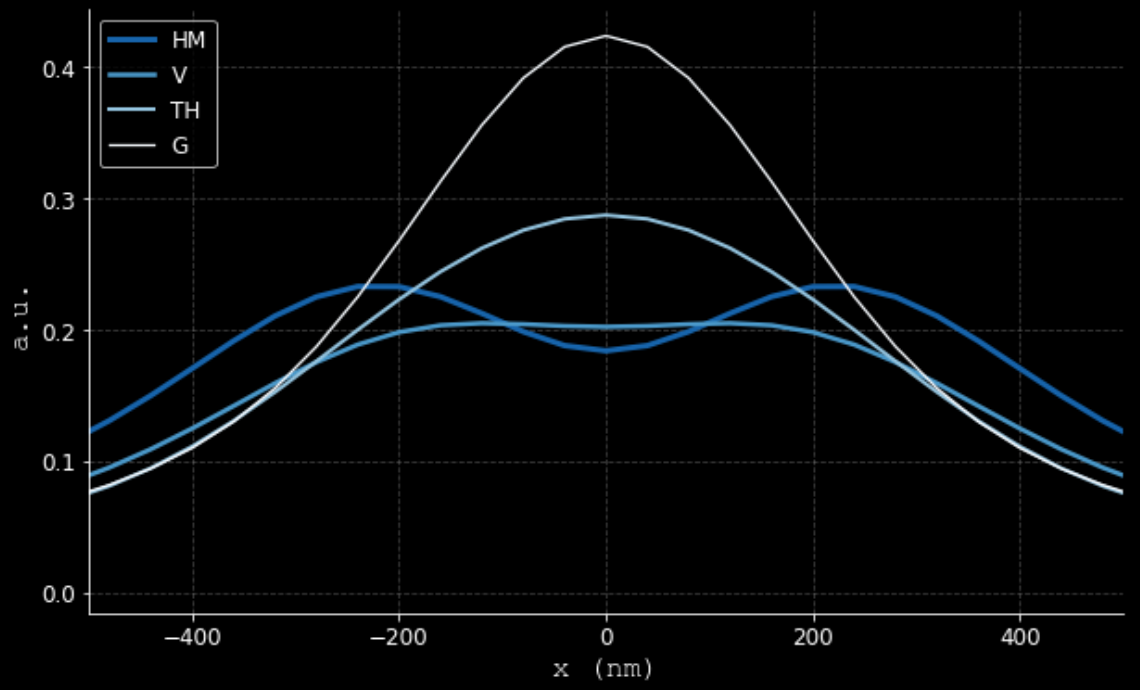
Photon Count

CRB

Estimator

Background Measurement





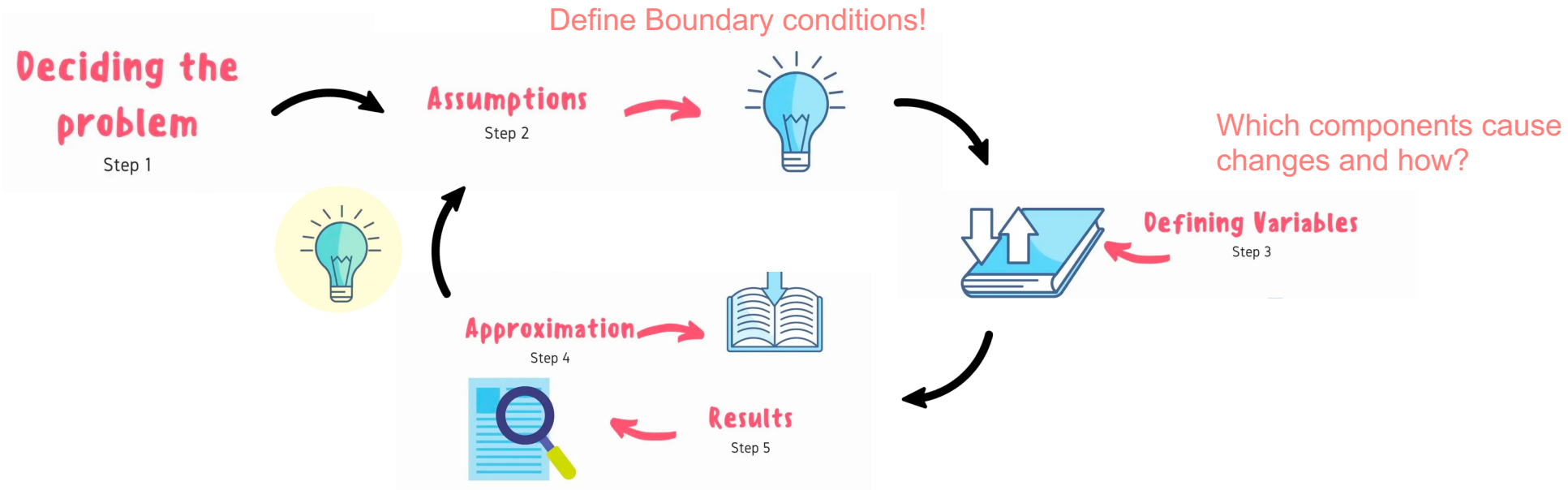
The model can be modified/specified for different cases

Can mathematics unlock nature’s secrets ?

It can certainly contribute to the process of unlocking!

Image generated with Midjourney

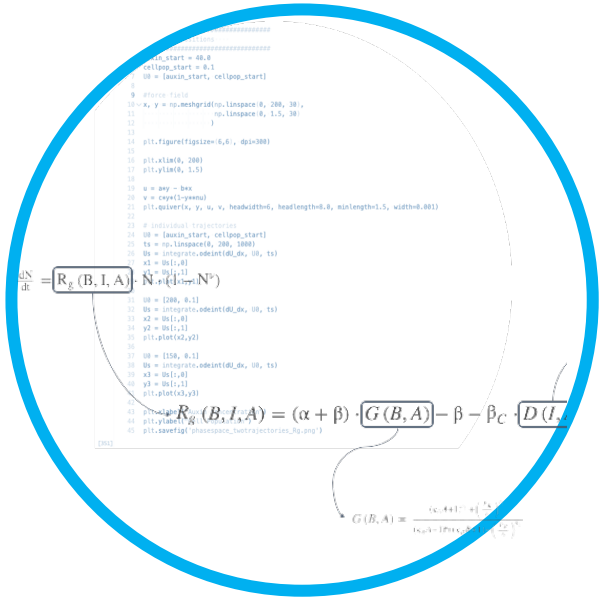
In Summary | A process



https://easemyphd.com/2020/09/mathematical-modelling-step-by-step.html

In Summary | The bigger picture

In silico Modeling



Deciding the problem

Assumptions
Step 2

Defining Variables
Step 3

Approximation
Step 4

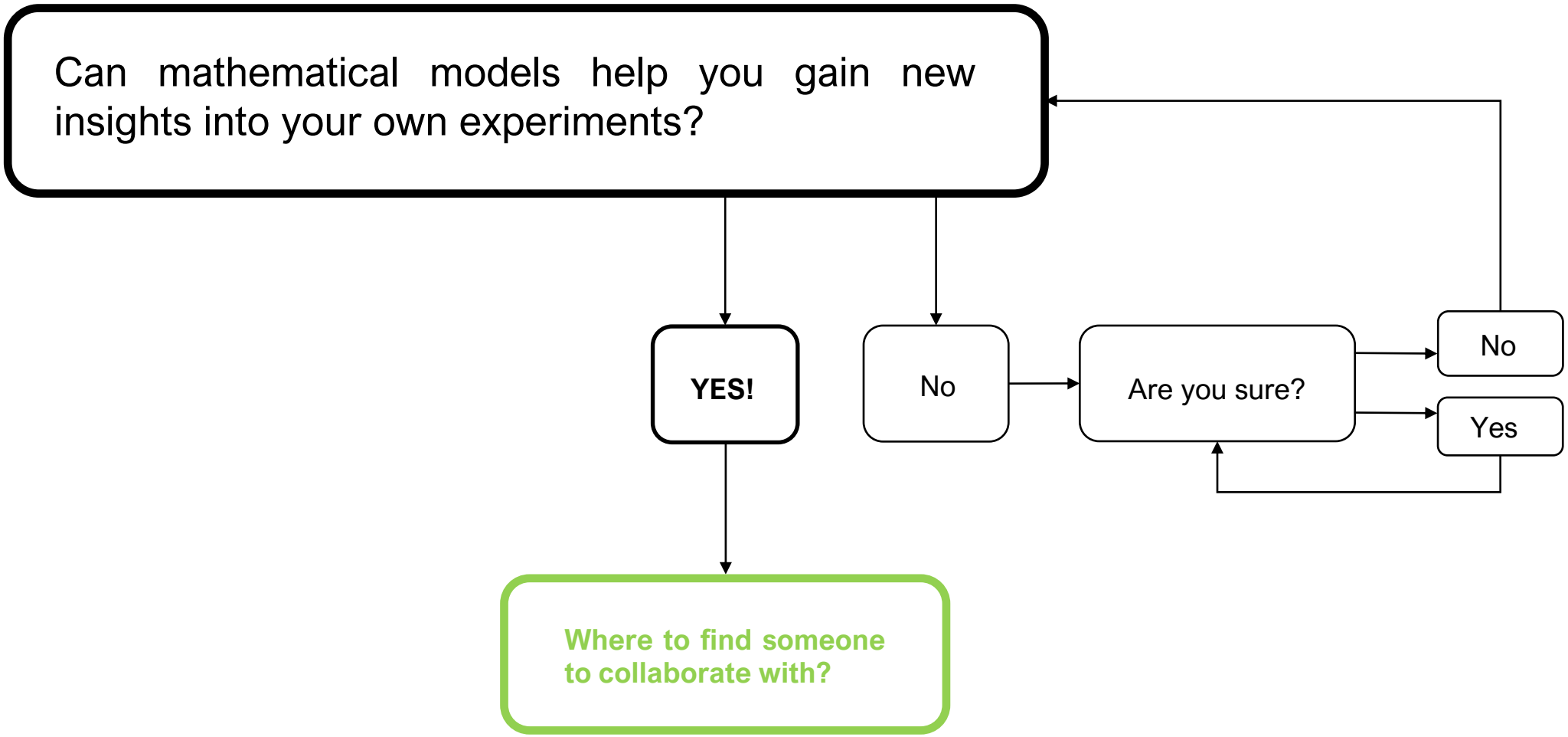
Results
Step 5

Understanding ~~Deciding~~ the problem + Finding a new one

Biological Experiments

https://www.nasa.gov/feature/ames/plants-muscles-microbes-and-cells-nasa-biology-experiments-are-space-station-bound

So, what now?


Can mathematical models help you gain new insights into your own experiments?
YES!
No
Are you sure?
No
Yes
Where to find someone to collaborate with?

So, what now?

Groups that work with mathematical models to understand biology and more:

ON CAMPUS

CIBIV | Arndt von Haeseler Group (VBC5)

Balzarotti Lab (IMP)

Menche Lab (VBC5/Math Dep)

Hermisson Group (VBC5/Math Dep)

Zagrovic Lab (VBC5)

Mathematics and BioSciences Group (MaBS)

CIBIV Center for Integrative Bioinformatics Vienna

MENCHE LAB

BEYOND CAMPUS

Merino-Aceituno Group (Math Dep)

Rendeiro Group (CeMM)

Bock Lab (CeMM/Med Uni)

Anastasia Molchanova, Post Doc (Math Dep)

Vienna School of Mathematics

BOCK LAB

Biomathematik

Mathematics of emergence in biology and social sciences

Disclaimer: this list is far from being complete, but it hopefully can get you started

THANK YOU!

HDYDI Series WS 2023

Can mathematics unlock nature's secrets?

Mehrta [Balzarotti Lab] / **Chris** [Menche Lab]

Image generated with Midjourney

Research Institute of Molecular Pathology
Institute of Molecular
GMI GREGOR MENDEL INSTITUTE OF MOLECULAR PLANT BIOLOGY
MAX PERUTZ LABS VIENNA
Part of Vienna BioCenter
universität wien
MEDIZINISCHE UNIVERSITÄT WIEN