BioQUEST Curriculum Consortium

biological (es+eem)

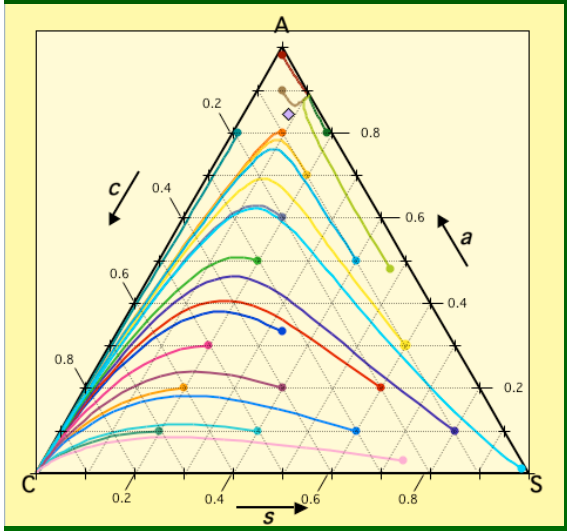
Excel Simulations and Tools for Exploratory, Experiential Mathematics

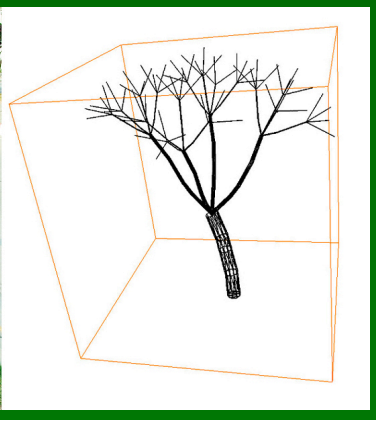
MAA Online
The Mathematical Association of America

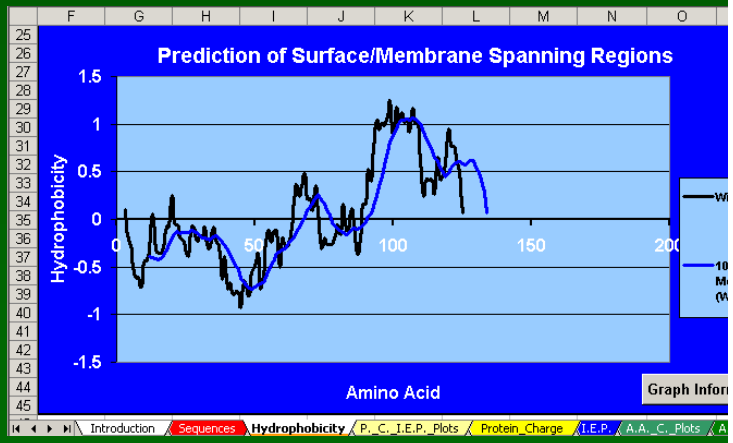
NSF

SHODOR EDUCATION FOUNDATION, INC.
A national resource for computational science education

The Biological ESTEEM Project







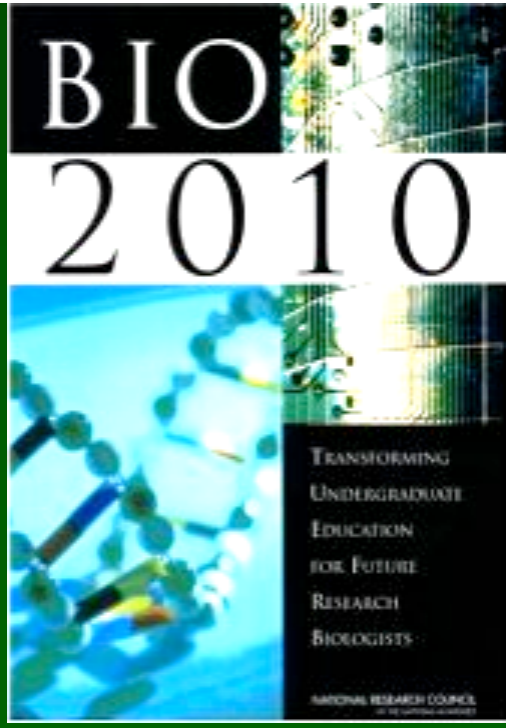
$$Imm. = \frac{P - S}{d}$$

$$Ext. = \frac{S}{a}$$

		A	T	C	G	C	T	T
	0	-7	-14	-21	-28	-35	-42	-49
	###	###	-14	###	###	###	###	###
C	-4 -14 -11 -21 -9 -28 -25 -35 -23 -42 -39 -49 -46 -56							
	-7	-14 -4 -11 -11 -18 -9 -16 -16 -23 -23 -30 -30 -37 -37						
	###	###	###	-9	###	###	###	###
G	-11 -11 -8 -18 -15 -16 -4 -23 -20 -30 -27 -37 -34 -44							
	-14	-21 -11 -18 -8 -15 -15 -22 -4 -11 -11 -18 -18 -25 -25						
	###	###	###	###	-4	###	###	###
C	-18 -18 -15 -15 -3 -22 -19 -11 1 -18 -15 -25 -22 -32							
	-21	-28 -18 -25 -15 -22 -3 -10 -10 -17 1 -6 -6 -13 -13						
	###	###	###	###	###	1	###	###
T	-25 -25 -13 -22 -19 -10 -7 -17 -14 -6 6 -13 -1 -20							
	-28	-35 -25 -32 -13 -20 -10 -17 -7 -14 -6 -13 6 -1 -1						
	###	###	###	###	###	###	6	###
C	-32 -32 -29 -20 -8 -17 -14 -14 -2 -13 -10 -1 2 -8							
	-35	-42 -32 -39 -20 -27 -8 -15 -14 -21 -2 -9 -1 -8 2						
	###	###	###	###	###	###	-1	###
T	-39 -39 -27 -27 -24 -15 -12 -21 -18 -9 3 -8 4 -5							
	-42	-49 -39 -46 -27 -34 -15 -22 -12 -19 -9 -16 3 -4 4						
	###	###	###	###	###	###	###	4

BIO 2010:
Transforming Undergraduate Education for Future Research Biologists

National Research Council (2003)



Recommendation #1:
"Those selecting the new approaches should consider the importance of mathematics..."

Recommendation #2:
"Concepts, examples, and techniques from mathematics…should be included in biology courses. …Faculty in biology, mathematics, and physical sciences must work collaboratively to find ways of integrating mathematics…into life science courses…"

BIO 2010:

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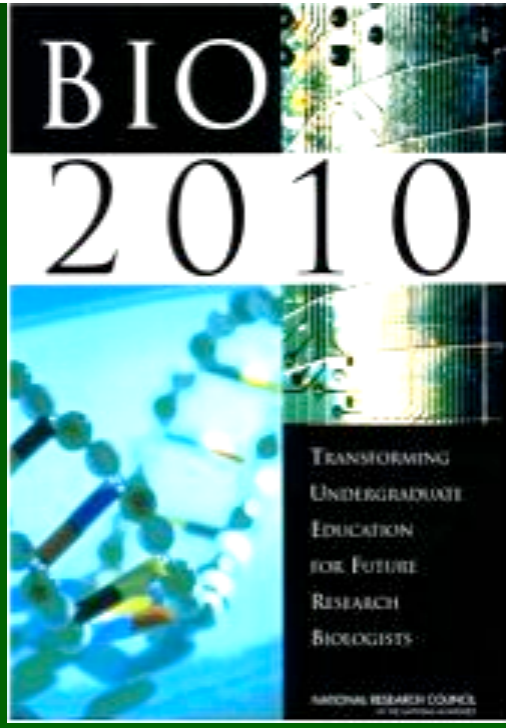
National Research Council (2003)



Specific strategies:

- A strong interdisciplinary curriculum that includes physical science, information technology, and math.
- Early opportunities for independent research.
- Meaningful laboratory experiences.

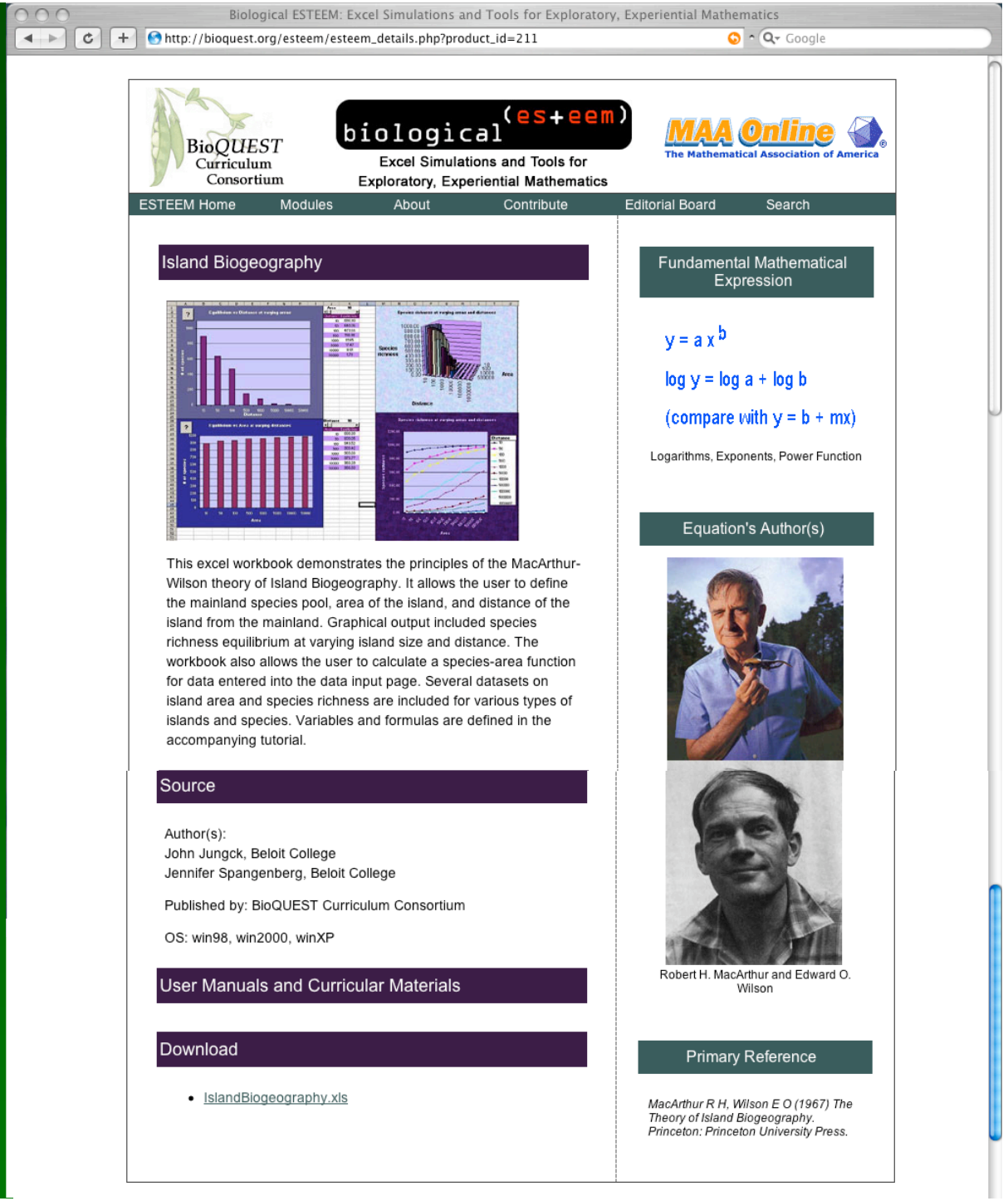
The ESTEEEM Project Homepage

http://bioquest.org/esteem

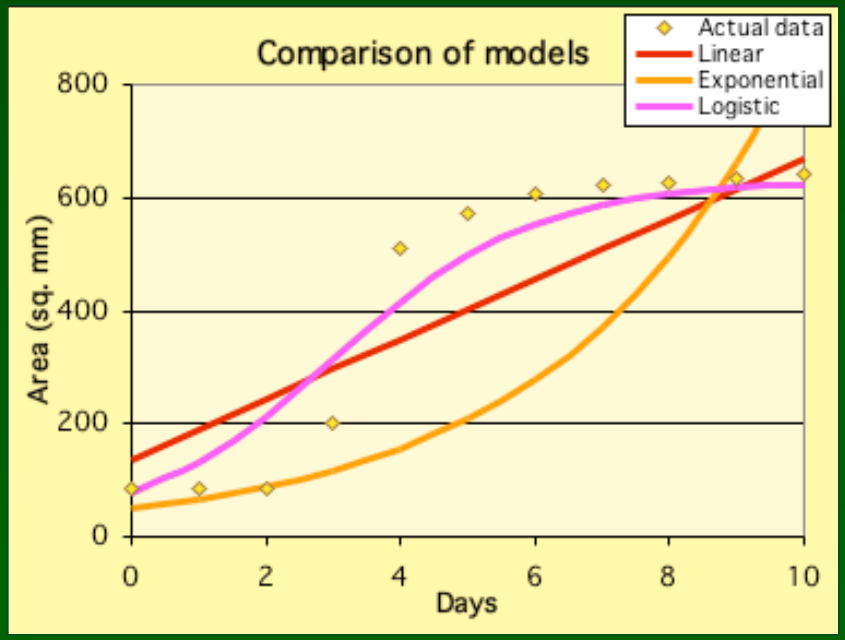
55 modules: Broad range of topics and data sets

Module Main Page

- Screenshots & brief description
- Mathematical expression
- Research articles & primary data
- User manual & curriculum materials (in progress)
- Downloadable *Excel* sheet



Population growth *(Continuous Growth Models)*



Bioinformatics (*Pairwise Alignment*)

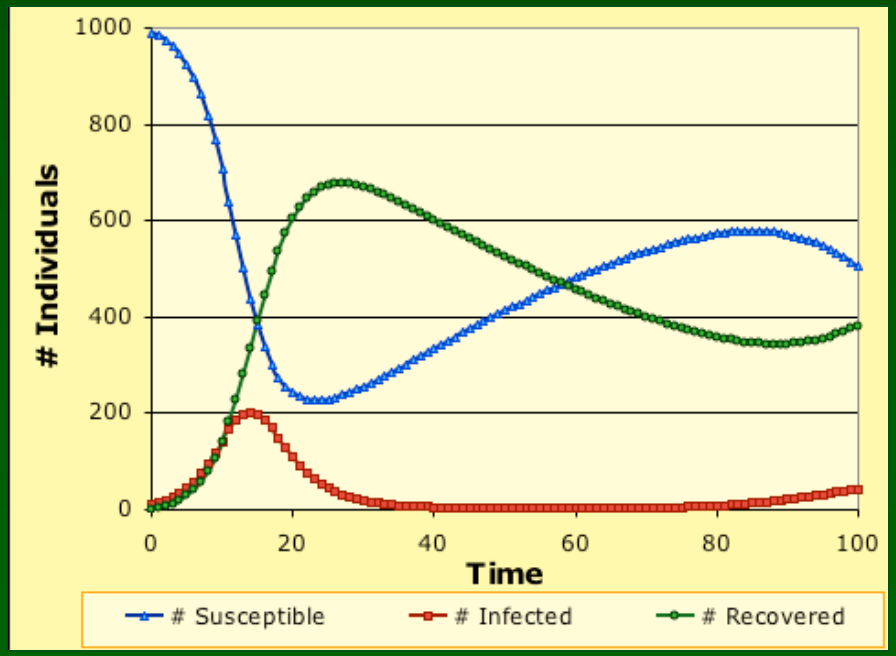
			A		T		C		G		C		T		T	
		0		**-7**		**-14**		**-21**		**-28**		**-35**		**-42**		**-49**
		###		###		-14		###		###		###		###		###
C			-4	-14	-11	-21	-9	-28	-25	-35	-23	-42	-39	-49	-46	-56
		-7	-14	**-4**	-11	**-11**	-18	**-9**	-16	**-16**	-23	**-23**	-30	**-30**	-37	**-37**
		###		###		###		-9		###		###		###		###
G			-11	-11	-8	-18	-15	-16	-4	-23	-20	-30	-27	-37	-34	-44
		-14	-21	**-11**	-18	**-8**	-15	**-15**	-22	**-4**	-11	**-11**	-18	**-18**	-25	**-25**
		###		###		###		###		-4		###		###		###
C			-18	-18	-15	-15	-3	-22	-19	-11	1	-18	-15	-25	-22	-32
		-21	-28	**-18**	-25	**-15**	-22	**-3**	-10	**-10**	-17	**1**	-6	**-6**	-13	**-13**
		###		###		###		###		###		1		###		###
T			-25	-25	-13	-22	-19	-10	-7	-17	-14	-6	6	-13	-1	-20
		-28	-35	**-25**	-32	**-13**	-20	**-10**	-17	**-7**	-14	**-6**	-13	**6**	-1	**-1**
		###		###		###		###		###		###		6		###
C			-32	-32	-29	-20	-8	-17	-14	-14	-2	-13	-10	-1	2	-8
		-35	-42	**-32**	-39	**-20**	-27	**-8**	-15	**-14**	-21	**-2**	-9	**-1**	-8	**2**
		###		###		###		###		###		###		-1		###
T			-39	-39	-27	-27	-24	-15	-12	-21	-18	-9	3	-8	4	-5
		-42	-49	**-39**	-46	**-27**	-34	**-15**	-22	**-12**	-19	**-9**	-16	**3**	-4	**4**
		###		###		###		###		###		###		###		4

Gene regulation *(Operon)*

Strand	Upstream Regulator	Promoter	Operator	*lacZ* (Galactosidase)	*lacY* (Permease)	*lacA* (Transacetylase)	Sugars present in medium	
	I (+/-/s)	P (+/-)	O (+/c)	Z (+/-)	Y (+/-)	A (+/-)	Lactose?	Glucose?
F-	+ (Wild-type)	+ (Wild-type)	c (Constitutive)	+ (Wild-type)	- (Nonfunct.)	+ (Wild-type)	Absent	Absent
F'	- (Nonfunctional)	+ (Wild-type)	+ (Wild-type)	- (Nonfunct.)	+ (Wild-type)	- (Nonfunct.)		

Strand	Super-repressing repressor produced?	Normally active repressor produced?	cAMP levels?	cAMP/CAP complex binds to promoter?	RNA polymerase binds to promoter?	Repressor binds to operator?	Polymerase can transcribe?	Galactosidase?	Permease?	Transacetylase?
F-	FALSE	TRUE	High	TRUE	TRUE	FALSE	TRUE	TRUE	**FALSE**	TRUE
F'	FALSE	TRUE	High	TRUE	TRUE	TRUE	FALSE	**FALSE**	**FALSE**	**FALSE**

Epidemiology *(SIR Model)*



Phylogenetics *(EvolSeq)*

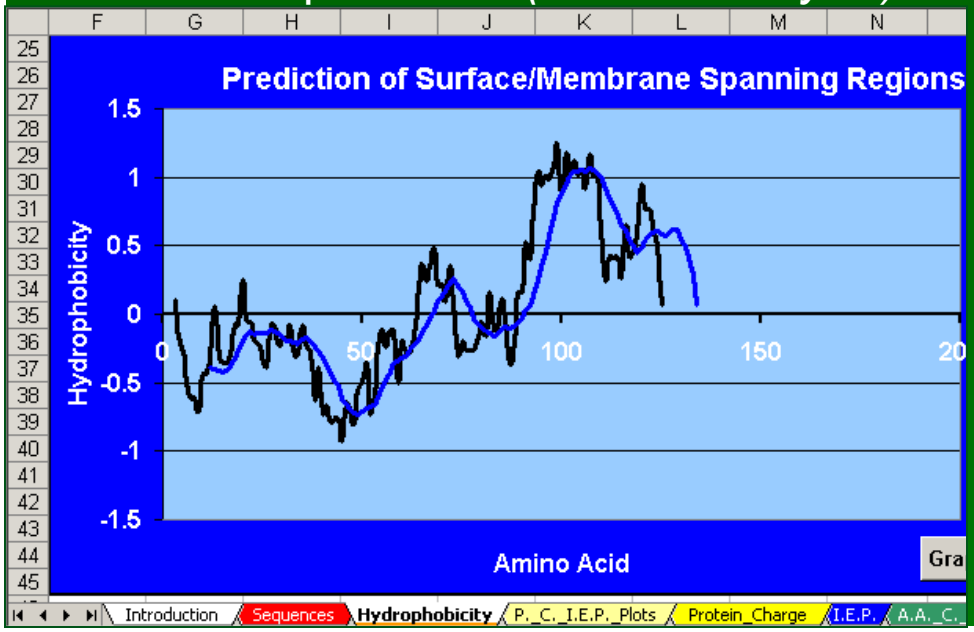
Distance matrix: Nucleotide Sequences

	Seq. 1	Seq. 2	Seq. 3	Seq. 4	Seq. 5	Seq. 6	Seq. 7
Seq. 1	0	10	2	6	10	10	12
Seq. 2		0	10	10	8	4	12
Seq. 3			0	6	10	10	12
Seq. 4				0	10	10	12
Seq. 5					0	8	12
Seq. 6						0	12
Seq. 7							0

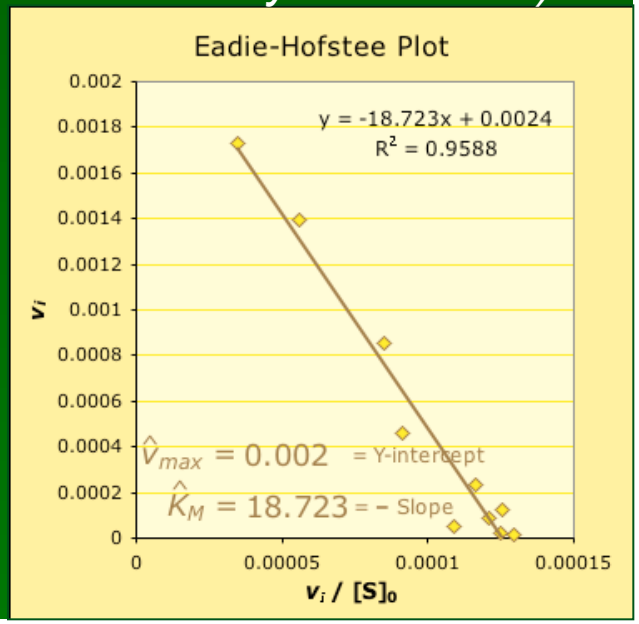
Distance matrix: Amino Acid Sequences

	Seq. 1	Seq. 2	Seq. 3	Seq. 4	Seq. 5	Seq. 6	Seq. 7
Seq. 1	0	6	2	3	4	7	8
Seq. 2		0	6	7	4	3	10
Seq. 3			0	3	4	7	8
Seq. 4				0	5	8	9
Seq. 5					0	5	8
Seq. 6						0	11
Seq. 7							0

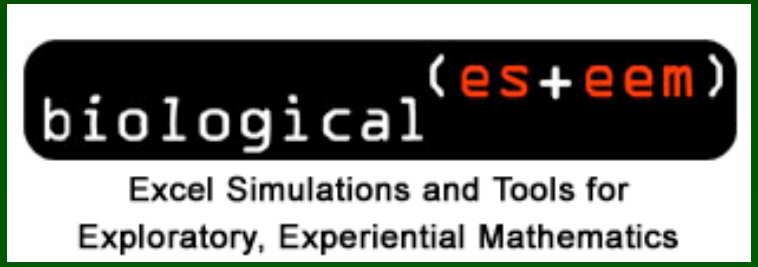
Structure prediction *(Protein Analysis)*



Biochemistry *(Michaelis-Menten Enzyme Kinetics)*



Unpacking "ESTEEM"



- *Excel*: ubiquitous, easy, flexible, non-intimidating
- Exploratory: apply to real-world data; extend & improve
- Experiential: students engage directly with the math

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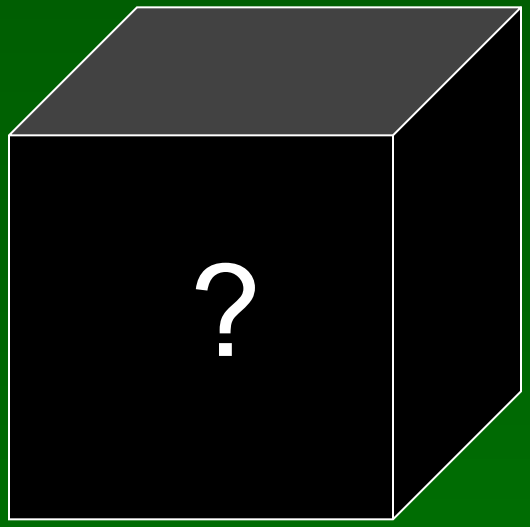
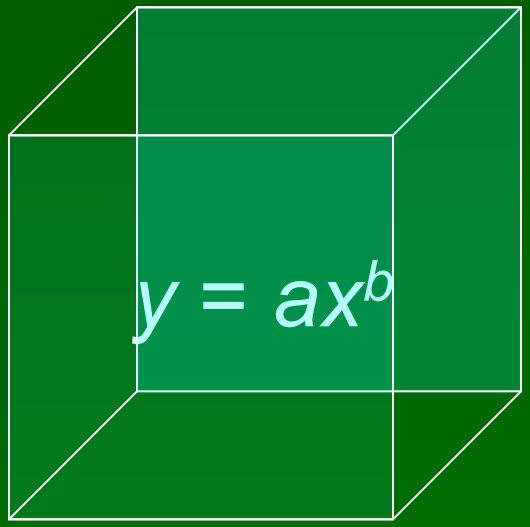
Three Boxes

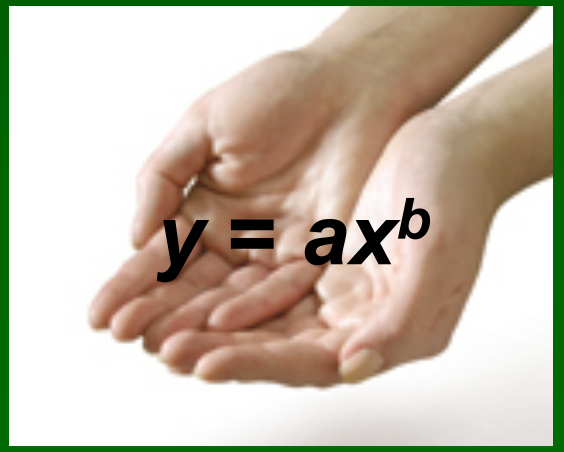
How do students interact with the mathematical model underlying the biology?



Black box:
Hide the model



Glass box:
Study the model

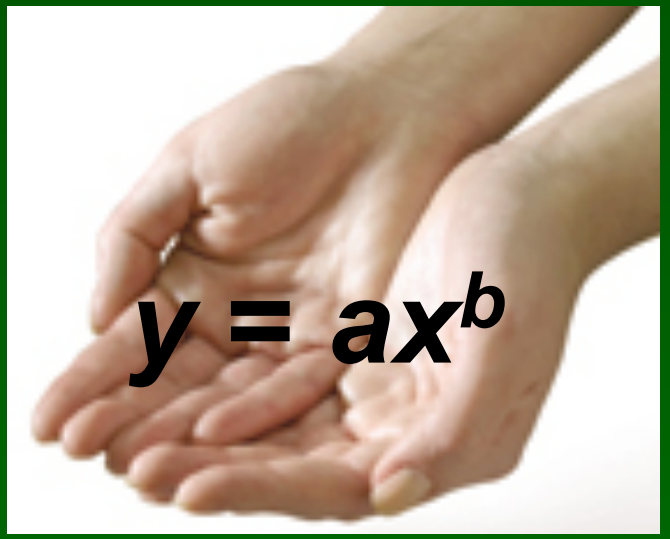


No box:
Build the model!

1. The No-Box Approach

a. Students try to build a conceptual model of how a particular biological system works.

b. They then translate that understanding into simple mathematical expressions and implement the model in *Excel*.



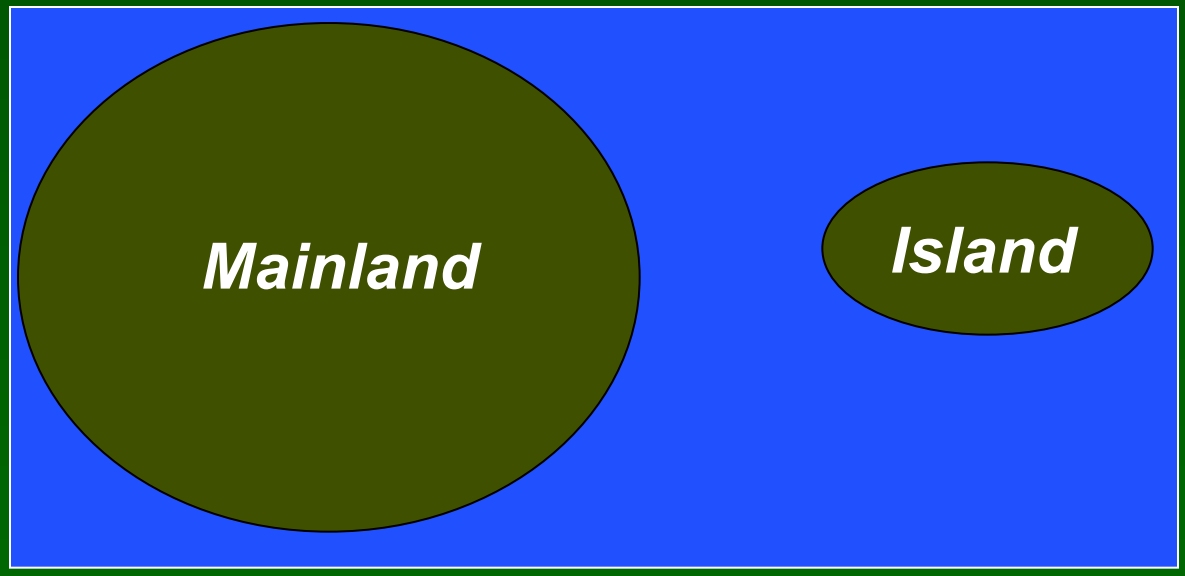
Examples: *Island Biogeography, SIR*

Island Biogeography

(J.A. Spangenberg & J.R. Jungck)

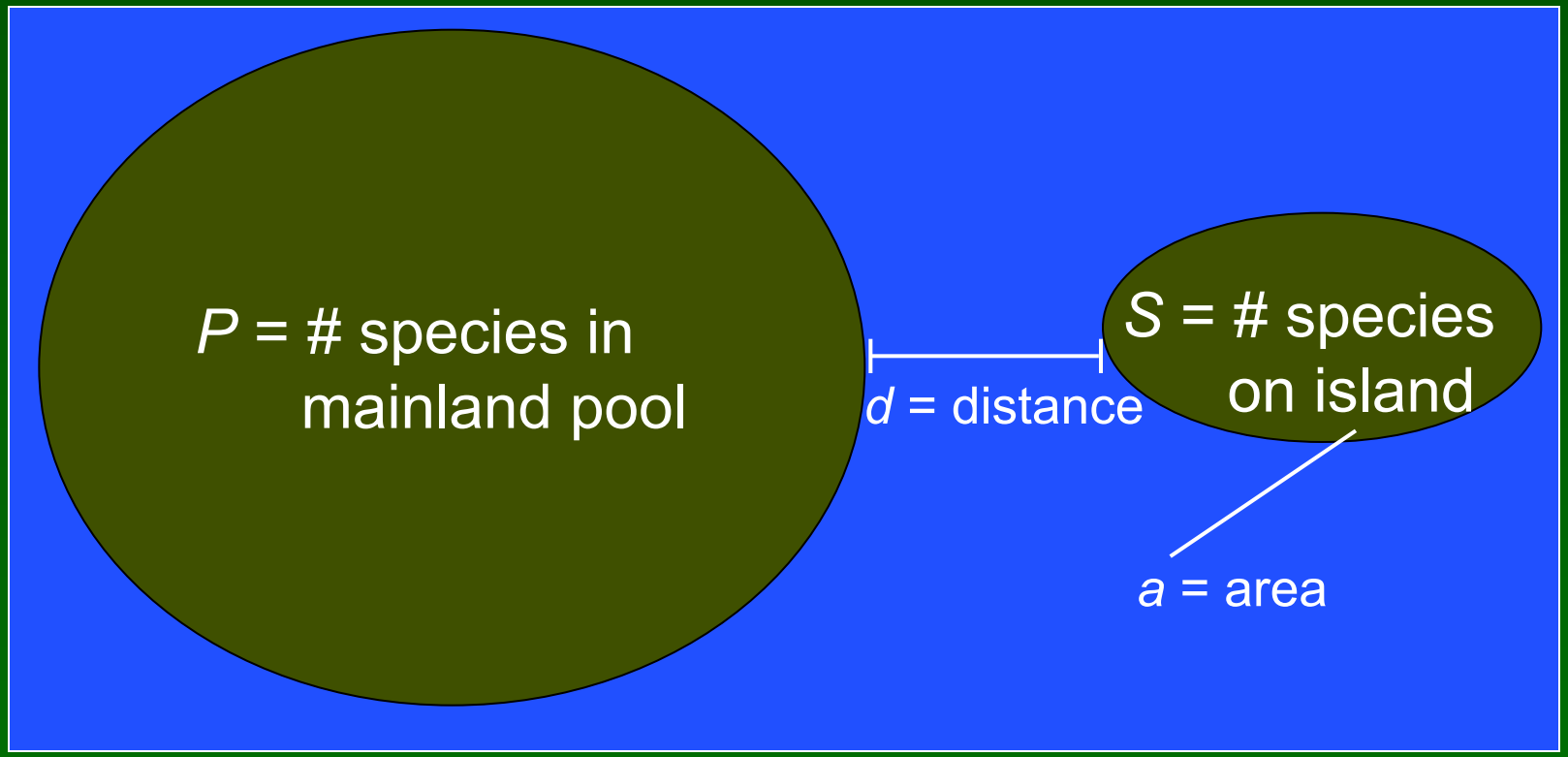
- Survey of plant species on islands off British mainland
- Which islands would you expect to have most species, and why?

Island Biogeography



1. What parameters most strongly influence immigration of species to the island or local extinction of species already there?

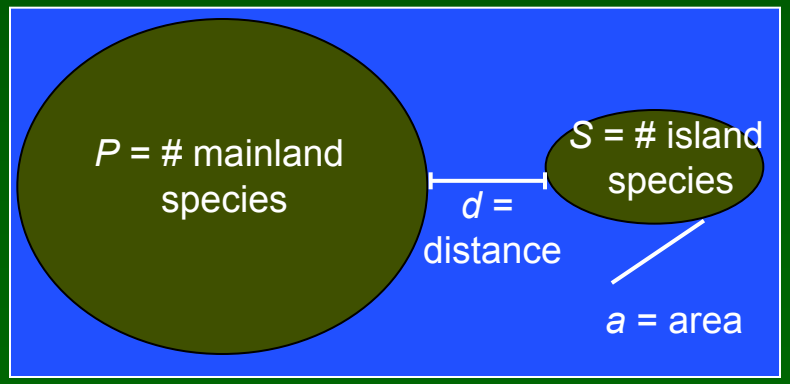
Island Biogeography



2. For each parameter, predict its *general effect* (+, 0, –) on immigration.

   Then do the same for extinction.

Island Biogeography



My predictions:

Parameter	Effect on immigration	Effect on extinction
P	+	0
S	–	+
d	–	0
a	0	–

Individual students' predictions may differ, depending on their assumptions

3. Write equations for immigration & extinction rates that reflect the behavior you predicted.

Island Biogeography:
Building a Simple Model

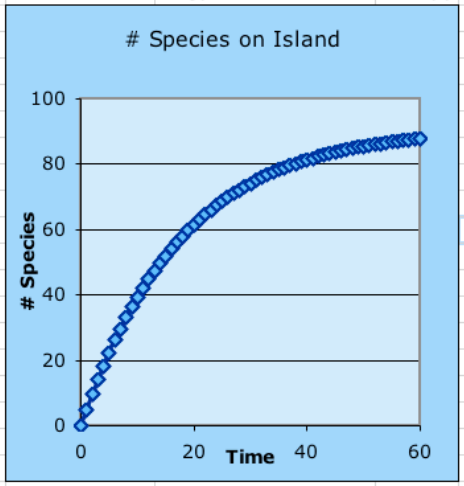
Model:

$$\text{Immigration} = \frac{P - S}{d}$$

$$\text{Extinction} = \frac{S}{a}$$

Island Biogeography – BuildMe.xls

	A	B	C	D	E	F	G
1	Time	# Species on Island	# Immigrating	# Local Extinctions		# Species in Pool:	100
2	0	0.00	5.00	0.00		Initial # on Island:	0
3	1	5.00	4.75	0.03		Distance:	20
4	2	9.73	4.51	0.05		Area:	200
5	3	14.19	4.29	0.07			
6	4	18.41	4.08	0.09			
7	5	22.40	3.88	0.11			
8	6	26.17	3.69	0.13			
9	7	29.73	3.51	0.15			
10	8	33.09	3.35	0.17			
11	9	36.27	3.19	0.18			
12	10	39.28	3.04	0.20			
13	11	42.12	2.89	0.21			
14	12	44.80	2.76	0.22			
15	13	47.34	2.63	0.24			
16	14	49.73	2.51	0.25			
17	15	52.00	2.40	0.26			
18	16	54.14	2.29	0.27			
19	17	56.16	2.19	0.28			
20	18	58.07	2.10	0.29			
21	19	59.88	2.01	0.30			
22	20	61.58	1.92	0.31			
23	21	63.20	1.84	0.32			



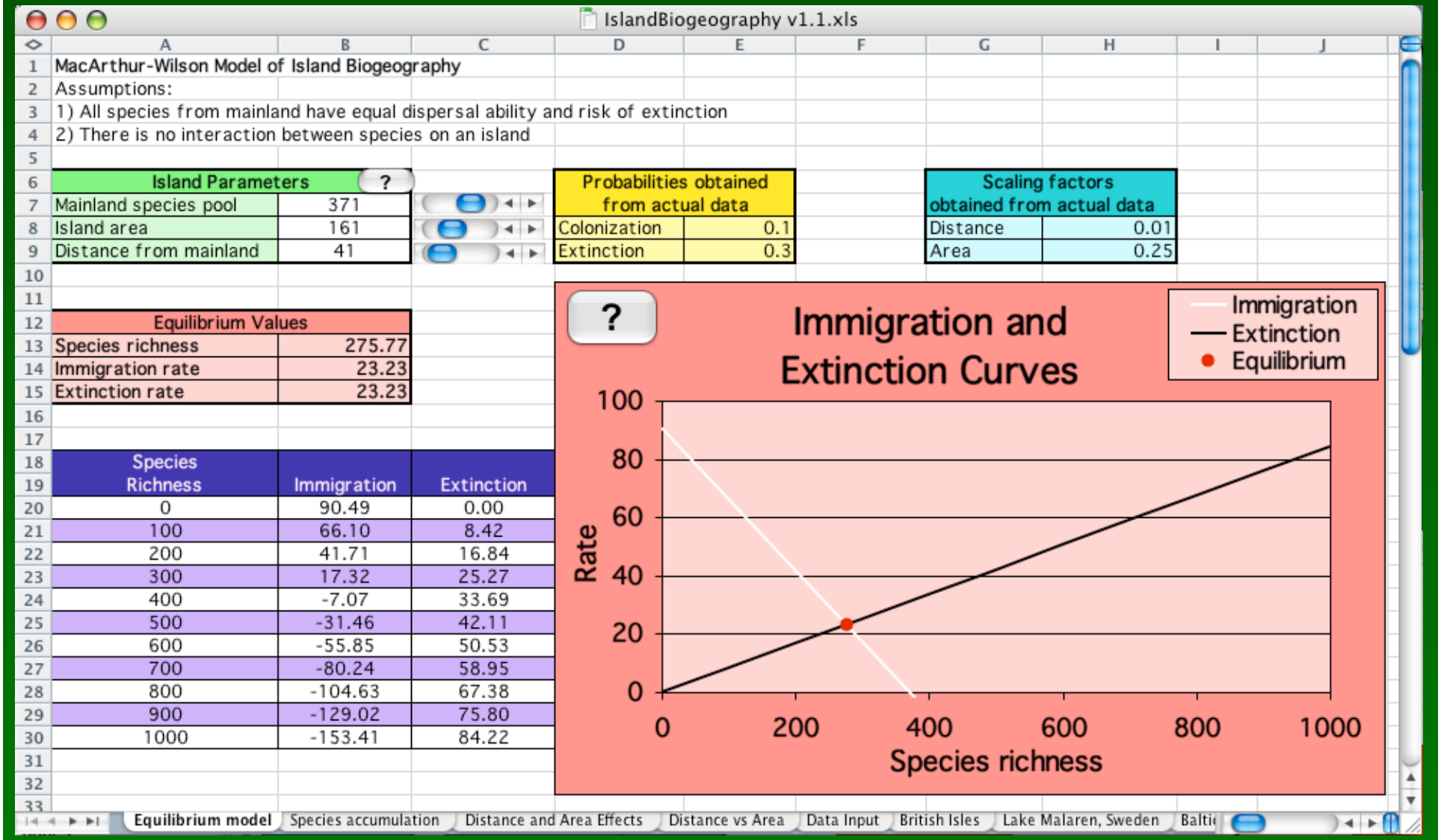
Sheet1 Sheet2 Sheet3

- How can we calculate <u>equilibrium</u> species richness $\hat{S}$?
  (Set immigration = extinction, solve for S)

- How do island area & distance from mainland affect $\hat{S}$?

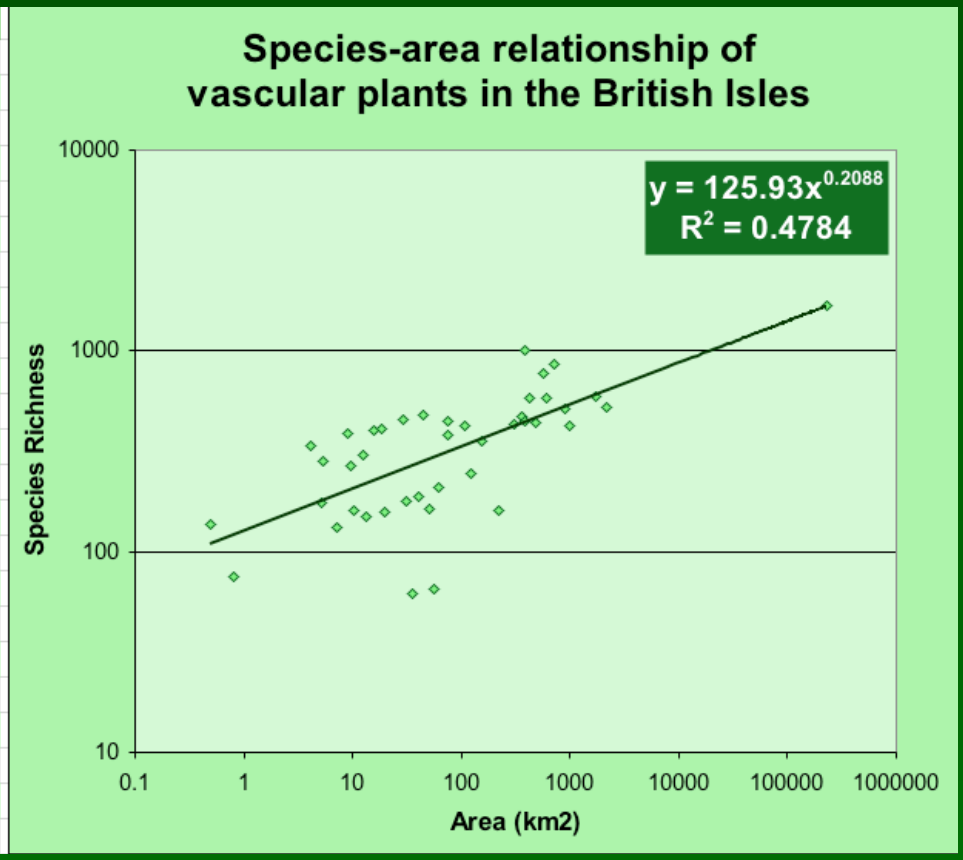
Beyond the No-Box Approach:

Using the prebuilt *Excel* workbook



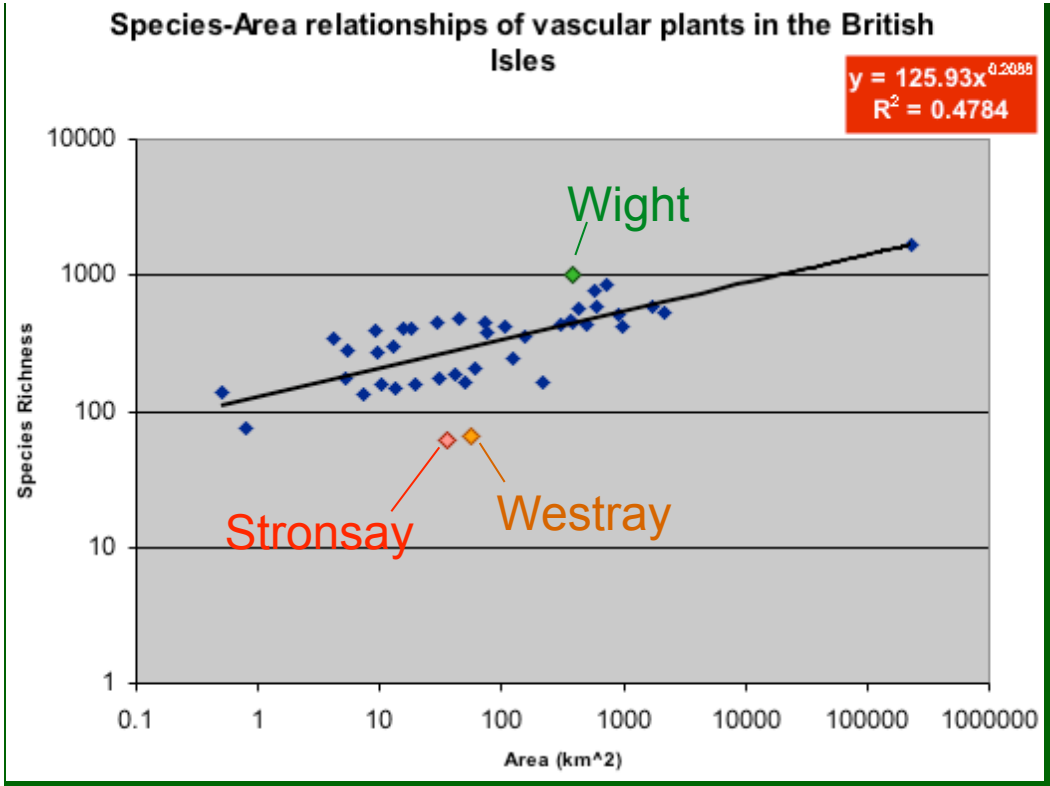
Data Set: British Isles

Island	Area (km^2)	Richness
May	0.5	137
Ailsa	0.8	75
Lundy	4.1	338
Fair	5.2	174
Muck	5.4	284
N. Ronaldsay	7.3	131
Iona	9.1	388
Mingulay	9.6	269
Rona	10.4	159
Canna	12.7	300
Foula	13.5	149
Gigha	15.5	401
Barra	18.4	409
Whalsay	19.7	158
Eigg	29	453
Bressay	31.1	177
Stronsay	35.2	62
Fetlar	40.9	189
Colonsay	44.8	482
Sanday	50.2	162
Westray	55.4	65
S. Ronaldsay	60.9	207
Coll	74.1	443



Questions for further investigation:

- How much does the relationship depend on 1-2 individual data points?
- Why are some individual data points so far from the trendline? Can we substantially improve the model by adding more factors?



Low outliers:

- high latitude (subarctic)
- distant from mainland

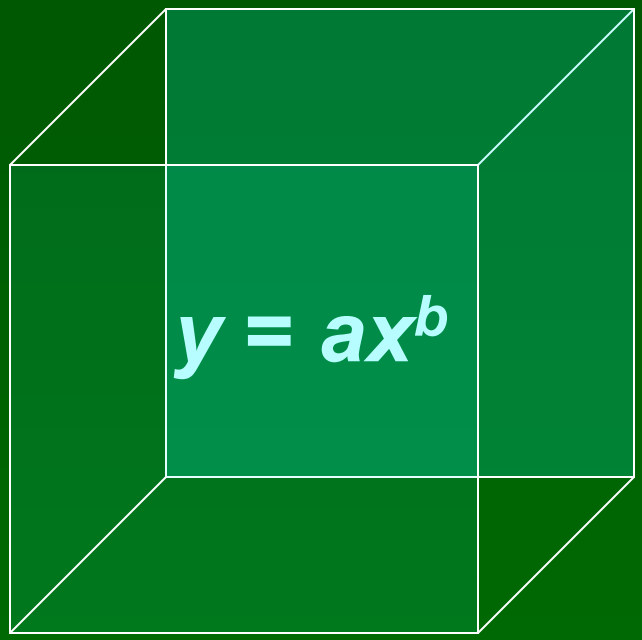
High outliers:

- low latitude (temperate)
- close to mainland

2. The Glass-Box Approach

a. Students analyze prebuilt software tools to understand specific relationships and techniques (e.g., logistic population growth, prediction of 2° protein structure)

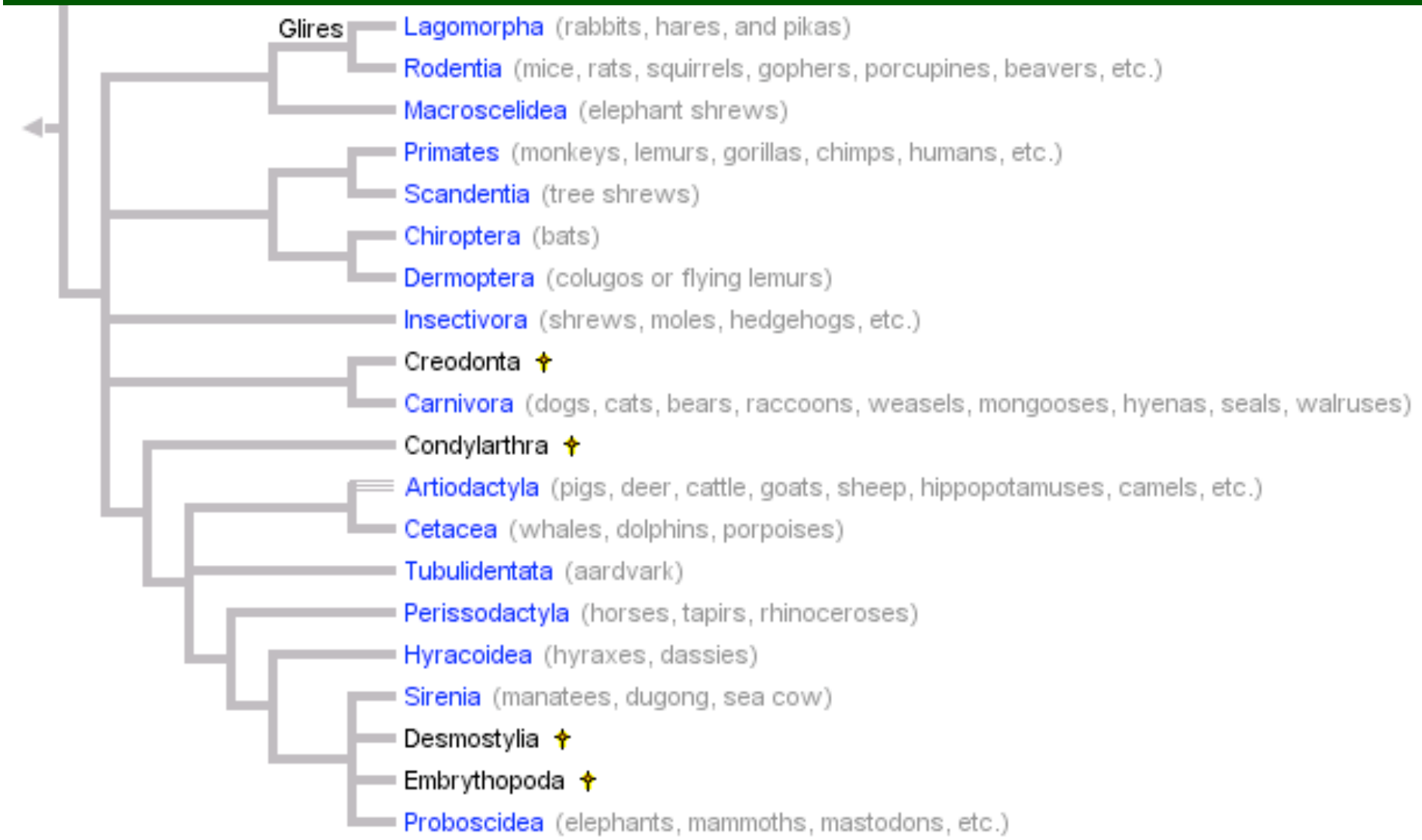
b. This involves exploring the inner workings of a model's equations or algorithms.



Examples: *Continuous Growth Models, EvolSeq, Mark/Recapture, Protein Analysis, Split Decomp*

EvolSeq

Where do trees like this come from?



EvolSeq

Ribulose 1,5-bisphosphate carboxylase (rubisco)

```
Zea          AAAGAAGACCACAGGGCCCTGCTGGAGATGAAGGCCACCC
Arabidopsis  AAAGAAGACCACGGAGGCCCTGCTGGAGCTGAAGGCCACCC
Sphagnum     AAAGAAGACCACGGAGGCCCTGCTGGAGCTGAAGGCCACCC
Picea        AGAGAAGACCAAGGAGGCCCTCCTGGAGCTGAAGGCCACCC
Cyathea      AGAGAAGACCAAAGAGGCCCTGCTGGAGCTGAAGGCGAGCCC
```

Task 1:

Calculate the evolutionary distance between each pair of sequences.

(Treat all differences alike, or assign greater weight to transversions? Depends on your assumptions re. molecular evolution!)

# of sequences:	7	(must be between 2 and 20 inclusive)	Distance matrix display: ○ Upper triangular ◉ Symmetric			

Distance matrix: Nucleotide Sequences

	Seq. A	Seq. B	Seq. C	Seq. D	Seq. E	Seq. F	Seq. G
Seq. A	0	8	12	12	10	12	10
Seq. B	8	0	12	12	10	12	10
Seq. C	12	12	0	4	12	4	12
Seq. D	12	12	4	0	12	2	12
Seq. E	10	10	12	12	0	12	6
Seq. F	12	12	4	2	12	0	12
Seq. G	10	10	12	12	6	12	0

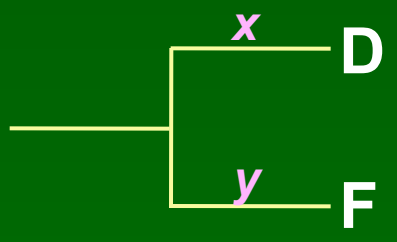
Task 2:
Construct a phylogenetic tree for these seven taxa.

BONUS: Include branchlengths!

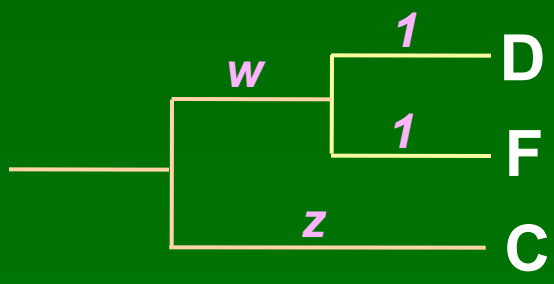
Distance matrix: Nucleotide Sequences							
	Seq. A	Seq. B	Seq. C	Seq. D	Seq. E	Seq. F	Seq. G
Seq. A	0	8	12	12	10	12	10
Seq. B	8	0	12	12	10	12	10
Seq. C	12	12	0	4	12	4	12
Seq. D	12	12	4	0	12	2	12
Seq. E	10	10	12	12	0	12	6
Seq. F	12	12	4	2	12	0	12
Seq. G	10	10	12	12	6	12	0

Strategy 1: cherry-picking

- Unite the 2 most similar taxa
- Assign branchlengths that fit all pairwise distances
- Repeat



($x + y = 2$)

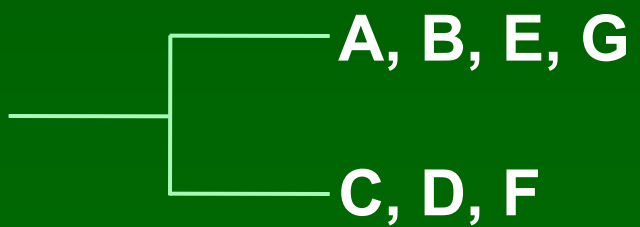


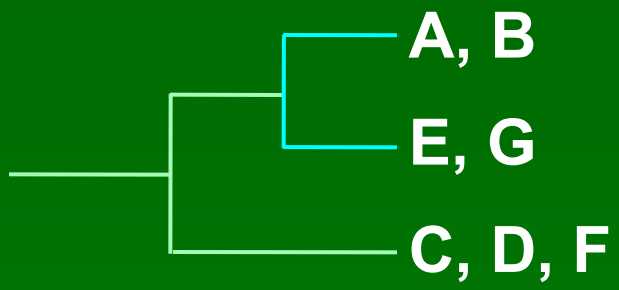
($w + z + 1 = 4$)

Distance matrix: Nucleotide Sequences							
	Seq. A	Seq. B	Seq. C	Seq. D	Seq. E	Seq. F	Seq. G
Seq. A	0	8	12	12	10	12	10
Seq. B	8	0	12	12	10	12	10
Seq. C	12	12	0	4	12	4	12
Seq. D	12	12	4	0	12	2	12
Seq. E	10	10	12	12	0	12	6
Seq. F	12	12	4	2	12	0	12
Seq. G	10	10	12	12	6	12	0

Strategy 2: splitting

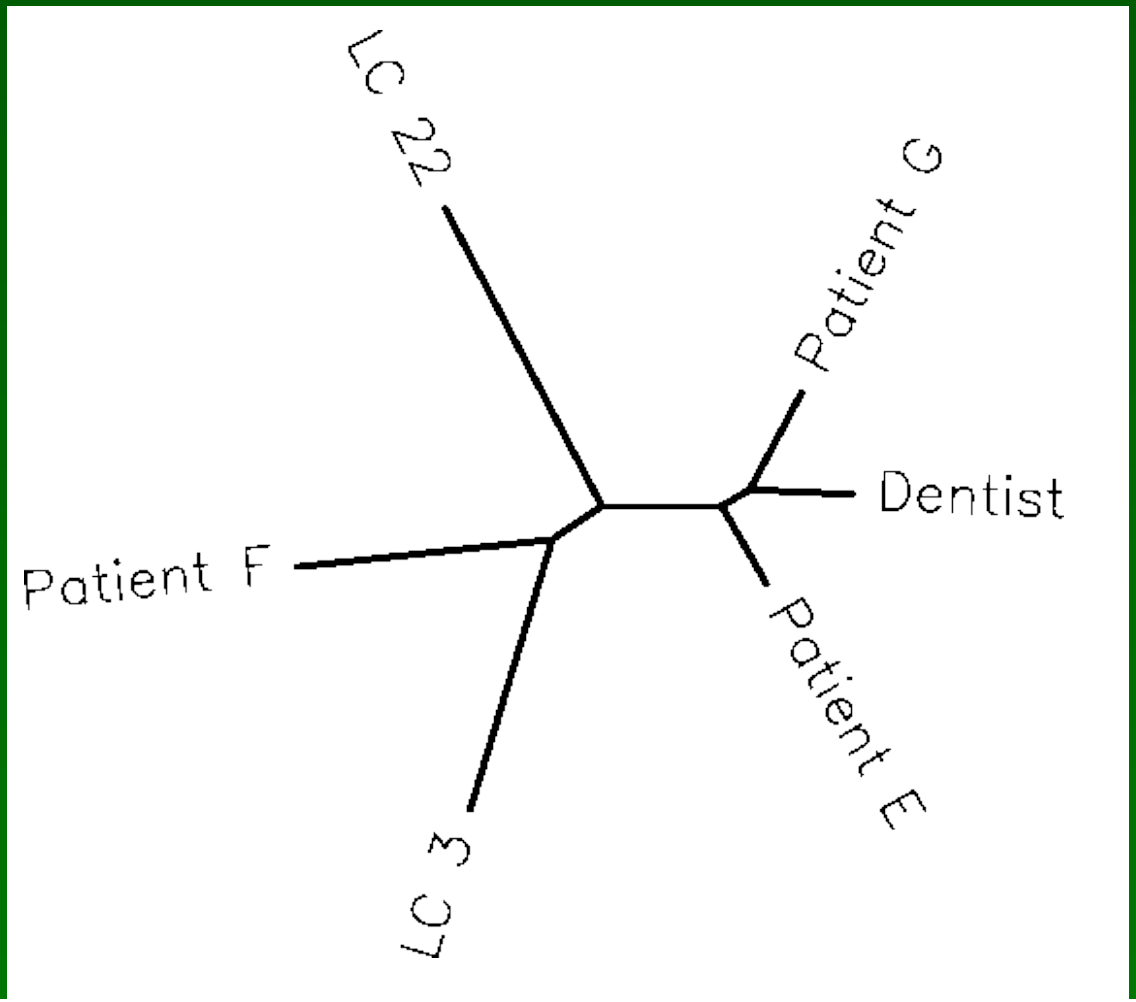
- Divide taxa into 2 groups separated by largest distance
- Repeat
- At end, assign branchlengths that fit all pairwise distances





SplitDecomp

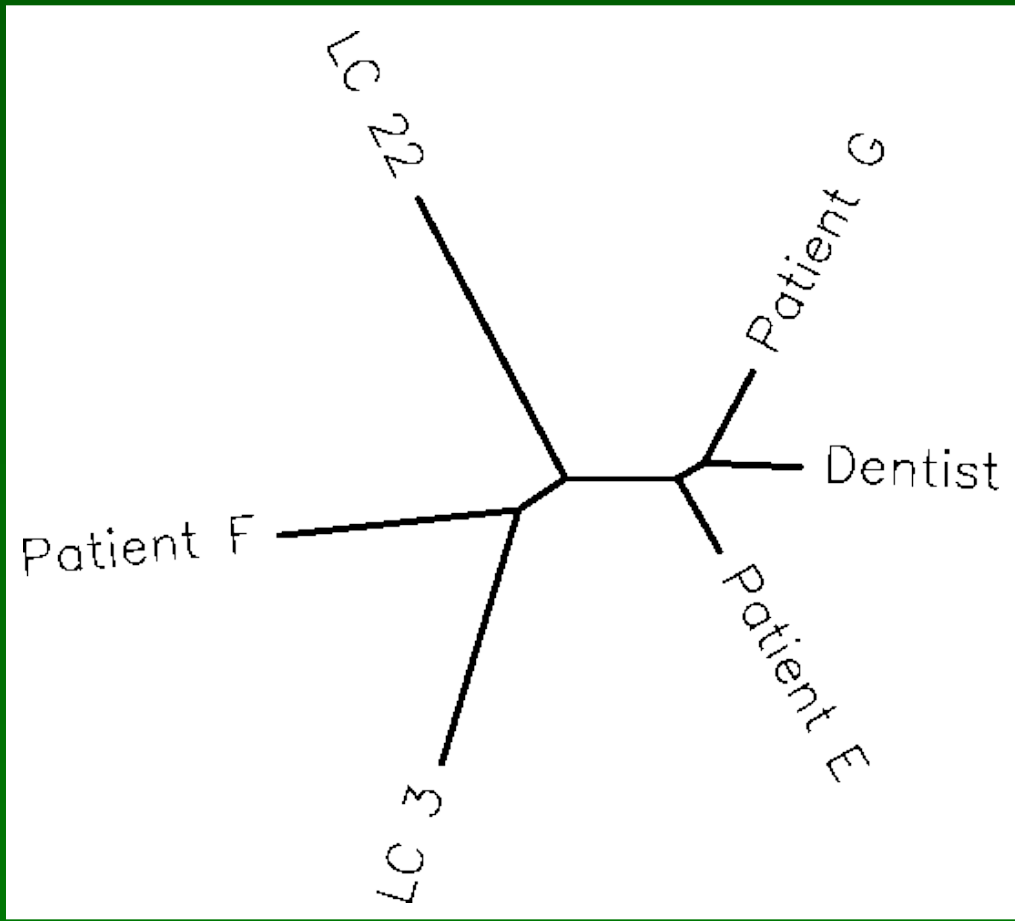
How much evidence supports a given branch?



Phylogenetics in the Courtroom

- In 1990, a Florida woman contracted HIV. Only known risk factor: invasive dental surgery by an HIV-positive dentist.
- HIV evolves so fast that viral DNA differs within and between indiv. patients!
- Examined sequences from dentist, several HIV+ patients, and local controls:

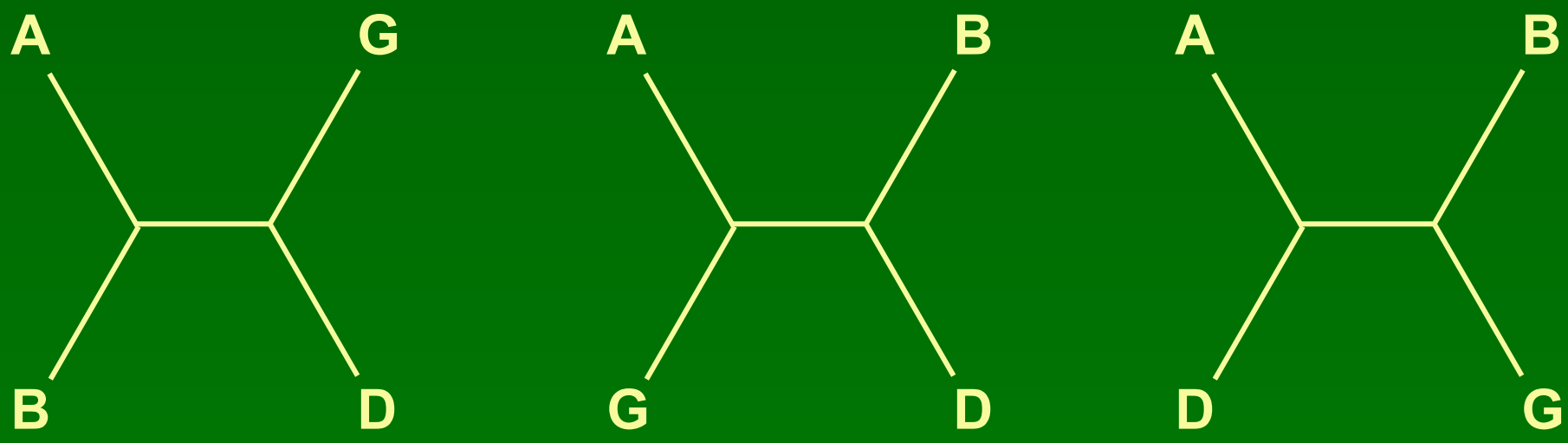
Interpretation? Significance?



Split Decomposition:
Evaluate Evidence for Internal Branches

```
Alpha     AAGAAGCAGGGGCTGGAGATGAAGGCCCATG
Beta      AAGAAGCGGAGGCTGGAGCTGAAGGCCCATG
Gamma     AAGAAGCGGAGGGTGGAGCTGAAGGCCCACG
Delta     GAGAAGAGGAGCCTGGAGCTGAAGGCCCACA
```

Three possible unrooted trees:

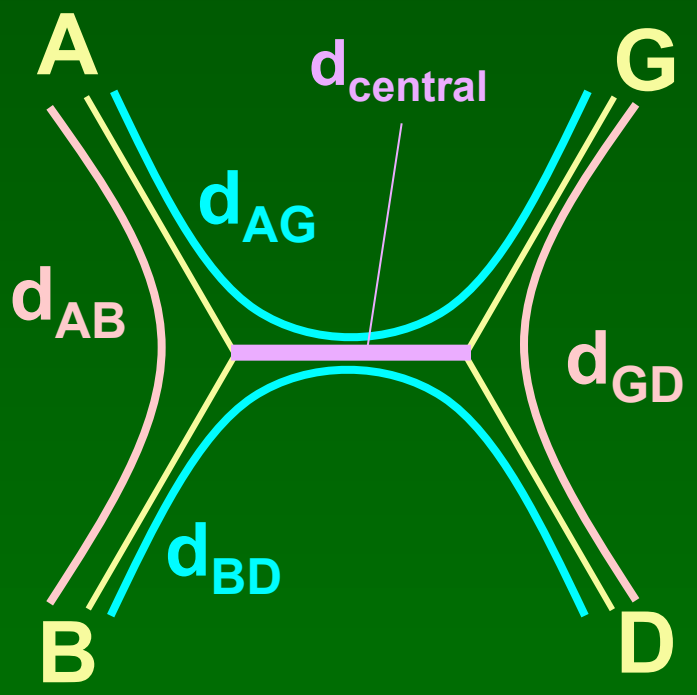


```
Alpha     AAGAAGCAGGGGCTGGAGATGAAGGCCCATG
Beta      AAGAAGCGGAGGCTGGAGCTGAAGGCCCATG
Gamma     AAGAAGCGGAGGGTGGAGCTGAAGGCCCACG
Delta     GAGAAGAGGAGCCTGGAGCTGAAGGCCCACA
```

d_{AB}

d_{GD}

How can we calculate the length of the central branch?



$$d_{central} = \frac{d_{AG} + d_{BD} - (d_{AB} + d_{GD})}{2}$$

ONLY for the *correct* tree!!!

2. SplitDecomp

Distance matrix

		A	B	C	D
		Dentist	Patient E	Local control 3	Local control 22
A)	Dentist		14	43	40
B)	Patient E			43	37
C)	Local control 3				44
D)	Local control 22				

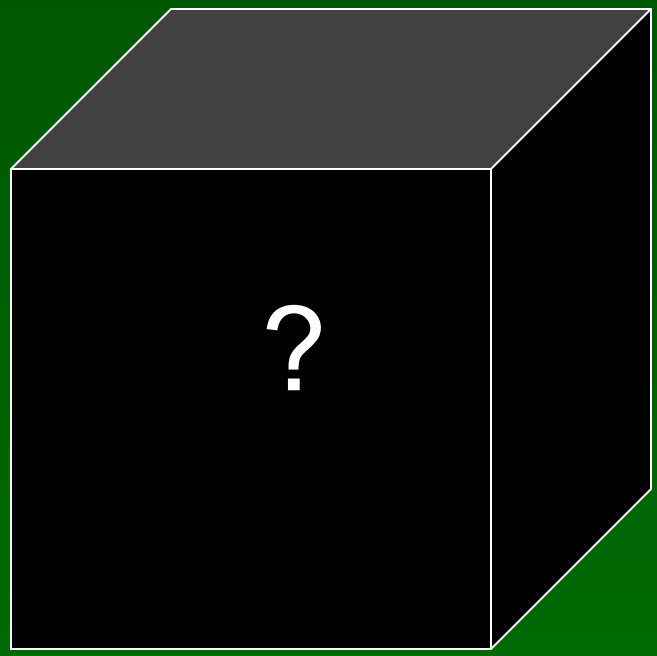
Split decomposition

Putative tree	Split index 1	Split index 2	Four-point condition	
((A,B), (C,D))	11	12.5	58	$=d_{AB} + d_{CD}$
((A,C), (B,D))	-11	1.5	80	$=d_{AC} + d_{BD}$
((A,D), (B,C))	-12.5	-1.5	83	$=d_{AD} + d_{BC}$

3. The Black-Box Approach

a. Students use prebuilt software tools to investigate open-ended biological questions.

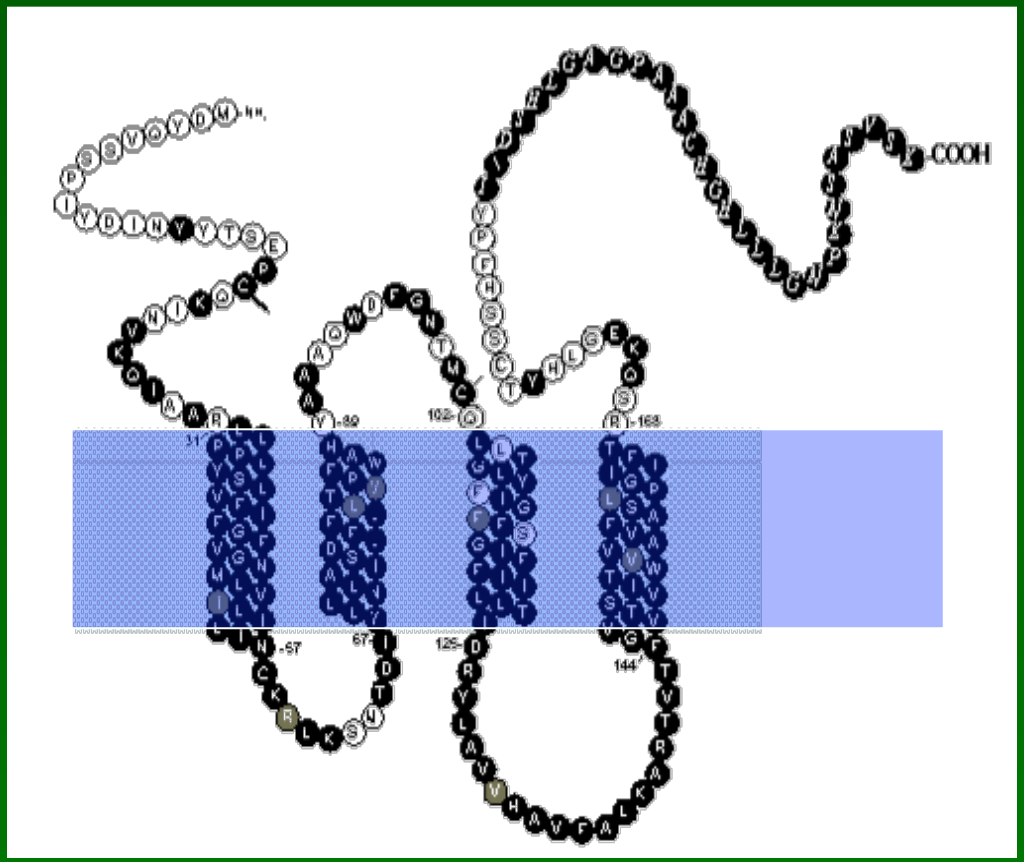
b. This may involve determining model's sensitivity to specific parameters, analyzing range of variation in stochastic models, etc.

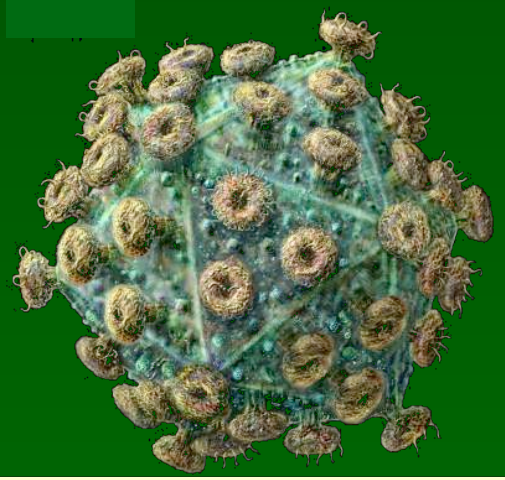


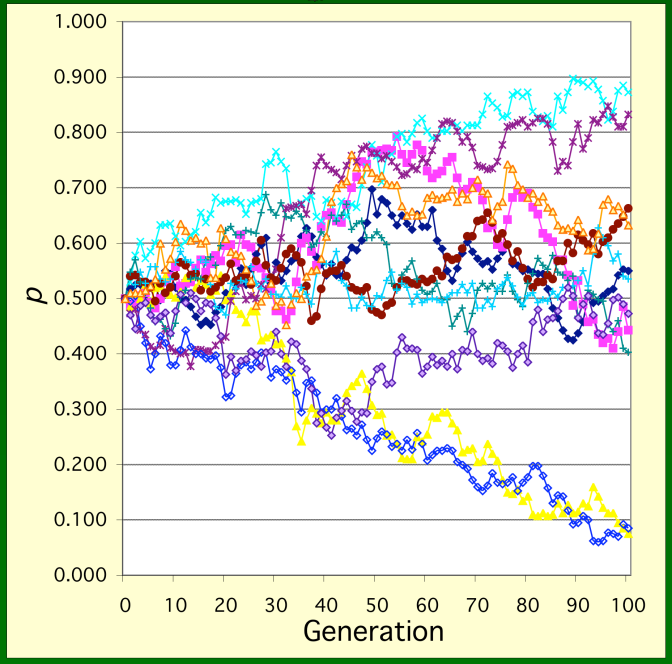
Examples: *3D FractaL-Tree, Deme, javaBenzer, Michaelis-Menten Enzyme Kinetics*

The Case of the Protective Protein

(under review at *Evolution Education & Outreach* as of 8/3/2009)

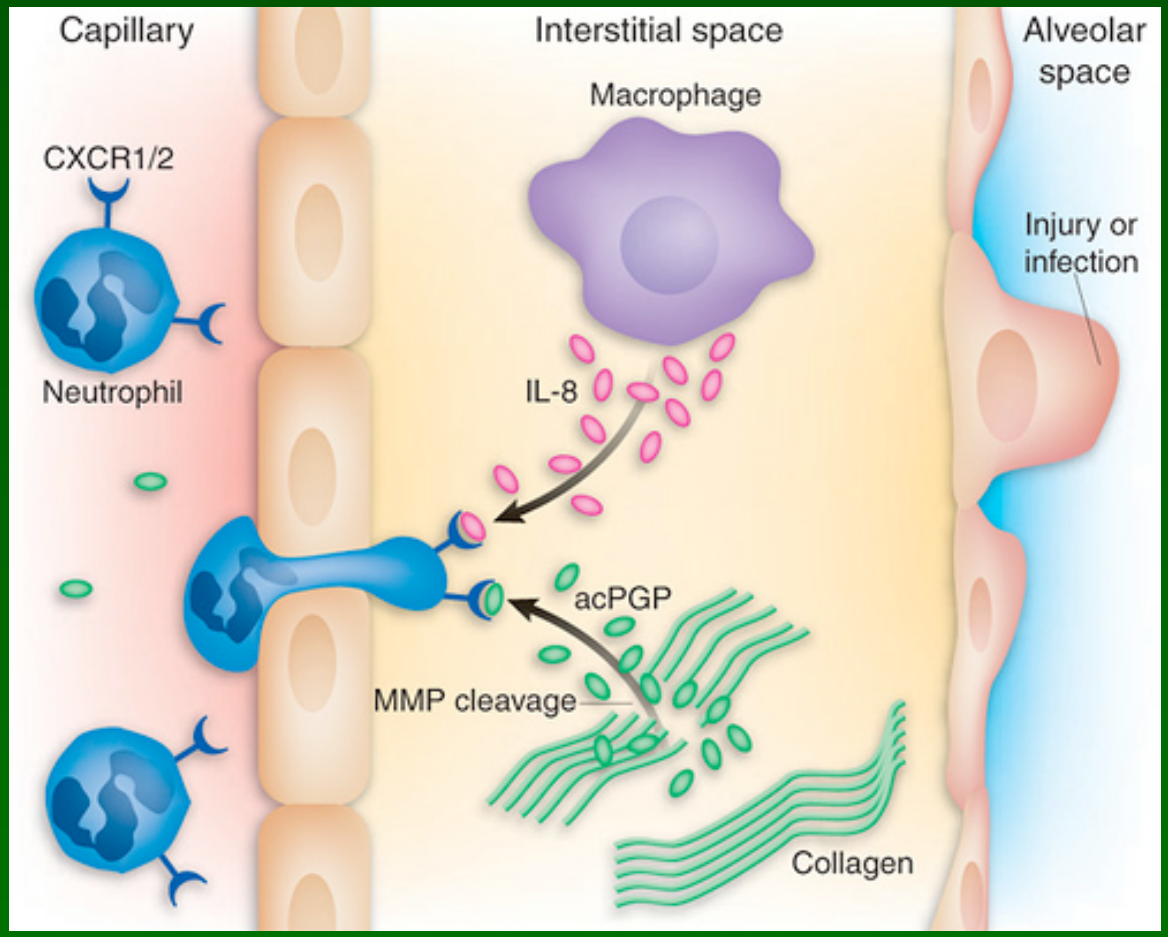






Chemokines

- A family of small proteins secreted by cells to control migration of nearby cells (e.g. during tissue development or immune response)

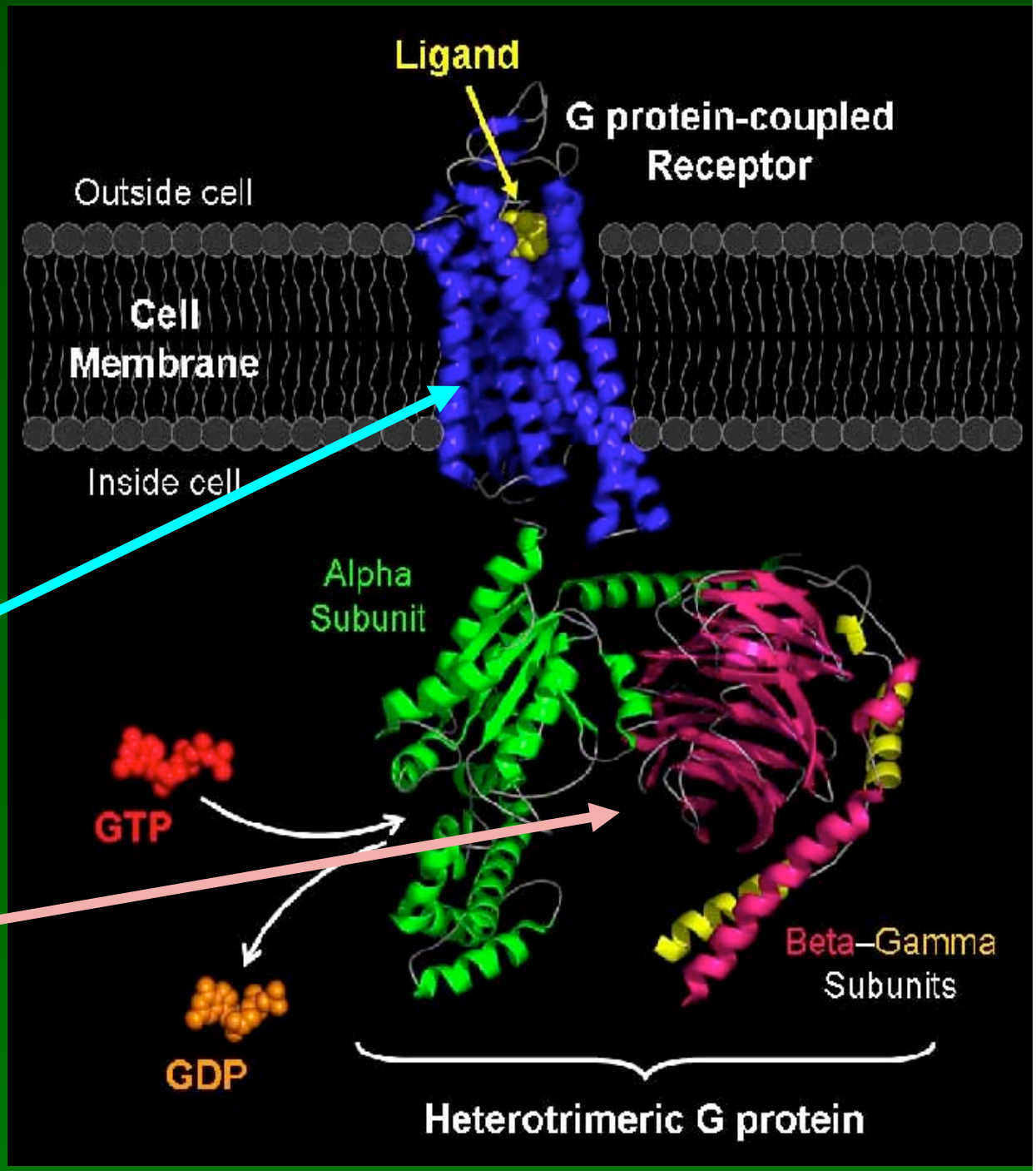


- At least 47 different chemokines known: vary in specific function.

Chemokine Receptors

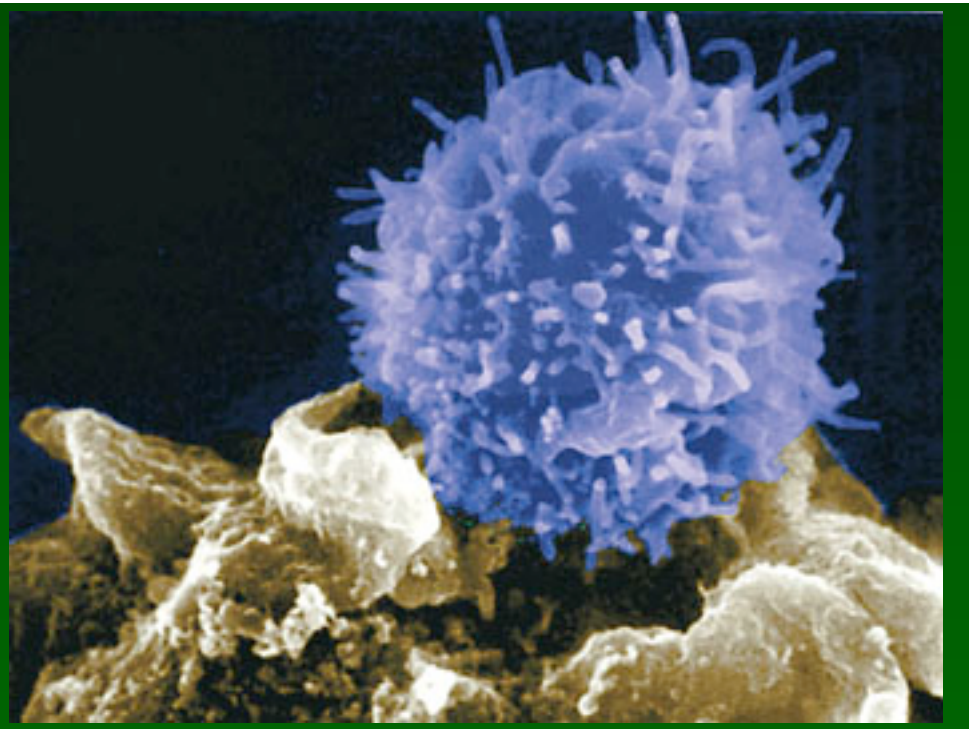
All known chemokine receptors share the same basic structure:

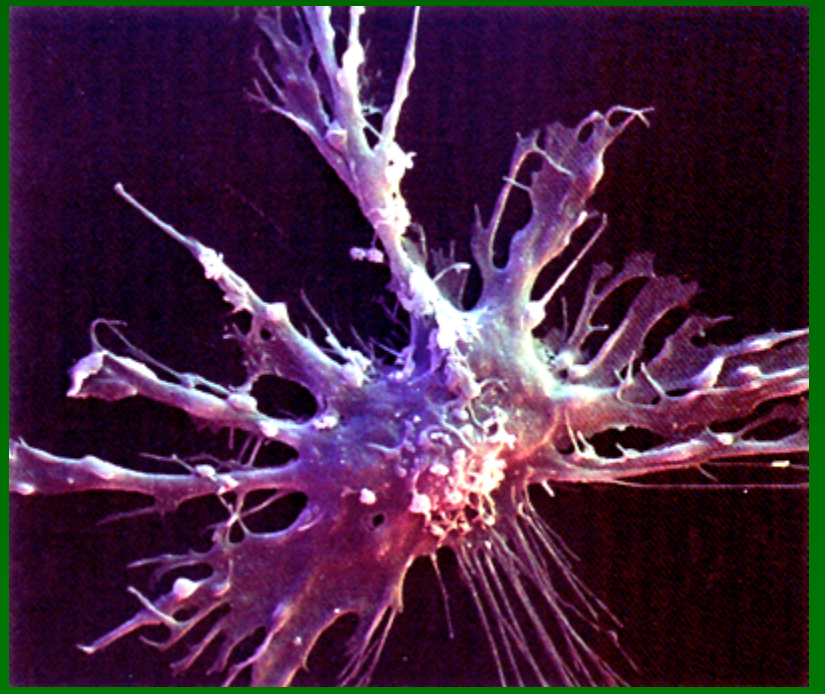
- 7 helices that span plasma membrane
- Signal transduction via a cytoplasmic G protein



CCR5

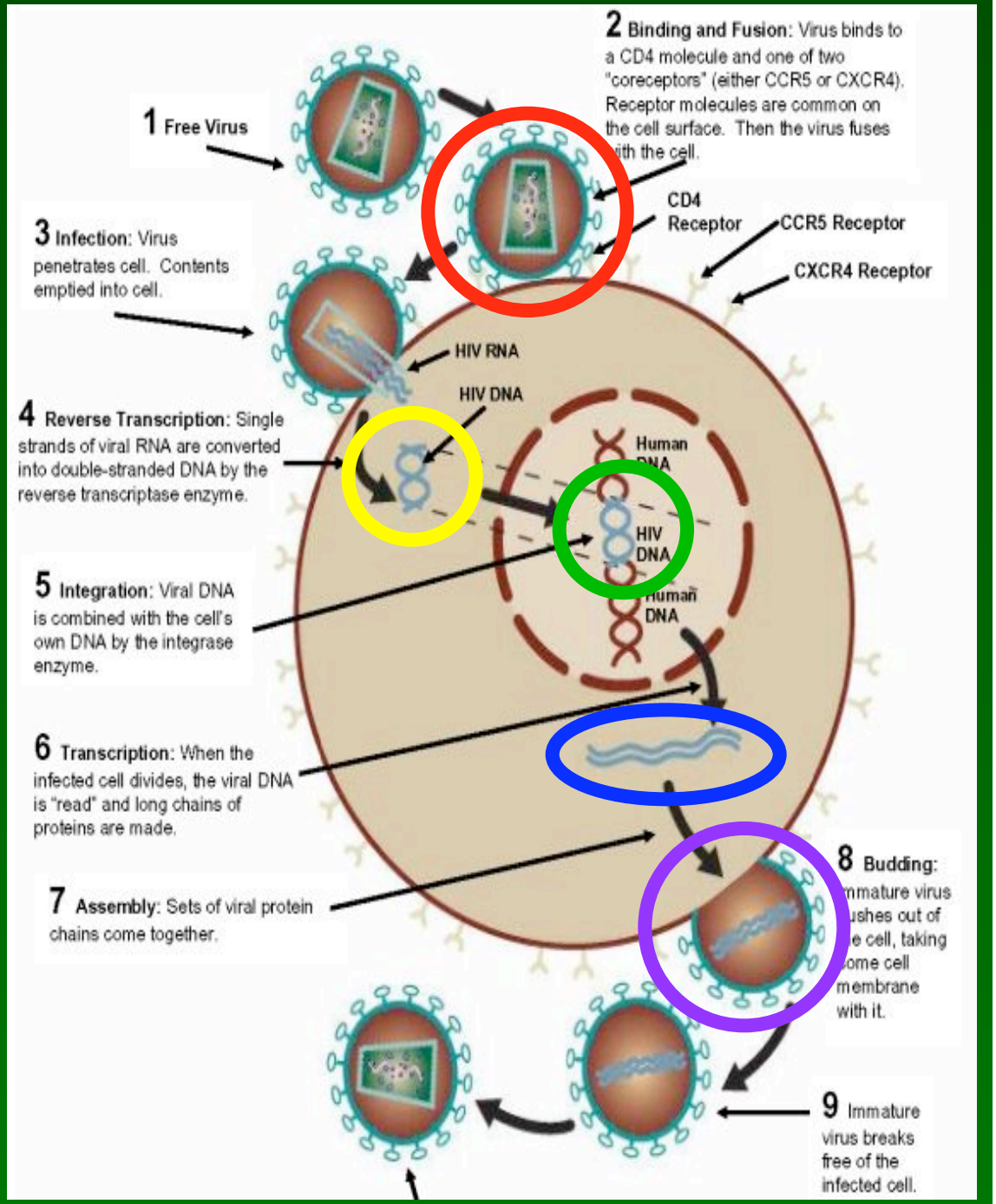
- Expressed on many immune cells: T cells, macrophages, and dendritic cells.
- Exact function unclear: no apparent effect detected in individuals without functional copies
- **Used by HIV as co-receptor for binding to and entry into host cells!**





Life Cycle of HIV

1. Virus docks with receptors on host cell (CD4 + co-receptor)
2. Reverse transcription: viral RNA → DNA
3. Viral DNA inserts into host's DNA
4. Viral RNA transcribed & proteins assembled
5. New virions bud from host cell, killing it



CCR5Δ32

- Allele of CCR5 gene, first described in 1996.

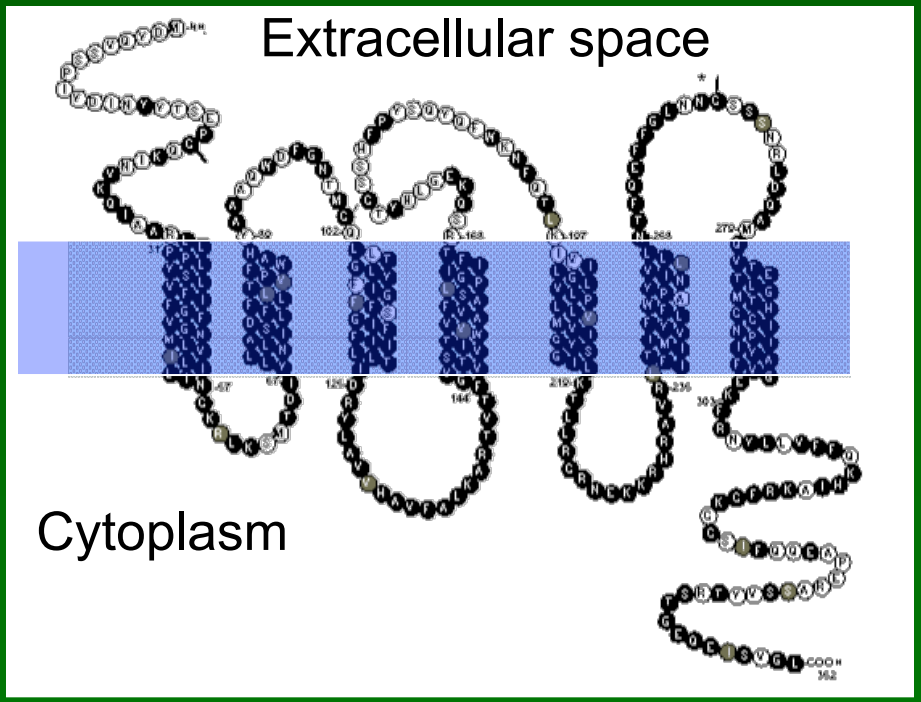
***CCR5*+ allele (wild-type)**

5′..TTT CCA TAC AGT CAG TAT CAA TTC TGG AAG AAT TTC
CAG ACA TTA AAG ATA GTC ATC TTG GGG CTG GTC CTG... 3′

Protein:
FPYSQYQFWKNFQTLKIVILGLVLPLLVMVICYSGILKTLLRCRNEKKR...

Normal CCR5 protein:

- 7 transmembrane helices
- Ligand-binding extracellular domain
- G-protein-binding cytoplasmic domain



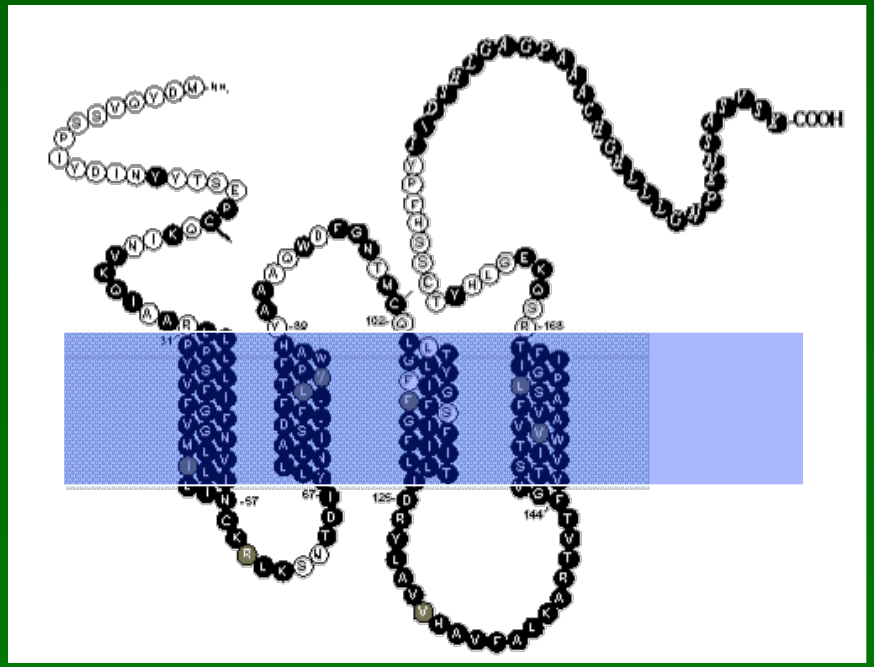
CCR5Δ32

- *Δ32* allele has a deletion of 32 bp, causing a frameshift and premature termination of the protein.

***CCR5Δ32* allele (mutant)**

5′..TTT CCA TAC AGTCAGTATCAATTCTGGAAGAATTTCCAGACATT
AAA GAT AGT CAT CTT GGG GCT GGT CCT GCC GCT GCT... 3′

Protein:
FPYIKDSHLGAGPAAACHGHLLLGNPKNSASVSK*



Mutant protein:

- Only 4 transmembrane helices
- No G-protein-binding cytoplasmic domain
- Nonfunctional both as a chemokine receptor and as an HIV-coreceptor

CCR5Δ32 and HIV

CCR5 genotype dramatically affects both risk of contracting HIV and course of the infection.

CCR5 Genotype	Risk of Contracting HIV	Mean Time to Onset of AIDS Symptoms
+ / +	standard	~ 10 years
+ / *Δ32*	standard?	12 – 13 years
Δ32 / *Δ32*	virtually zero	unknown

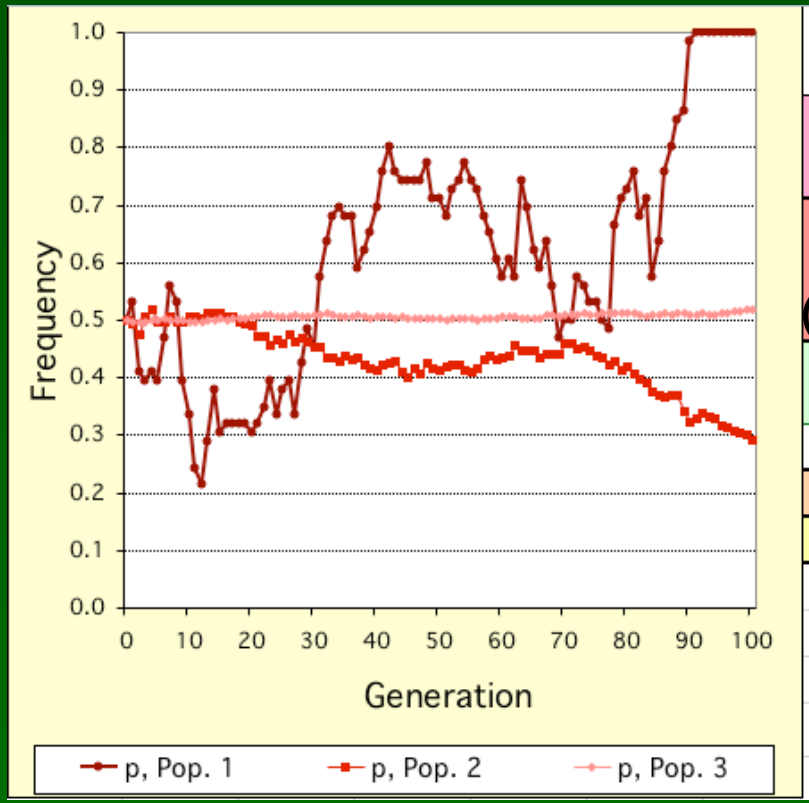
Hypothesis 1:
Δ32 is neutral.

- Initial estimates based on linkage disequilibrium:
  Δ32 arose ~700 years ago (28 generations).

Stephens *et al.* (1998). *Amer. J. Hum. Gen.* 62: 1507–15

Is it plausible that a new neutral mutation could reach 10% frequency in only 28 generations?

ESTEEM Module: *Deme*

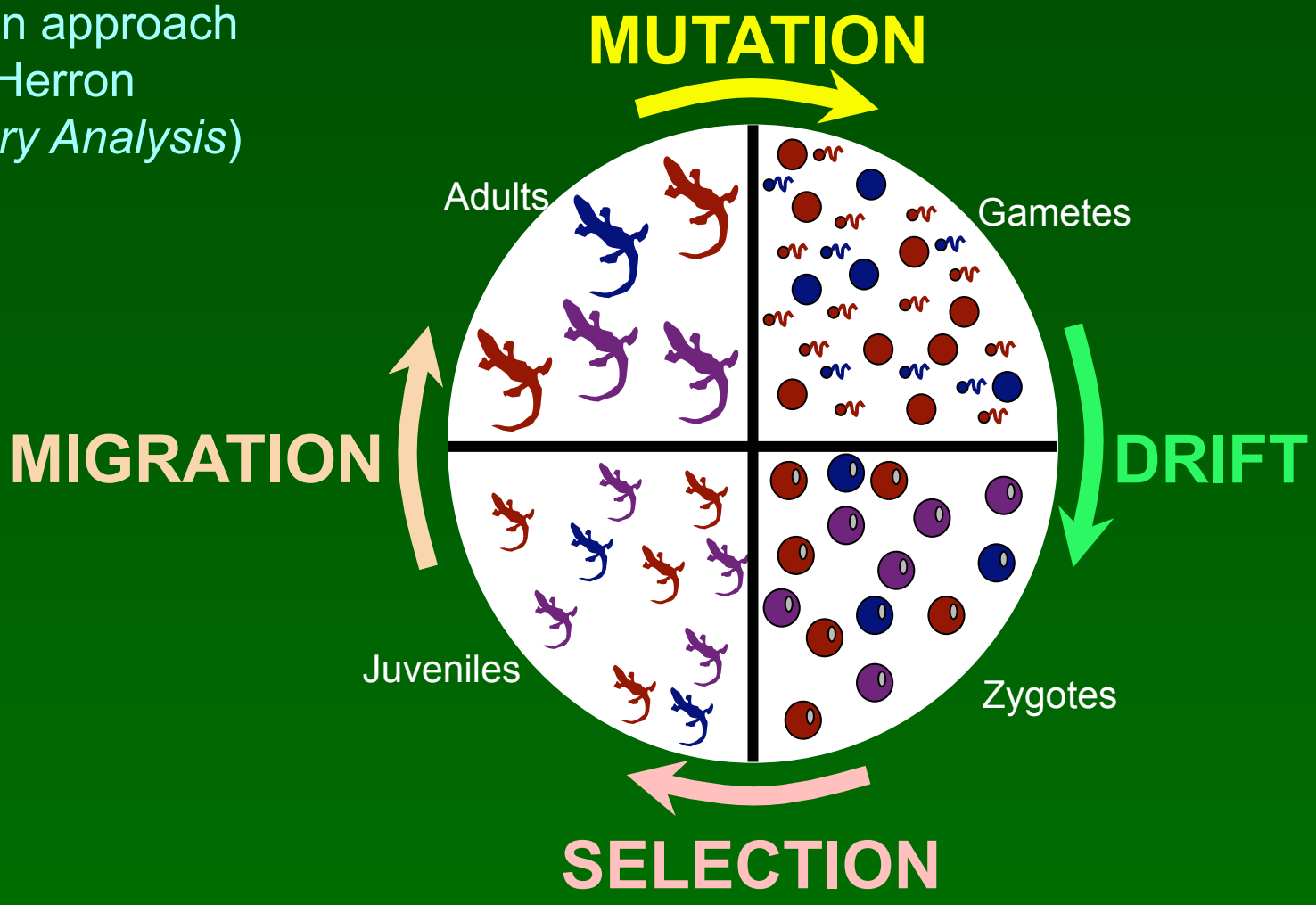


		Pop. 1	Pop. 2	Pop. 3
Starting conditions	p_0	0.500	0.500	0.500
	q_0	*0.500*	*0.500*	*0.500*
Selection (Fitness)	W_{AA}	0.990	0.990	0.990
	W_{AB}	1.000	1.000	1.000
	W_{BB}	0.990	0.990	0.990
Drift (On / Off)	N	33	1,000	30,000
Migration	m	0.00		
Mutation	μ	1.00E-06		

Plot Variables
- [x] p
- [ ] H
- [ ] Mean fitness
- [ ] N

- Models evolution of up to 3 pops. simultaneously
- User controls four evol. forces:
  1. Selection
  2. Drift (Pop. size)
  3. Migration
  4. Mutation

Following an approach used by J. Herron (*Evolutionary Analysis*)



- Each generation, *Deme* steps through the life cycle
- Solves for genotype/allele frequencies at each step using standard equations from population genetics

Hypothesis 1:
Δ32 is neutral.

Procedure (Prospective Model)

- Set N_e = 5000 (following Stephens *et al.*)
- Set $p_0 = 1 / 2N_e$ (one copy of Δ32)
- Set $W_{\Delta\Delta} = W_{+\Delta} = W_{++} = 1$ (neutrality)
- Calculate time to reach $p = 0.10$

What do you predict will happen to the frequency of Δ32 over time?

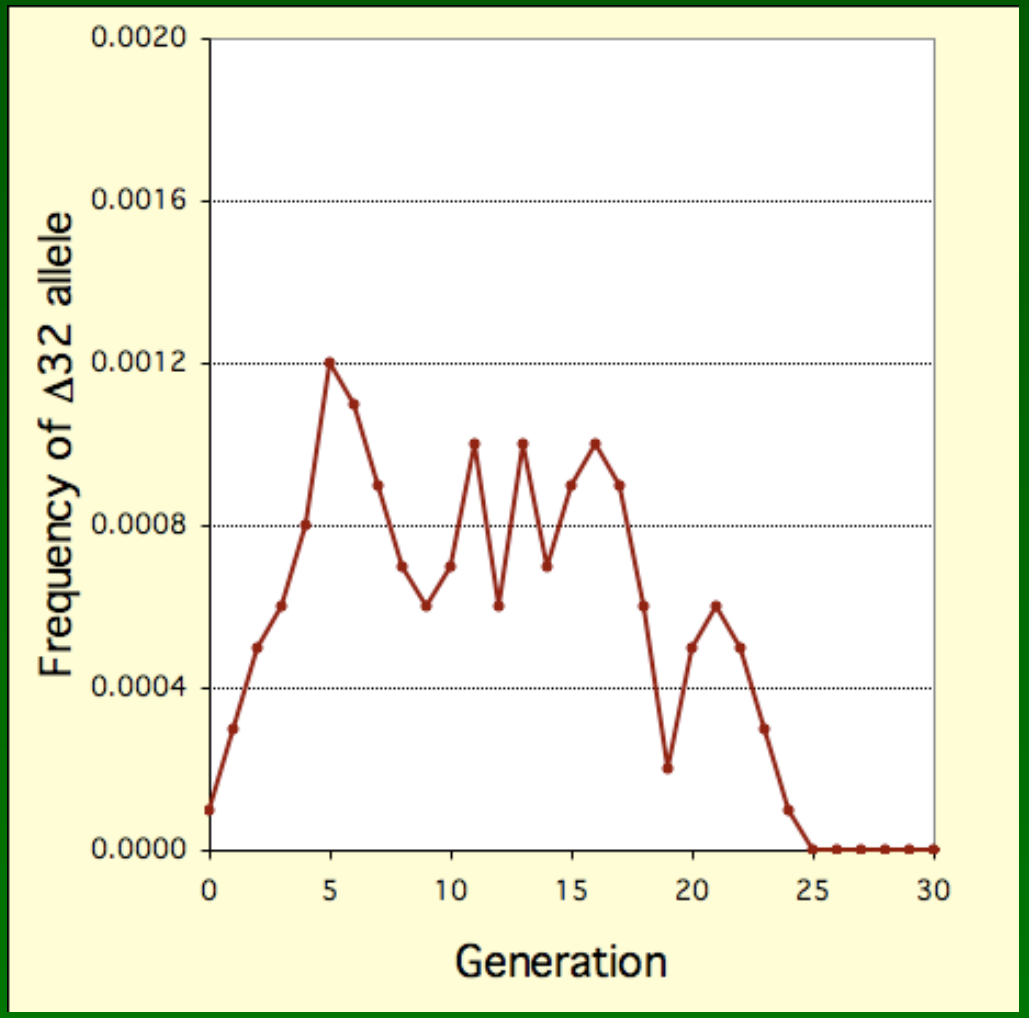
Hypothesis 1:
Δ32 is neutral.

Problem:

- In ~99% of trials, Δ32 is lost before reaching $p = 0.10$ — why?

- Our question: ***given*** that Δ32 ***does*** eventually reach $p = 0.10$, how long does that process take?

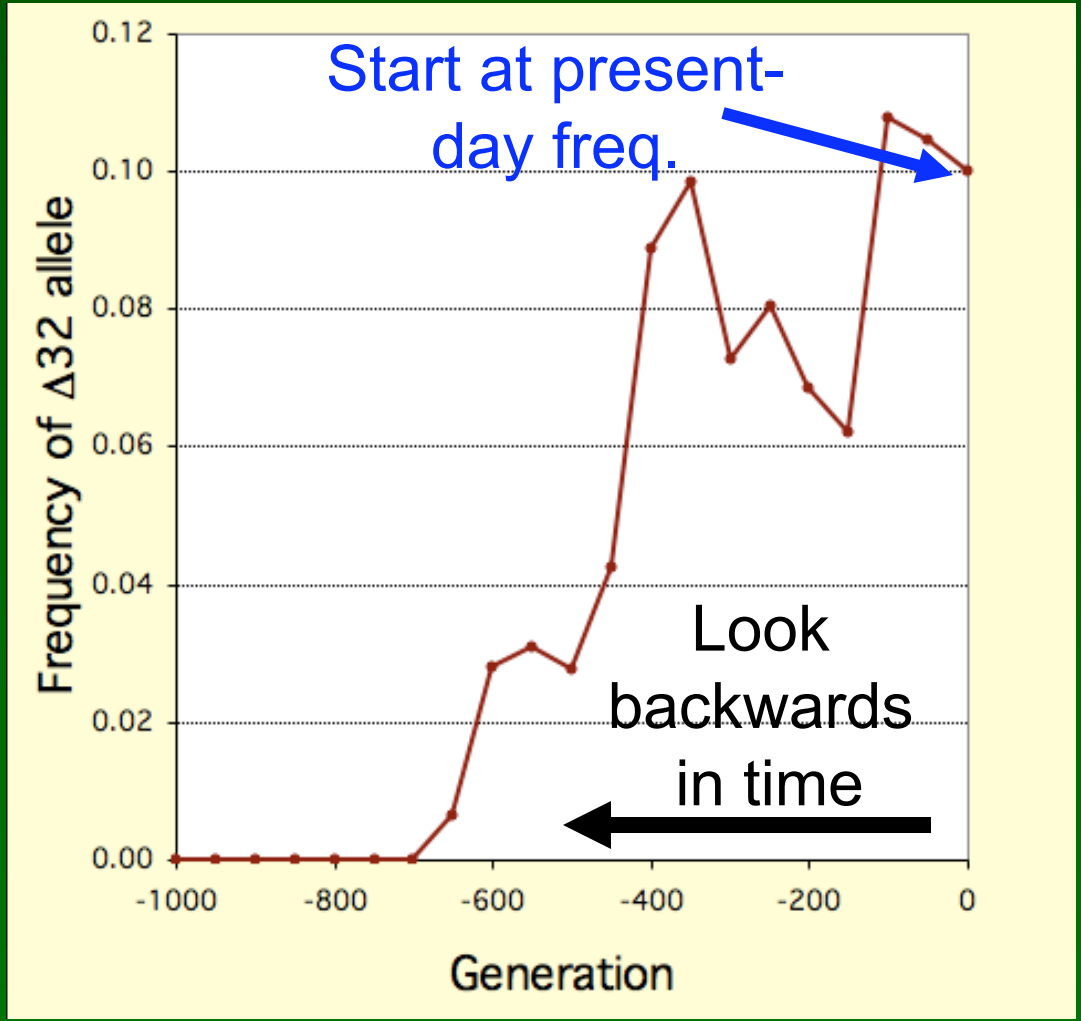
- Either run 100 trials to get 1 usable result, or reframe the problem.



Hypothesis 1:
Δ32 is neutral.

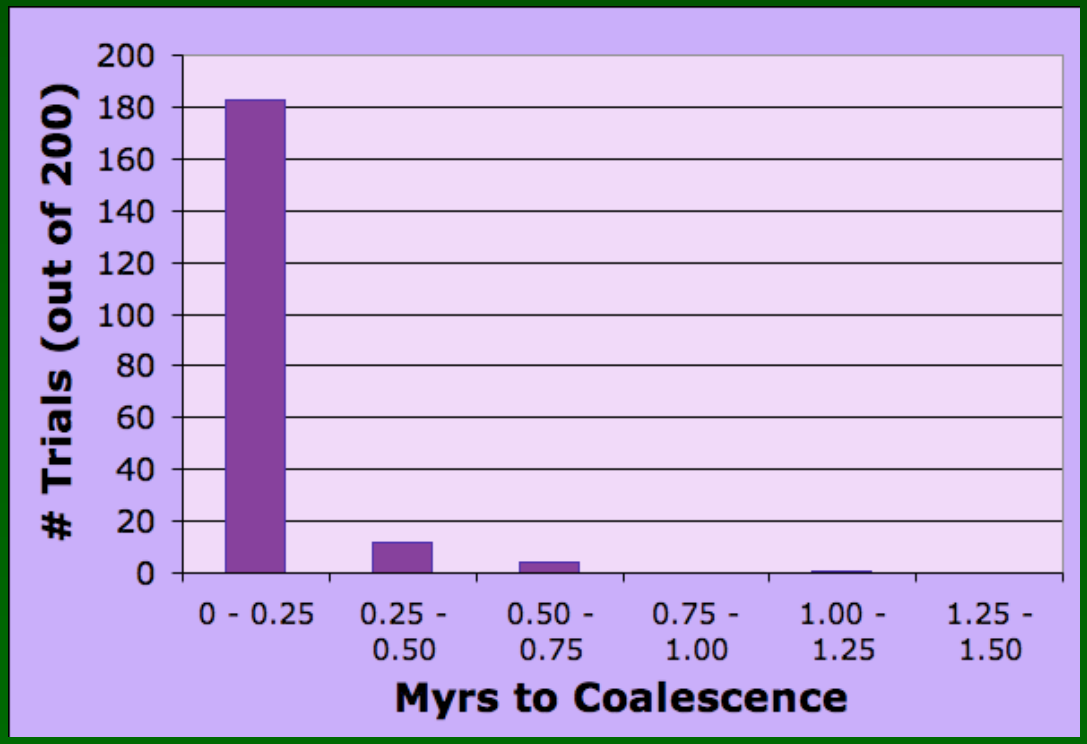
Procedure
(Coalescent model)

- Set p_0 = 0.10 (observed frequency)
- ***Invert*** the standard pop. gen. equations
- Calculate time to reach p = 0



Hypothesis 1: Δ32 is neutral.

Mean	103,794 y
Std. Dev.	137,879 y



Estimated age based on LD : 700 y

95% CI under neutrality : 11,725 – 421,100 y

Assuming LD estimate is accurate, ***reject*** hypoth. of neutrality.

Hypothesis 2:
Historical selective advantage for Δ32.

Assume $W_{\Delta\Delta} = 1$; $W_{+\Delta} = 1 - s/2$; $W_{++} = 1 - s$

(additive genetic effect)

Question:
What values of *s* are consistent
with reaching *p* = 0.10 in 700 y?

Hypothesis 2:

Historical selective advantage for Δ32.

s	Mean age (y)	Variance	95% CI
0.10	2457.4	688.3	~~1650 - 4400~~
0.20	1264.4	131.1	~~825 - 1975~~
0.25	1001.3	78.8	675 - 1500
0.30	817.1	49.3	550 - 1250
0.35	682.0	28.9	475 - 1000
0.40	573.1	27.0	400 - 850
0.45	491.1	17.0	350 - 750
0.50	417.4	11.3	~~300 - 600~~

Hypothesis 2:
Historical selective advantage for Δ32.

What would *s* = 0.25 - 0.45
mean in the real world?

What could cause this intensity of selection in
Caucasians over the past 700 years?

Is CCR5Δ32 a genetic legacy of epidemics past?

"…the cumulative results point to a selective sweep and to one with enormous selective mortality within historic times, perhaps mediated by a widespread epidemic."

"The bubonic plague, which claimed the lives of 25%–33% of Europeans during the Black Death…and which has had multiple outbreaks before and since, is an obvious candidate… If the mechanism of *Yersinia*-induced macrophage apoptosis involved macrophage chemokine receptor 5, the CCR5-Δ32 mutation would be an attractive candidate for a strong selective pressure 600–700 years ago."

—Stephens *et al.*, 1998

Take-home message for students

- "Stochastic" ≠ "totally random"!
  We can still narrow the probable outcomes
  or likely parameter values to some range.

- Even fairly simple mathematical models
  can help us investigate important
  (and cool!) questions in biology.

- All scientific conclusions are provisional.
  New genetic maps of Δ32: ~5000 yrs. old.
  Redo analysis: consistent with drift alone!