

A grayscale microscopic image showing numerous spherical cells, some of which are connected by thin, thread-like structures. The cells vary in size and are distributed across the left side of the frame.

# ***Variability of an artificial tandem repeat***

Ted Pak  
HURS 2007

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Ted Pak  
HURS 2007

# *Tandem Repeats*

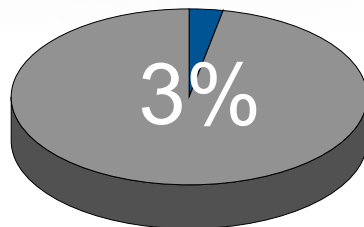
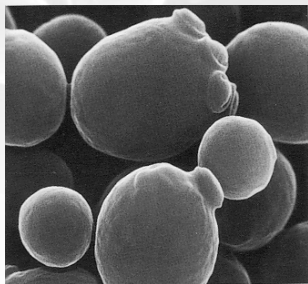
- ★ Consecutive iterations of short sequences of DNA
- ★ “Junk DNA”: Previously ignored by genomic researchers
- ★ Highly polymorphic: very prone to errors during DNA replication

...**A**CACACACAC...      ...**GCCTAG**CCCTAGCCCTAGCCCTA...

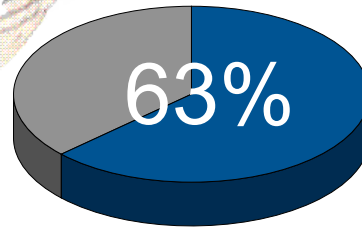
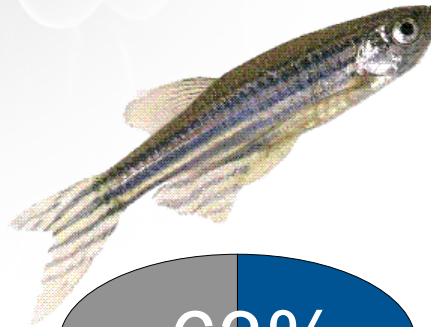


# *Abundance in genomes*

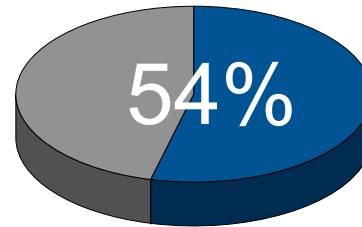
★ Tandem Repeats are very common in eukaryotic genomes!



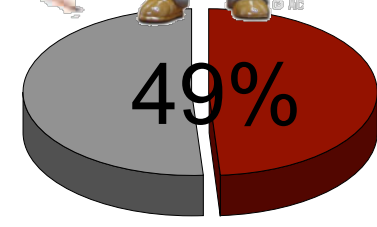
*S. cerevisiae*



*D. rerio*

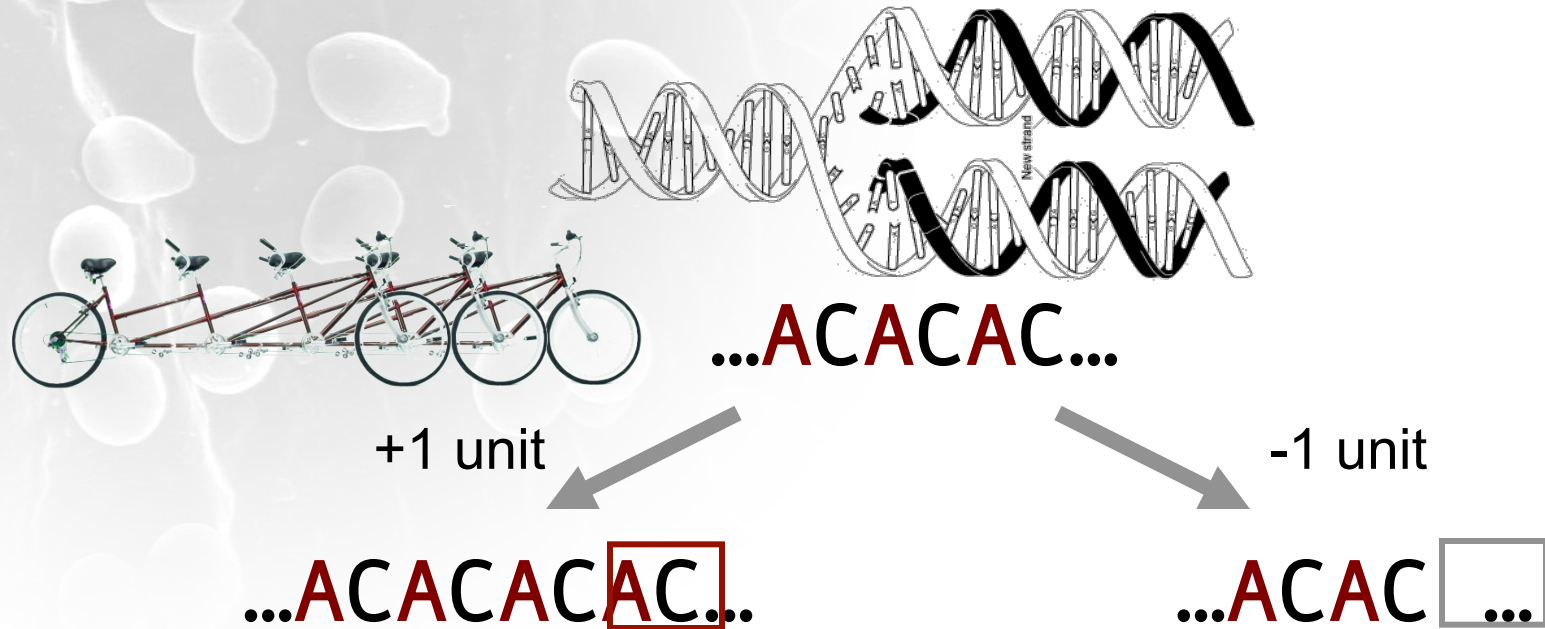


*M. musculus*



*H. sapiens*

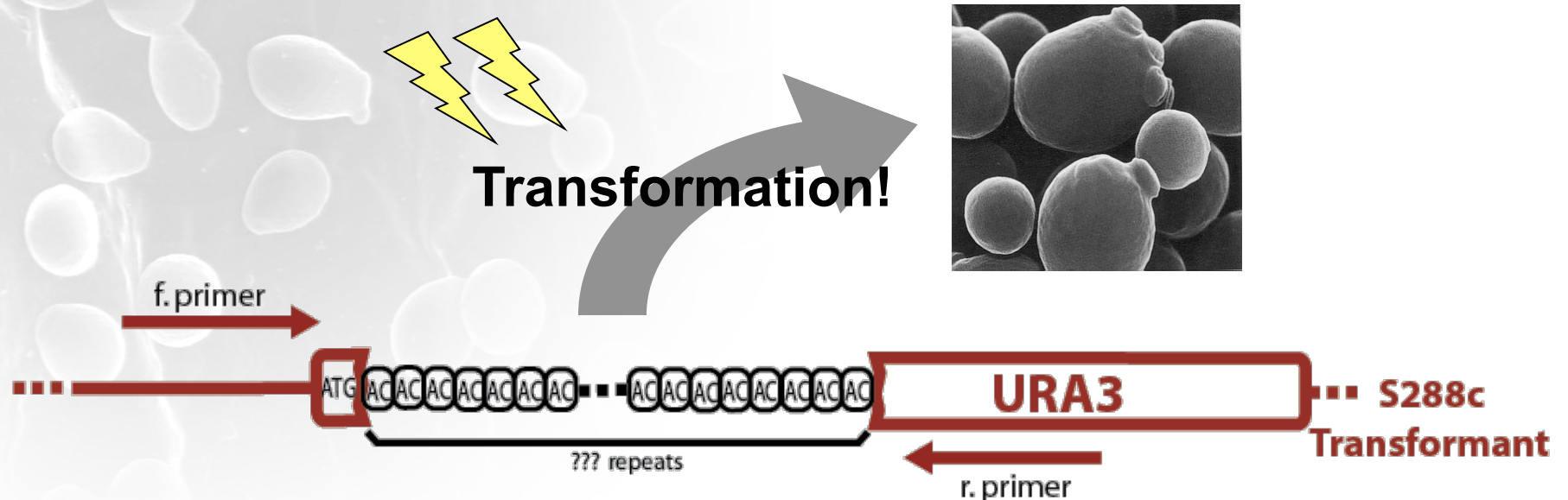
# *Highly polymorphic*



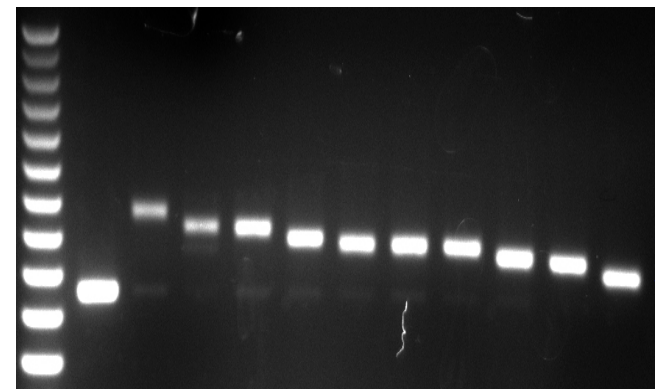
- ★ Occurs 100-1000 times more frequently than other DNA replication errors
- ★ Causes/mechanism for this is unknown.
- ★ Repeat expansion causes a number of human diseases.



# Artificial TR Construct

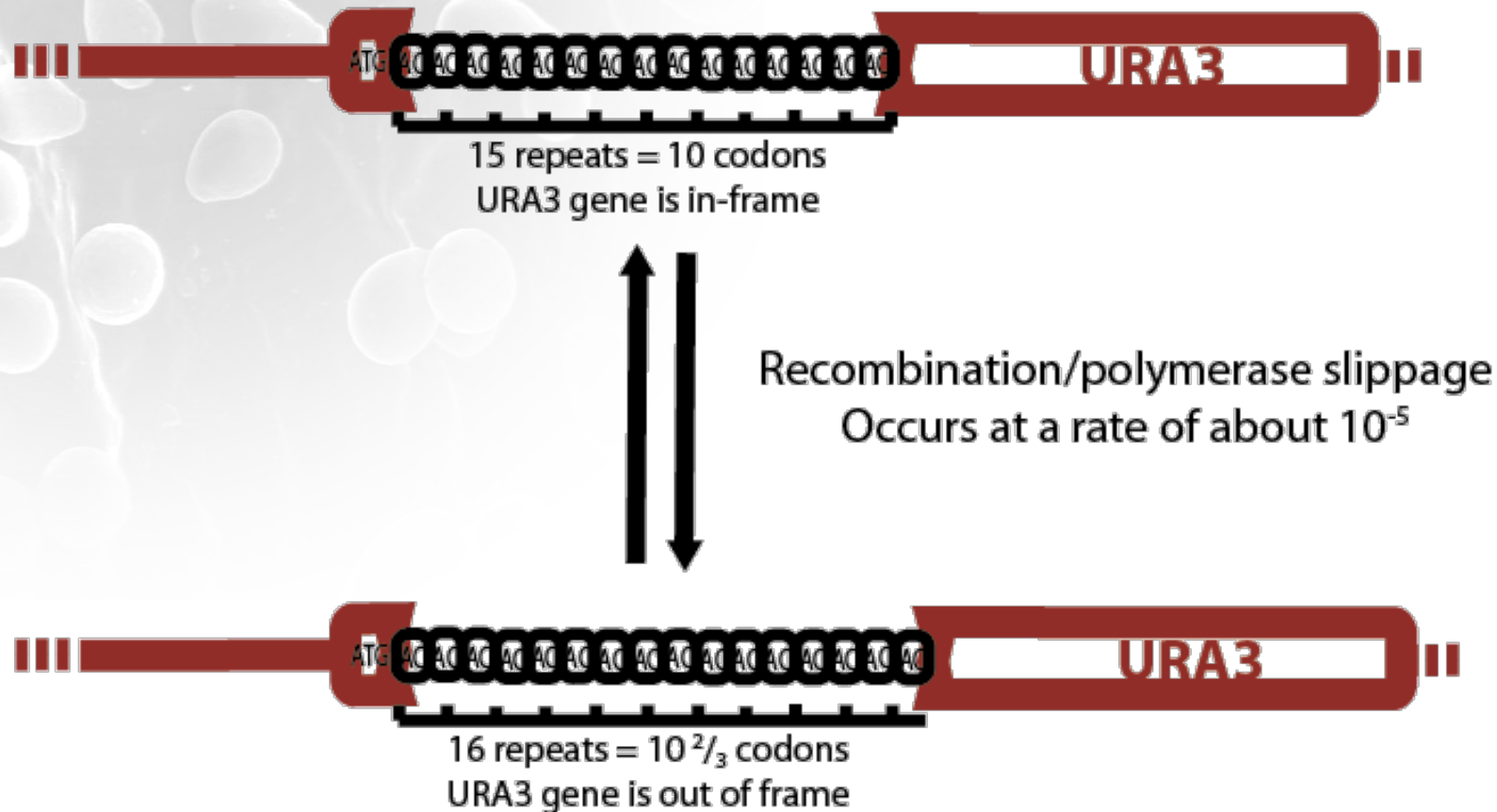


- ★ Artificial tandem repeat was inserted into a marker gene in *S. cerevisiae*

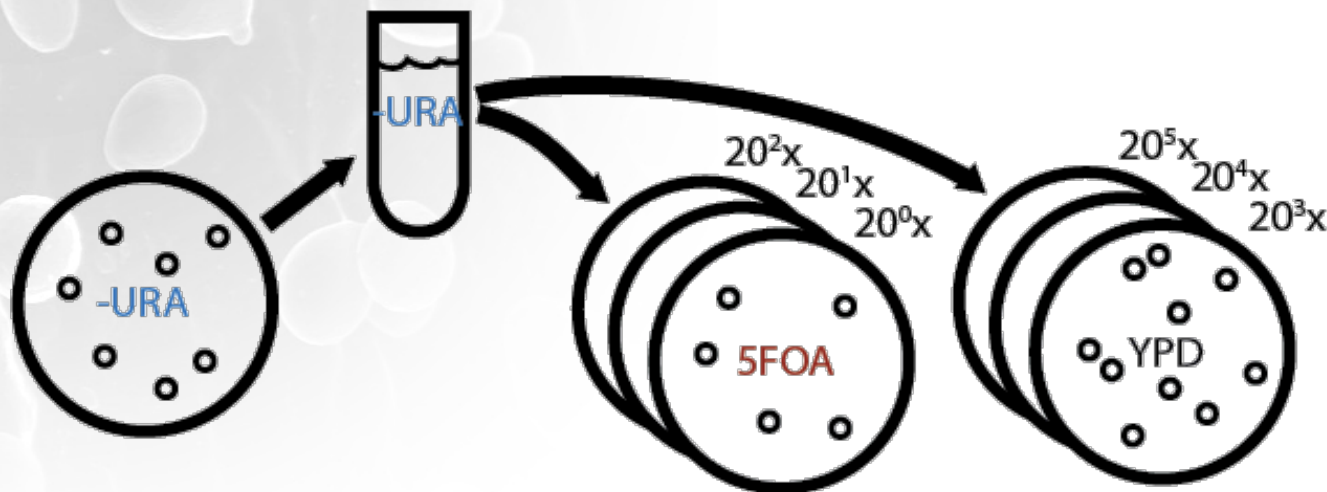




# Switching Mechanism



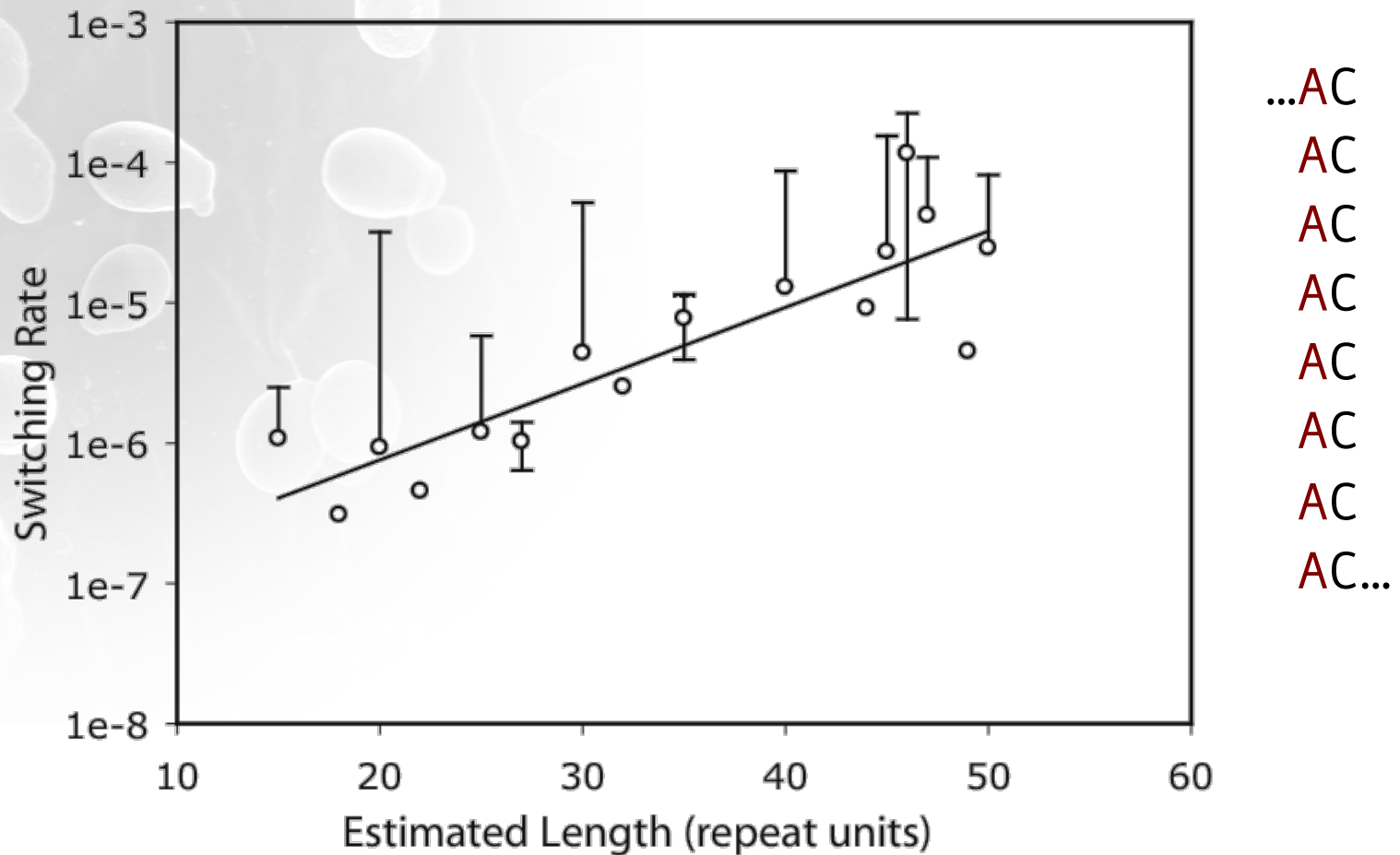
# *Measuring switching rate*



Grow cells in selective liquid medium, e.g., -URA

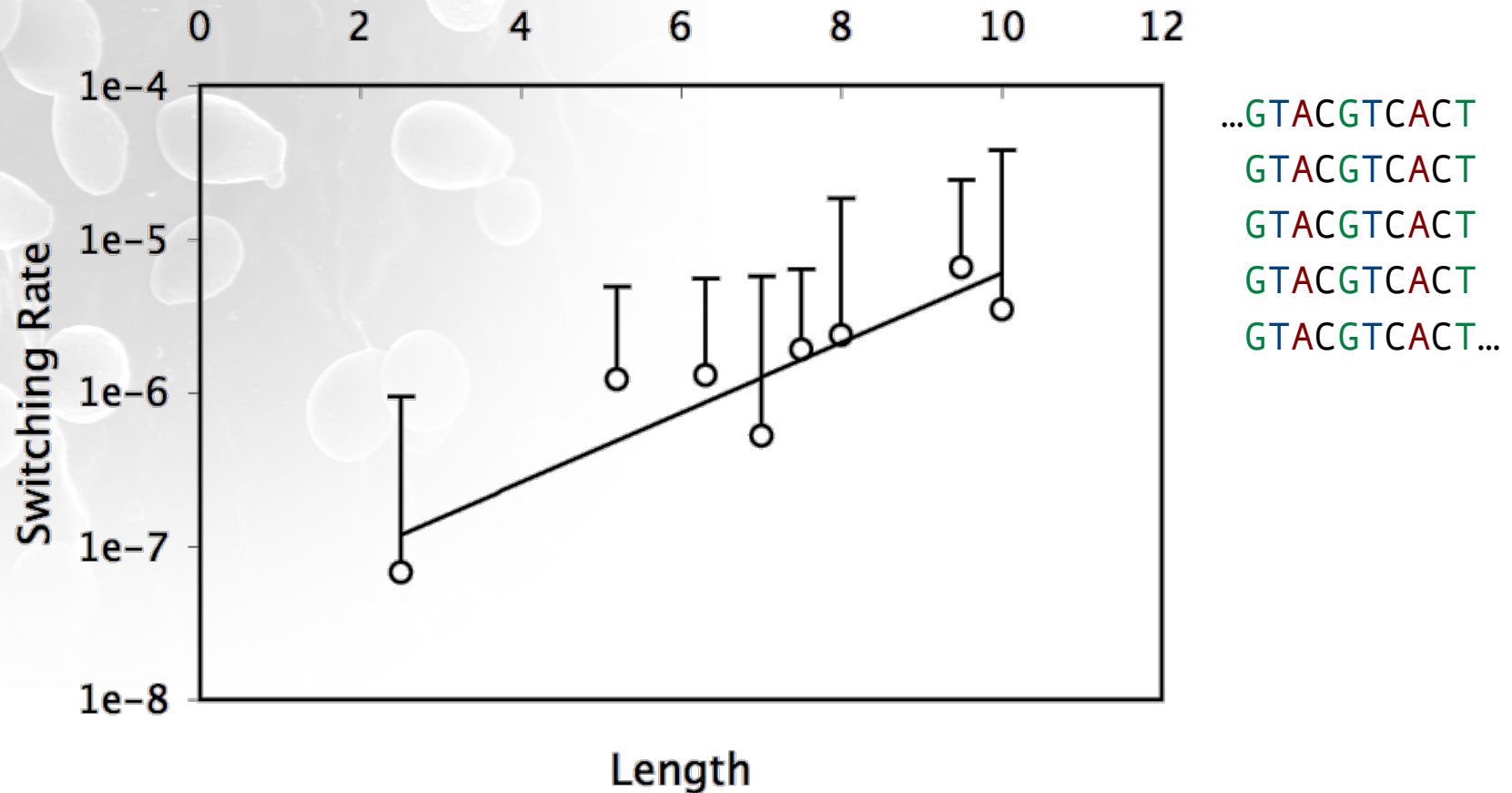
Plate dilution series on the opposite selective medium and YPD. By counting colonies, the fraction of cells that have switched out of frame can be determined.

*First switching data:  
Long AC dinucleotide repeats*



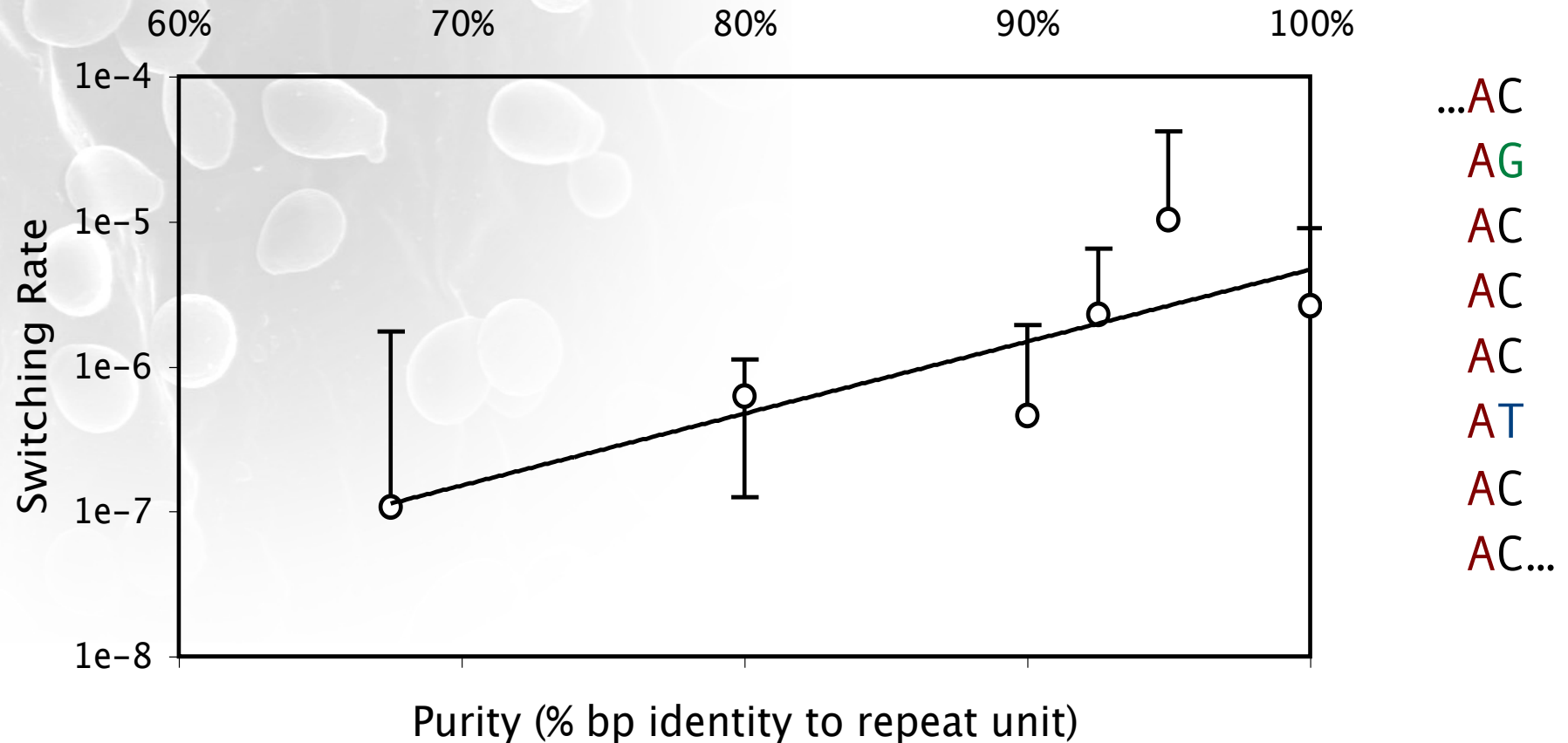
- ★ We first tried a basic AC dinucleotide repeat
- ★ Longer repeats change length faster!

## Confirming the trend: Long 10mer repeats



- ★ Same trend is observed with 10-mers

## *Other trends: Purity in AC dinucleotide repeats*



- ✦ Increasing purity of a dinucleotide tract increases its variability



## *Sequence properties alter variability*

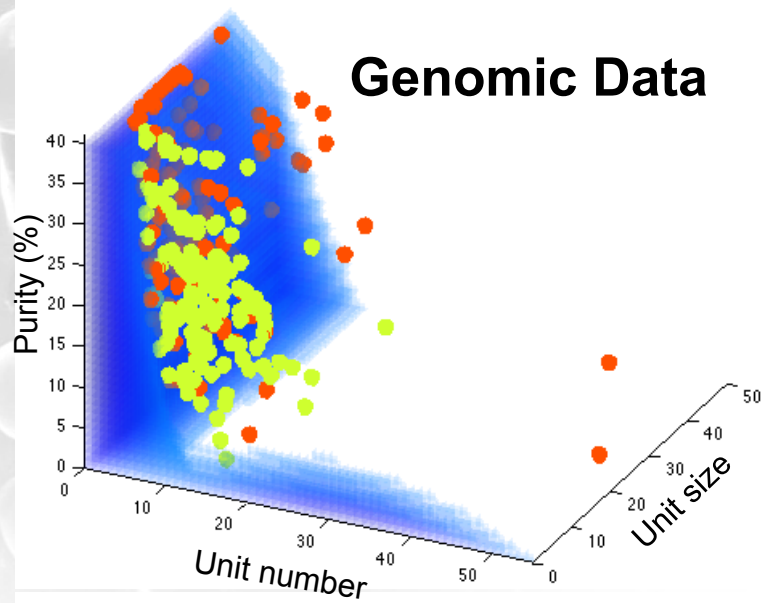
- ★ Several trends have been observed:
  - ★ More repeat units = ↑ variability
  - ★ Greater purity of repeat = ↑ variability
  - ★ Longer repeat units = ↑ variability

*so given the above...*

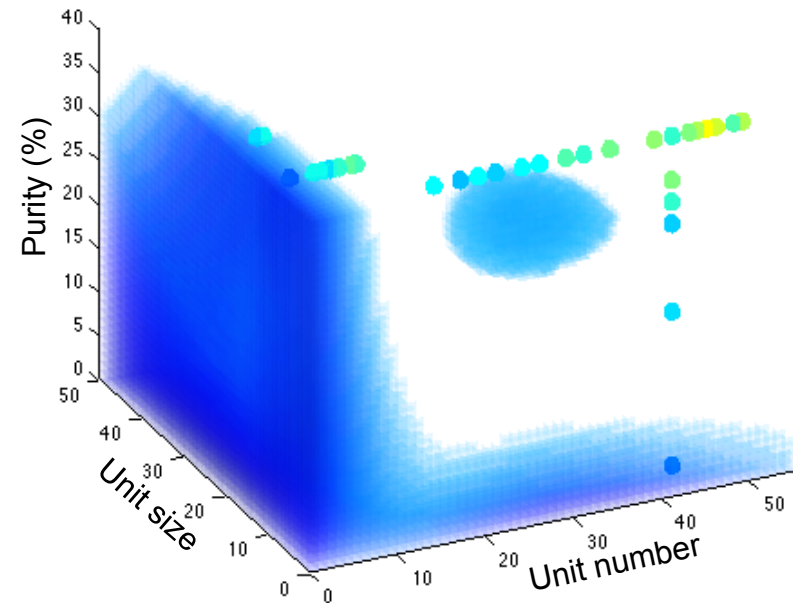
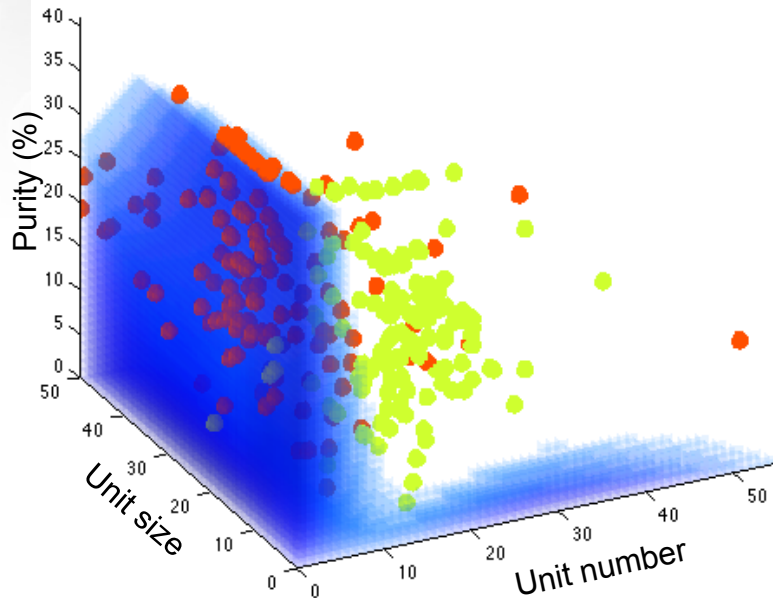
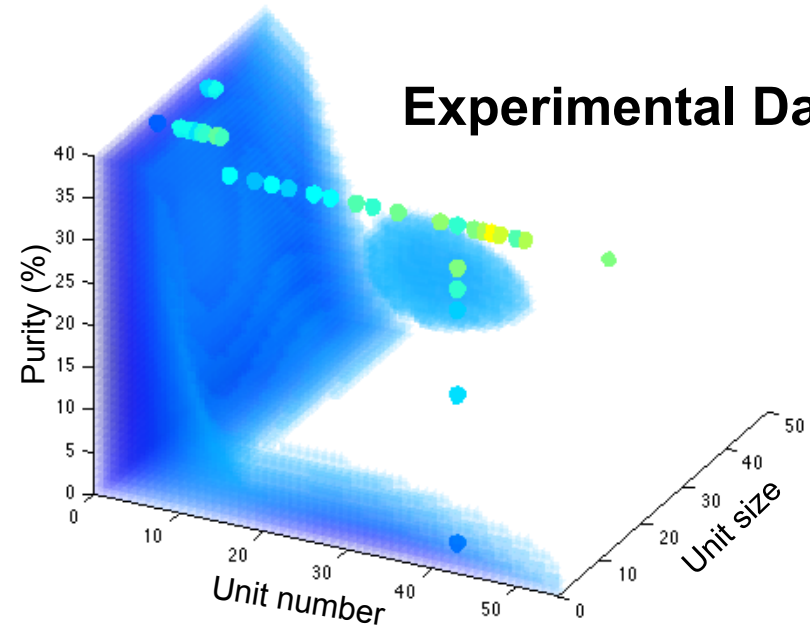
- ★ A model should be able to be constructed that predicts the variability of a repeat based on its DNA sequence.

# *Predictive Computational Model*

**Genomic Data**

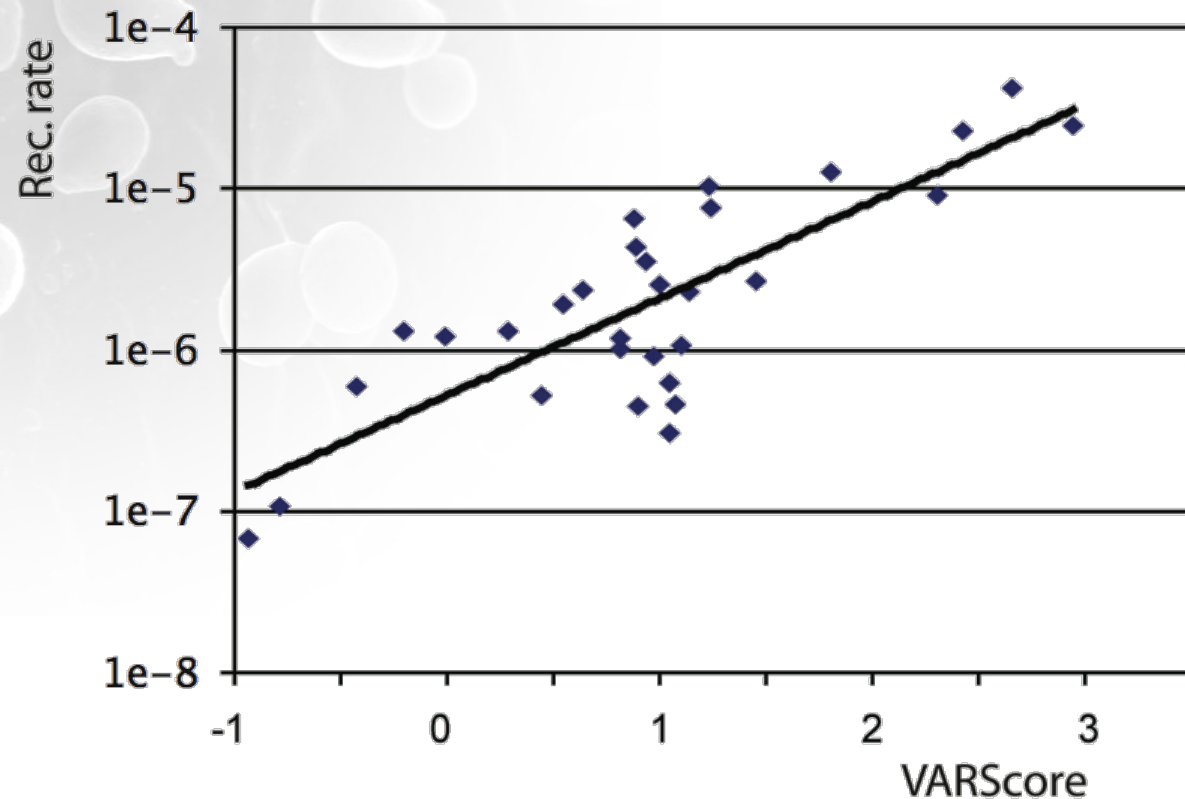


**Experimental Data**





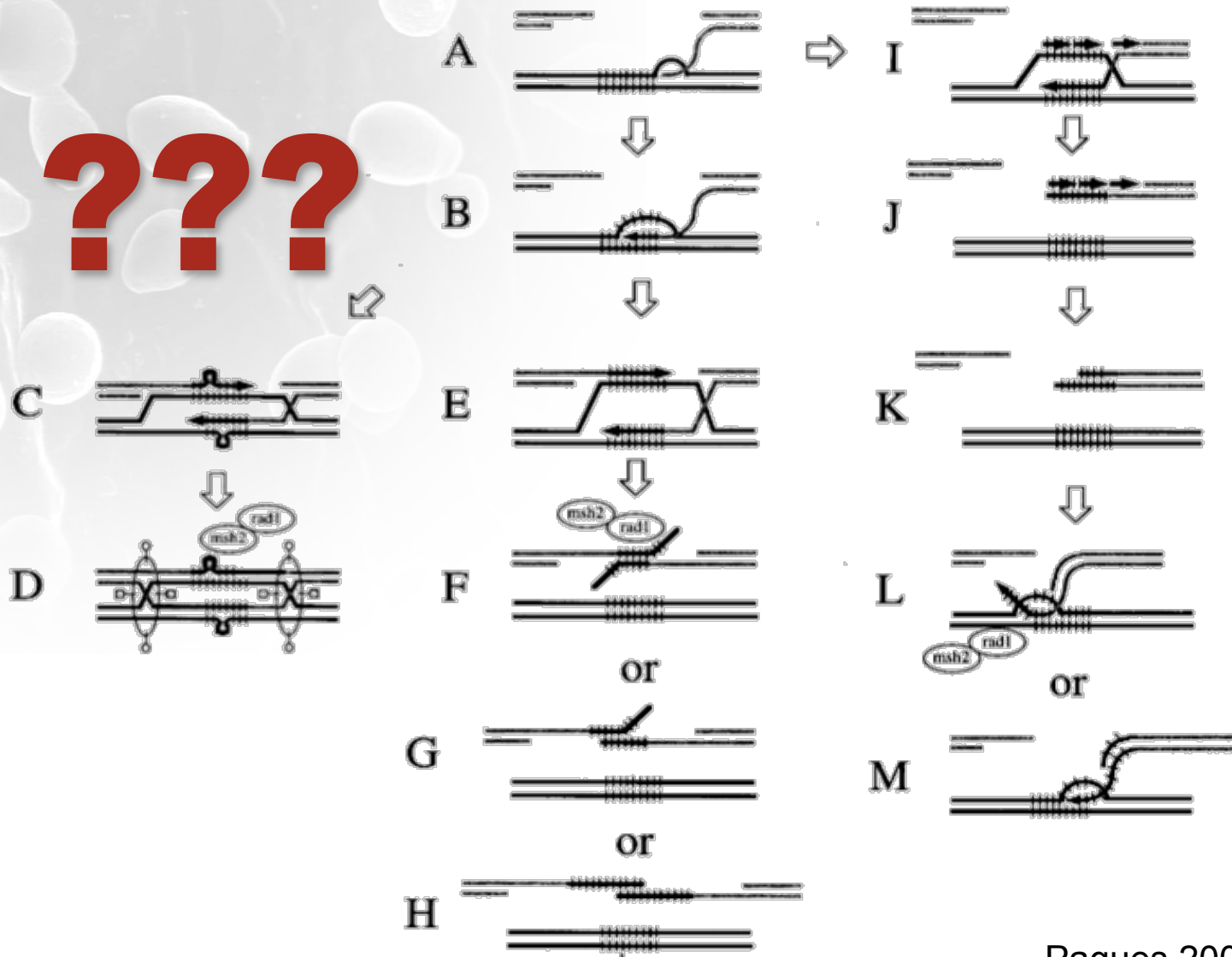
# *Correlation between model and experimental data*



Matthieu Legendre, Nathalie Pochet, Theodore Pak, and Kevin J. Verstrepen.  
**Sequence-based estimation of minisatellite and microsatellite repeat variability.**  
Genome Res. doi:10.1101/gr.6554007

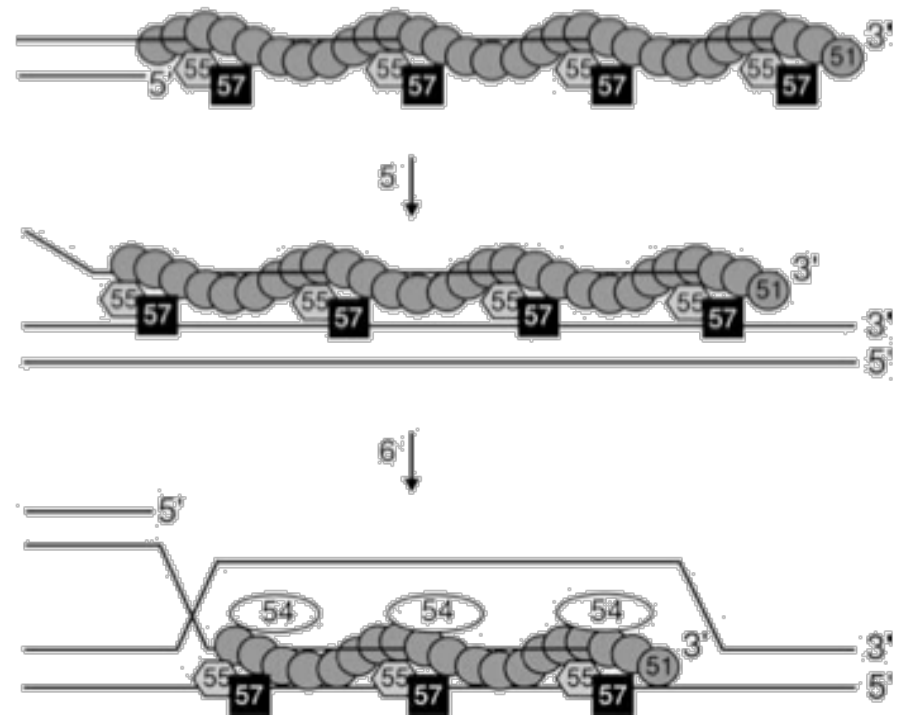
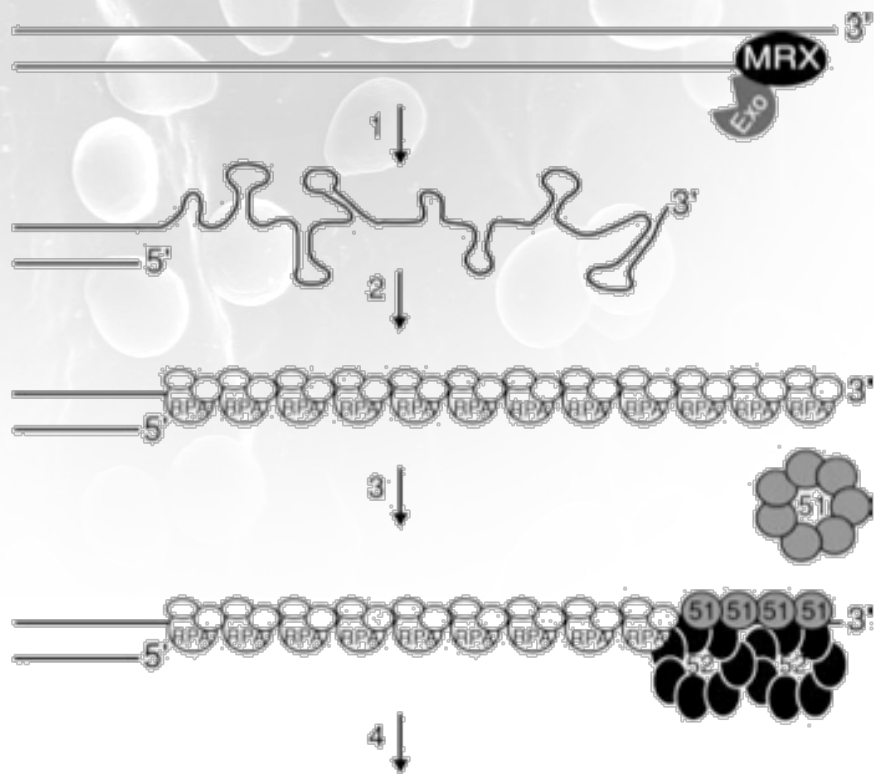
# Switching Mechanism?

???



# *Recombination Proteins*

RAD genes, the MRE complex



Krogh 2004

A grayscale microscopic image showing numerous spherical cells, some of which are in the process of dividing, with visible internal structures and filaments.

## *Future directions*

- ★ Delete genes in the recombination pathway and examine effects on variability

**OR**

- ★ Attempt to create a more sophisticated model for Tandem Repeat variability based on experimental data

# *Acknowledgements*

Kevin J. Verstrepen, PI

Matthieu Legendre, Nathalie Pochet

Marcelo Vincens, Chris Brown

The Verstrepen Lab

My labmates Chen, Bianca, Amy, Barry, Bena...

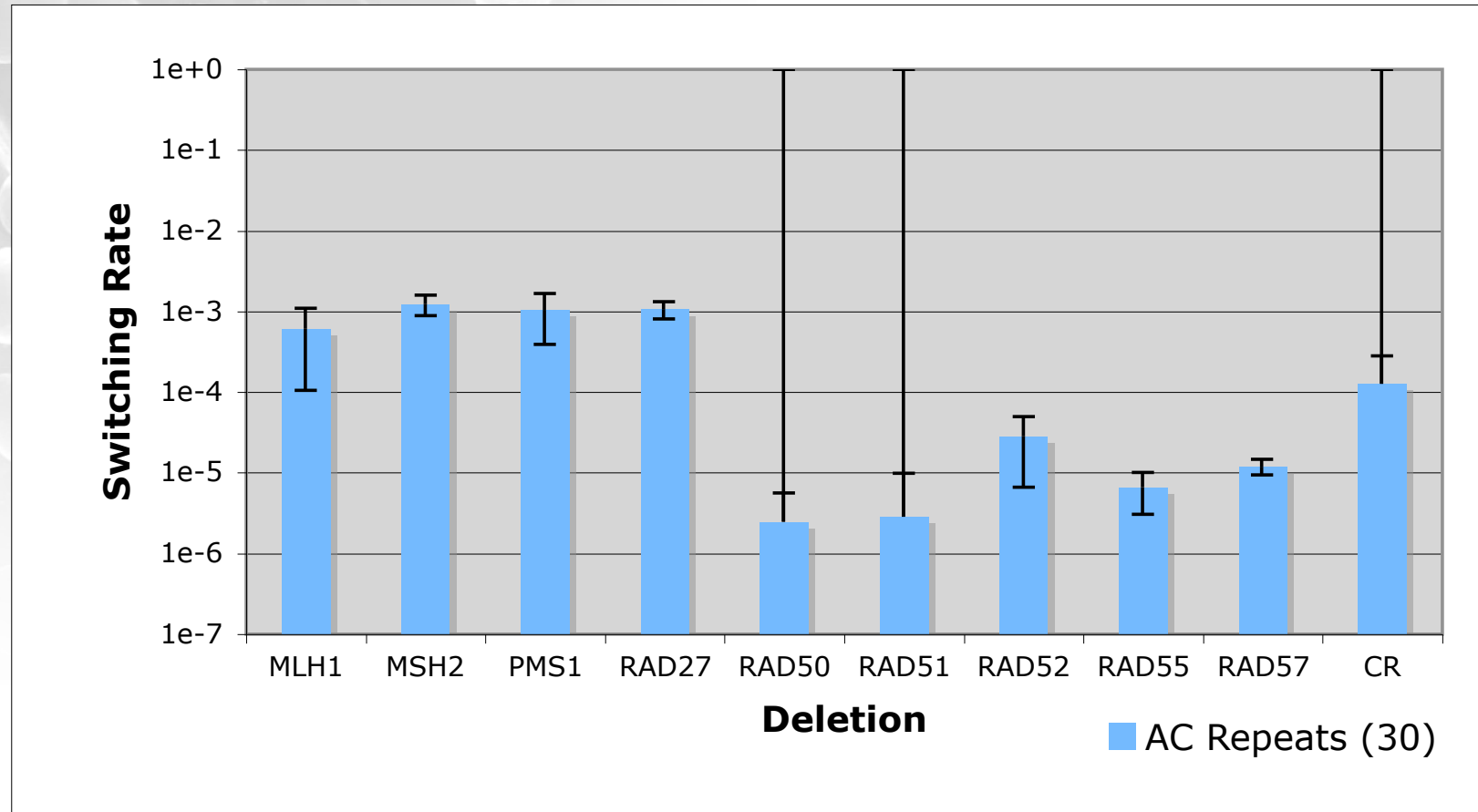
HURS, HCRP, PRISE

The FAS Center for Systems Biology



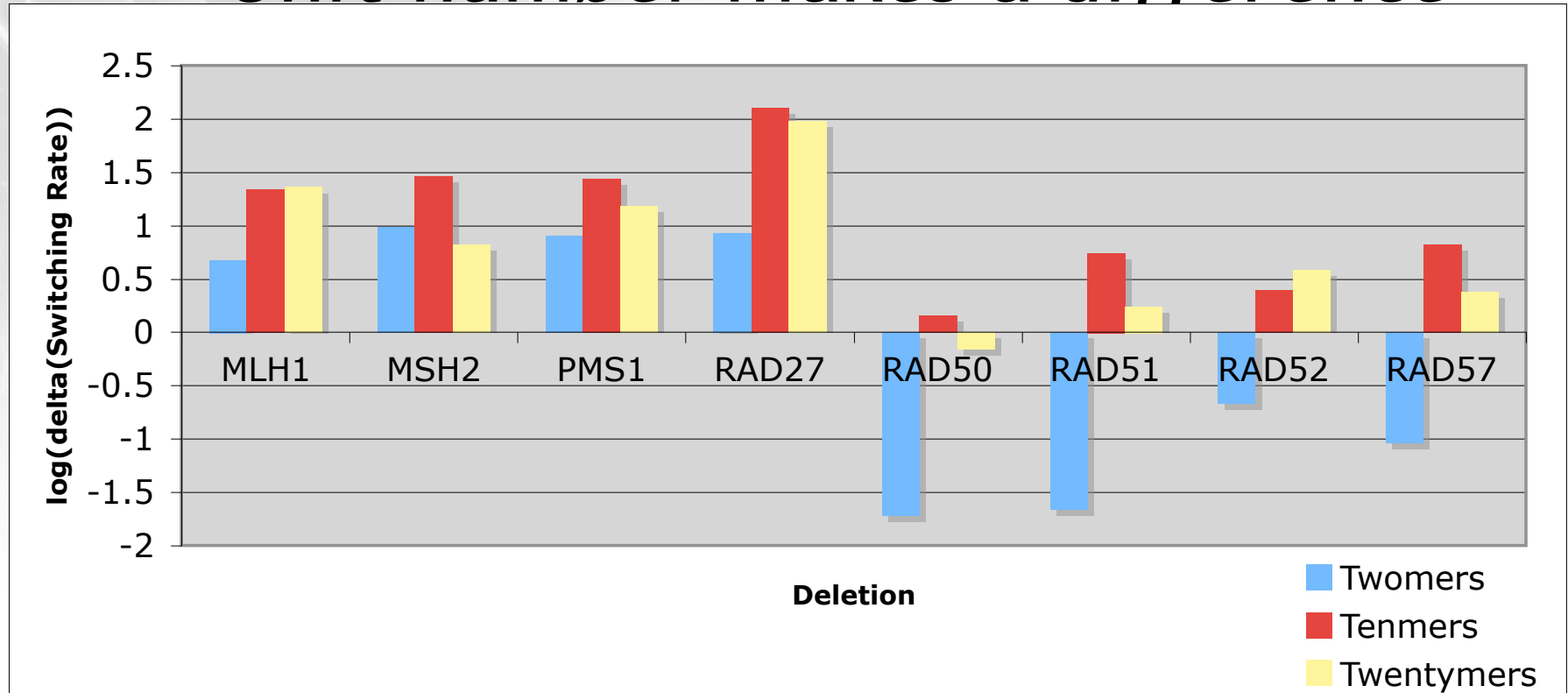
# *Mechanisms?*

## *Long dinucleotide repeats w/ deletions*



Deleting genes related to the recombination pathway appears to affect switching rates.

## *Unit number makes a difference*



- Examine REC pathways, hypothesize why this might be the case
- Additional genes. THO complex - required for transcription of repeats?