



28 November 2008



From Animal Genetic Resources To Animal Genome Revolution

John Woolliams



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1. Why are we here?



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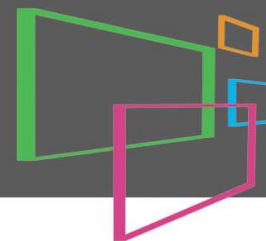


The Case For Conservation





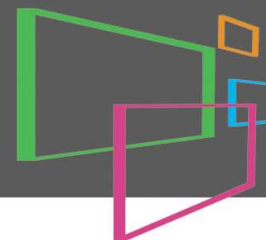
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Drivers for Change

- Livestock are a focal point for
 - » Lifting people out of poverty into sustainable livelihoods
 - » Satisfying global demands for livestock products
 - » Promoting international trade
- Production must
 - » Respond to new patterns of demand
 - » Reduce impact on environment
- Need for sustainable intensification!!!



Policy Drivers for Livestock

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Change!

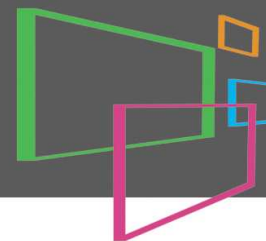


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Breed Erosion

- Change creates new market pressures on breeds
 - » changing economics of inputs and outputs
 - » changing market demands
 - » breeds survive if 'fit for purpose' else ...
- Current markets favour breeds of high inputs with high outputs
 - » these breeds survive
- Other low-input or adapted breeds decline
- Vulnerable breeds are lost
 - » conflict, disease, flood, drought



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- Other breeds decline and become vulnerable
- Vulnerable breeds are lost
 - » conflict, disease, flood, drought

**Breed Variation is
Disappearing!**



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How Severe is Breed Erosion?

Risk Status	Actual %
At Risk	20
Not at Risk	35
Unknown	36
Extinct	9

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Risk Status	Actual %
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- More than 1 in 3 breeds of 'unknown' status !
- Likely status of 'unknown'
 - » 40% 'at risk' !

How Severe Is Breed Erosion?

Risk Status	Actual %	Predicted %
At Risk	20	34
Not at Risk	35	56
Unknown		
Extinct	9	10

- > 1 in 3 breeds are predicted to be 'at risk'
- ~ 1 in 10 'extinct'
- ~ 1 in 2 'secure'



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Is This Loss A Problem?

- No ... not with certainty and stability



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Is This A Problem?

- But we have no longer have certainty and stability!
- We have rapidly changing demands and markets
 - » an uncertainty, but a 'familiar' one



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Is This A Problem?

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Uncertainty!



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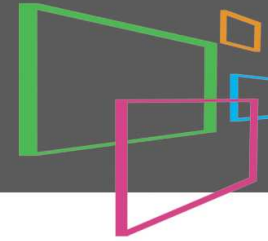


Is This A Problem?

- But we have no longer have certainty and stability!
- We have rapidly changing demands and markets
 - » an uncertainty, but a 'familiar' one
- Now there is a scientific consensus:
 - » climate change is happening
 - » we should expect a rapid global warming
 - » humans have contributed and continue to do so
 - » Intergovernmental Panel on Climate Change 2007



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Is This A Problem?

- But we have no longer have certainty and stability!
- Scientific consensus on:

- » there is climate change
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**Change not
stability!**



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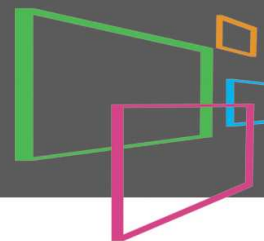


How Much Change?

- Degree of climate change is open to debate
- Not all climate model parameters known accurately



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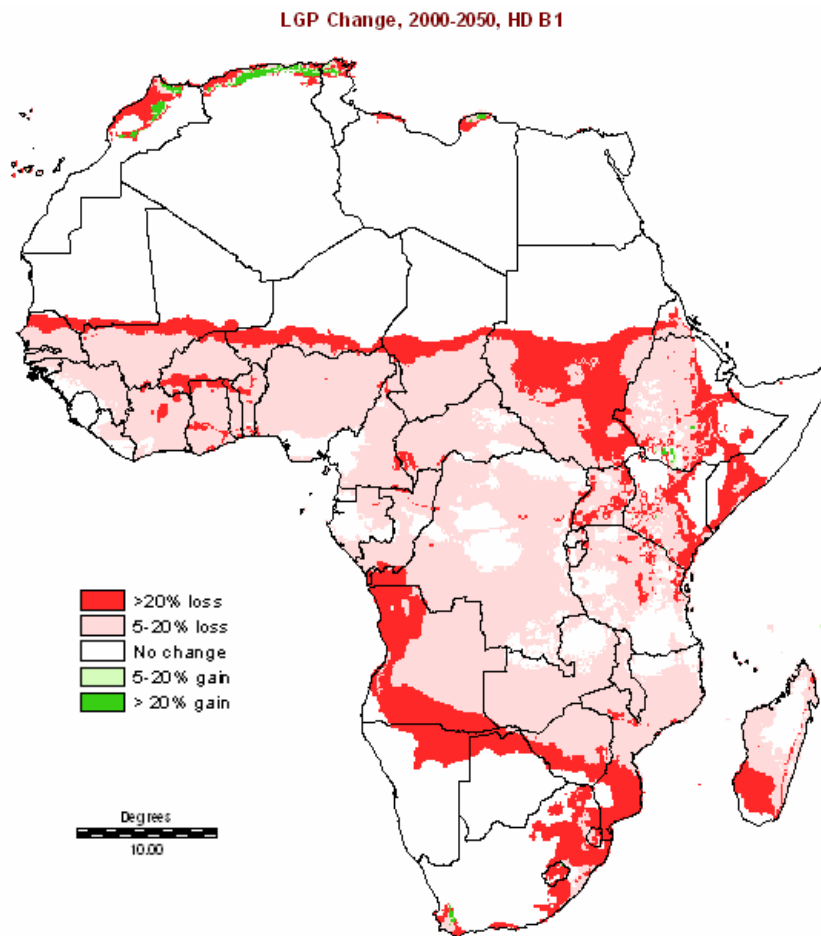
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Uncertainty!

Some Predictions

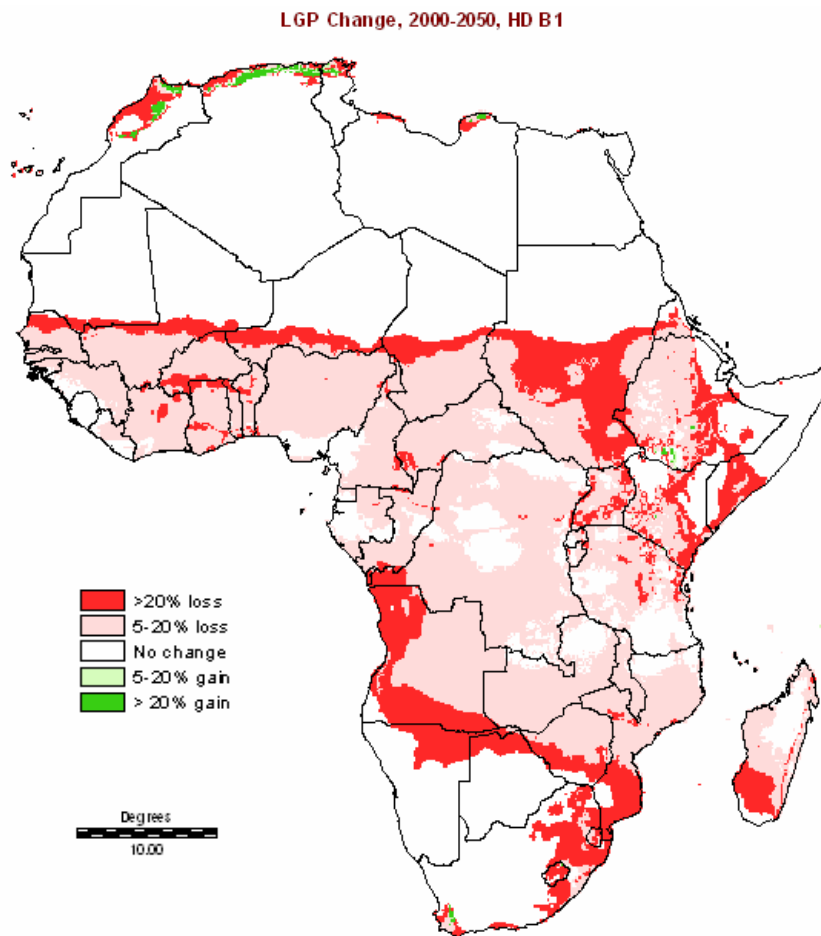


Length of Growing Season

- expectations for Africa
- widespread reduction predicted

Thanks to CGIAR for map.

Some Predictions



Length of Growing Season

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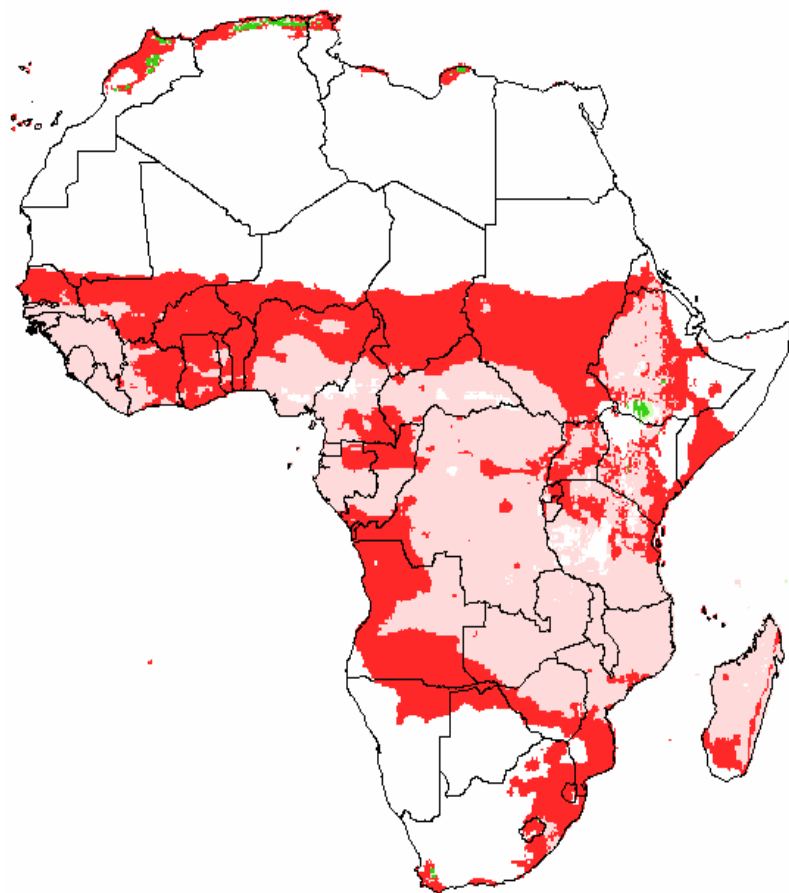
BUT

- model assumes global cohesive response

Thanks to CGIAR for map.

Some Predictions

LGP Change, 2000-2050, HD A1



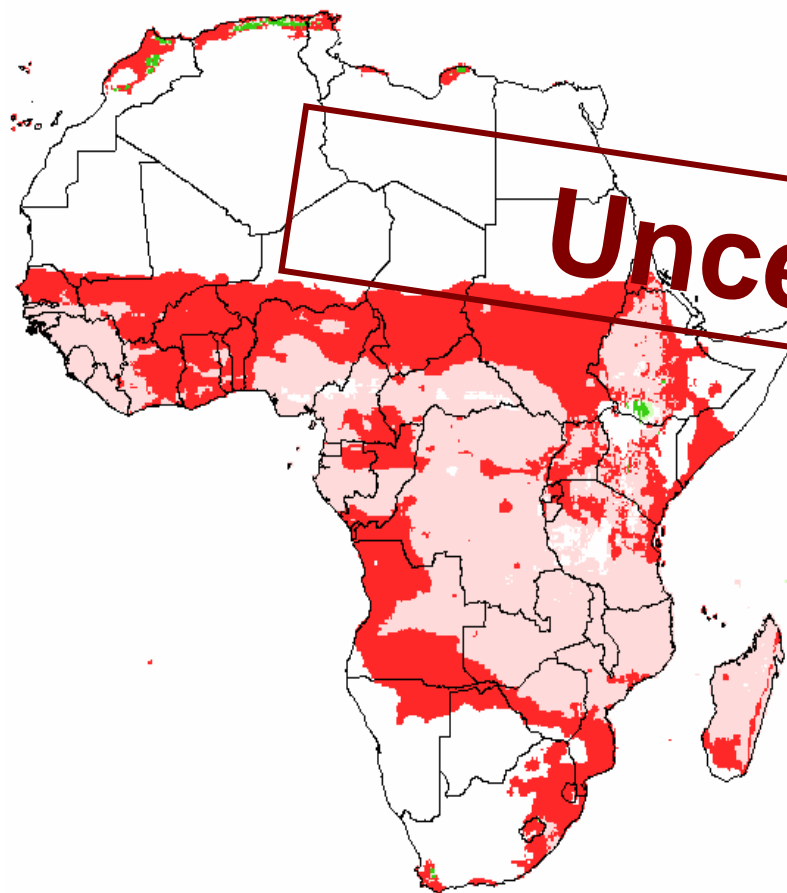
Length of Growing Season

- this model assumes less cohesion

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Some Predictions

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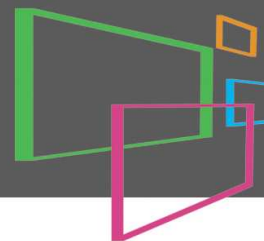
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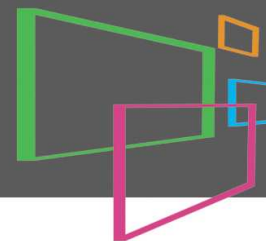
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What Will Be Required of Livestock?

- Other implications of climate change
 - » production systems will change to meet the trends
 - » e.g. crops for bio-fuels
 - » changes in market values
 - » cause of conflict for resources



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- Other implications of climate change
 - » production systems will change to meet the trends
 - » e.g. crops for bio-fuels
 - » changes in market values
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Uncertainty!

- What will be required of our livestock?



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Meeting the Needs of our Children

- Needs of our children & children's children less likely to be met than at any previous time!



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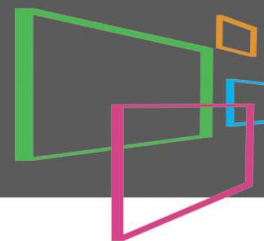
Meeting the Needs of our Children

- Needs of our children & children's children less likely to be met than at any previous time!

A lack of strategic planning!



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Meeting the Needs of our Children

- Needs of our children & children's children less likely to be met than at any previous time!
- Need full range of genetic diversity to secure the needs of tomorrow
 - » a coherent risk management strategy
 - » risk is not theoretical !



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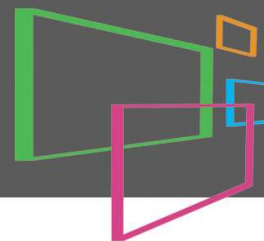


Breed Variation is Vital

- Commonly held that 50% of variation is between breeds
- For fitness and adaptation maybe more
- Within breed variation is
 - » important but limited
 - » cannot be selected fast enough
- Breed variation
 - » major source for fitness & adaptation
 - » can be deployed quickly
 - » paradoxically same reason that underlies much of breed loss!



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Breed Variation is Vital

- Commonly held at 50% of variation is between breeds
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 - » limited
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 - » major source
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 - » paradoxically same reason that underlies much of breed loss!

**Breed variation IS
important to future
food security !**



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Summary

- Time of rapid change
- Uncertain future
 - » needs, markets, production environments, production systems
- Breed variation holds important variation
- Breed variation is being selectively lost
 - » towards a single 'basket' suited only for current needs
 - » high input & outputs favoured over adapted & low inputs
- Need for breed conservation strategy now that is
 - » comprehensive & global



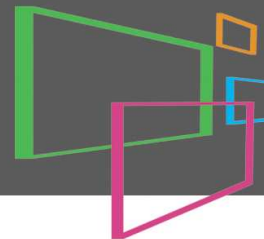
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2. What is the genomic revolution?



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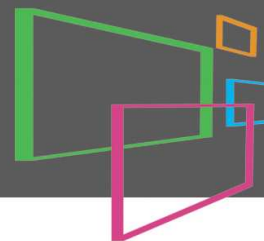
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DNA Markers

- Conservation has mostly used anonymous DNA markers
 - » genetic divergence or similarities or distances
- Look back 10 years:
 - » a review of studies in 2001 had median of 5 markers per study
 - » 300 microsatellite markers on 300 animals took >1 year
 - » personal experience!



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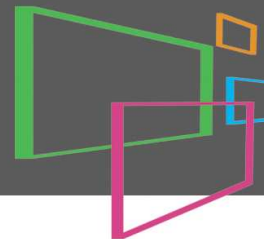
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DNA Markers

- DNA in conservation has used neutral markers
 - » genetic divergence or similarities or distances
- Look back 10 years:
 - » review of studies in 2001 had median of 5 markers per study
 - » 300 microsatellite markers on 300 animals took >1 year
 - » personal experience!
- In 2007:
 - » 50k bovine SNP markers on 300 animals in 1 month
 - » personal experience!



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What's Changed?

- Single Nucleotide Polymorphisms (SNP)
- SNP genotyping!
 - » high throughput, high reliability, low cost/genotype
- Dense SNP chips (50k) available (200 Euro/animal)
 - » cattle ... soon to increase 2-5 fold
 - » sheep ... still restricted access
 - » pigs ... imminent, if not released
 - » chickens ... working towards 50k?
 - » horses, dogs, ..
- Human 500k chips, anticipated to increase soon



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... and Sequencing & Bioinformatics

- Human genome project
 - » powered development of sequencing
 - » contributed to increased rate of SNP discovery
 - » bioinformatic annotation of genome
 - » interpretation of sequence beyond coding regions
- Livestock genome sequences available
 - » chickens, horse, cattle, pigs (imminent)
 - » others?



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Sequencing & Re-Sequencing

- Sequencing is *de novo*
- Re-sequencing provides extended sequence information *if* a full reference sequence is available
 - » machines sequence bits of DNA
 - » ‘read length’ (bp, base pairs) long enough to ‘uniquely’ identify the location within the reference sequence
 - » requires ~25 bp or more
 - » many different bits sequenced simultaneously



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Sequencing & Re-Sequencing

- Yesterday

	Read Length	Bases/7h	Cost/Mb
ABI 3730	800 bp	440 kb	?

Adapted from Mardis, Trends in Genetics, 2008



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Sequencing & Re-Sequencing

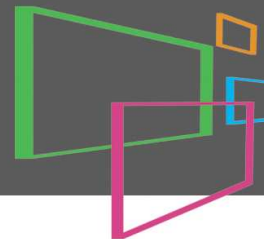
- Yesterday ... and today

	Read Length	Bases/7h	Cost/Mb
ABI 3730	800 bp	0.4 Mb	?
454	250 bp	100 Mb	~\$80
Illumina Solera	32-40 bp	~100 Mb	~\$6
SOLiD	35 bp	175 Mb	~\$6

Adapted from Mardis, Trends in Genetics, 2008



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... & Tomorrow?

- For example, Pacific Biosciences
 - » 1000+ bp reads
 - » reads $\sim 10^4$ times per base faster than some current technology
 - » massively parallel like today's technologies
 - » Scienceexpress, 20 November 2008/10.1126/science.1162986
 - » expected 2010
- \$1000 genome coming soon
- Whatever the system
 - » 3rd generation is close
 - » another order of magnitude advance!



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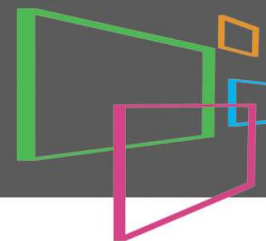


Summary

- Genome technology is advancing by orders of magnitude



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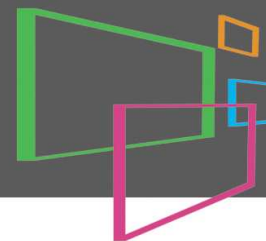


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3. Examples of Conservation Benefits from Genome Revolution



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3. Examples of Conservation Benefits from Genome Revolution

Part 1: Global Perspective



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Why is there no global action?

- Focus on short term goals
- Adapted resources largely in developing countries
 - » especially for global warming threats
- Hard to measure the adapted phenotypes
 - » geography & nature of adaptation e.g. drought survival
- Difficult for developed countries to value for their own self-interest
 - » e.g. how likely is UK to develop and select an adapted composite to replace the Holstein
 - » conservation becomes 'philanthropic'



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Why is there no global action?

- If knew genes, targeted gene introgression may provide a more efficient and attractive option
- BUT what gene?



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Why is there no global action?

- If knew genes, targeted gene introgression may provide a more efficient and attractive option
- BUT what gene?
- Could consider using selective sweeps for identifying such genes

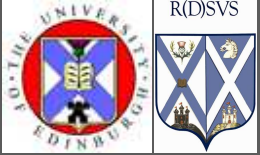


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What is a Selection Sweep?

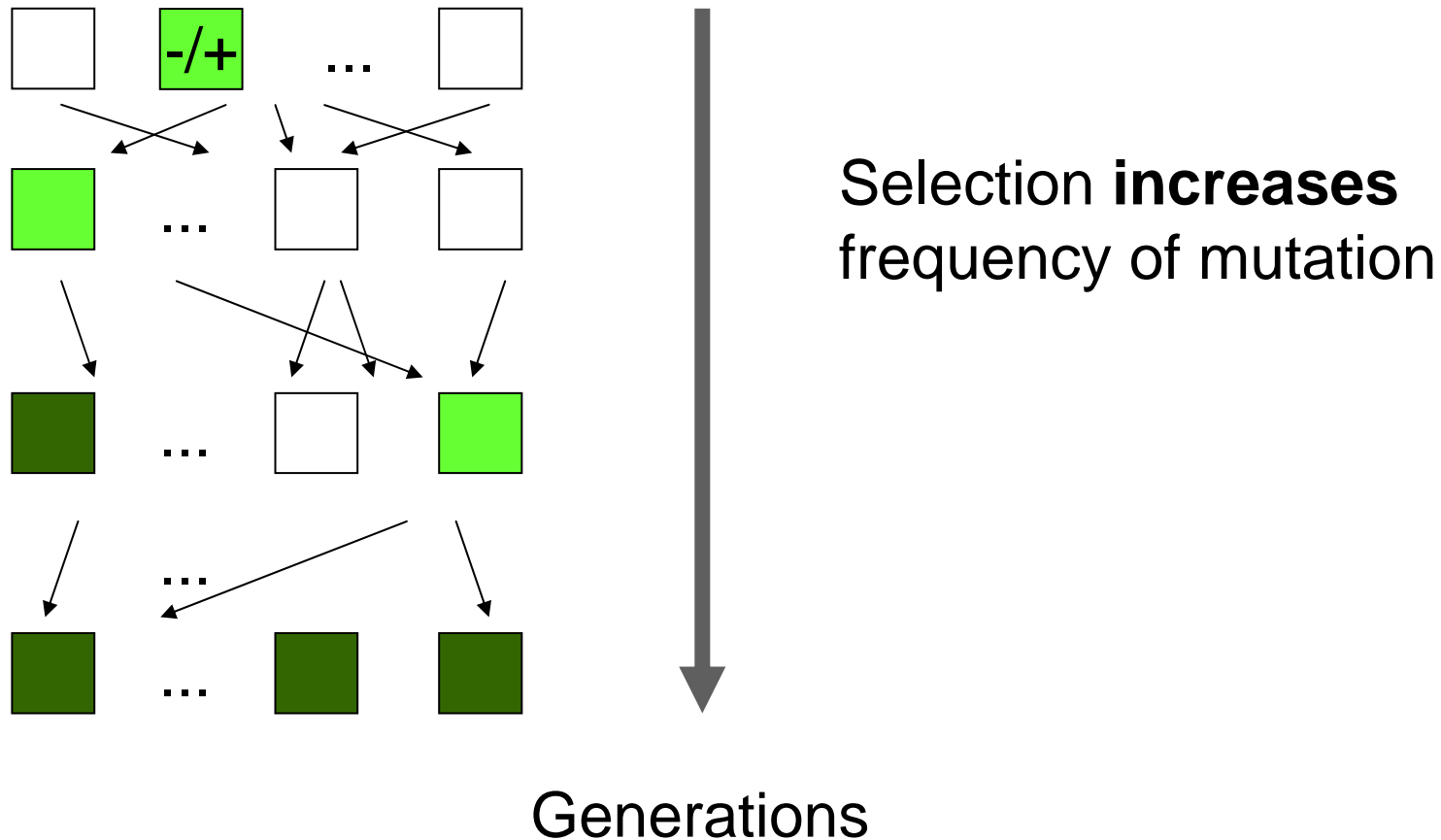
- What happens when a new mutation enters a population and has a selective advantage?



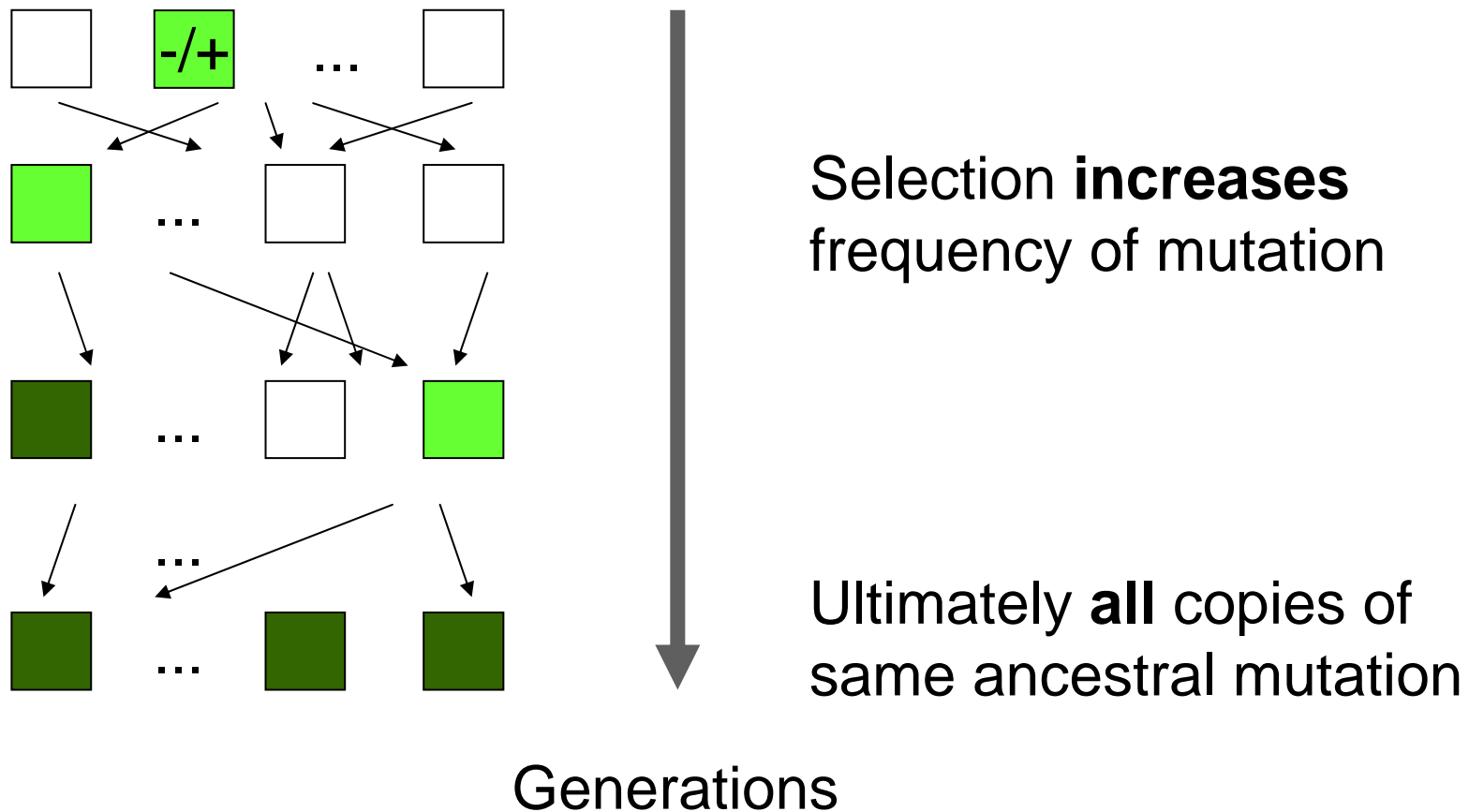
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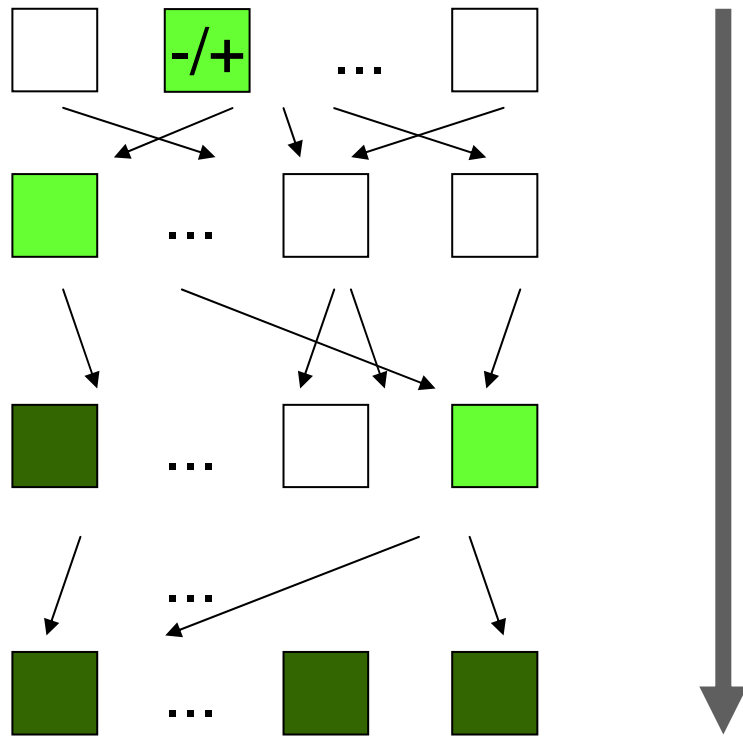
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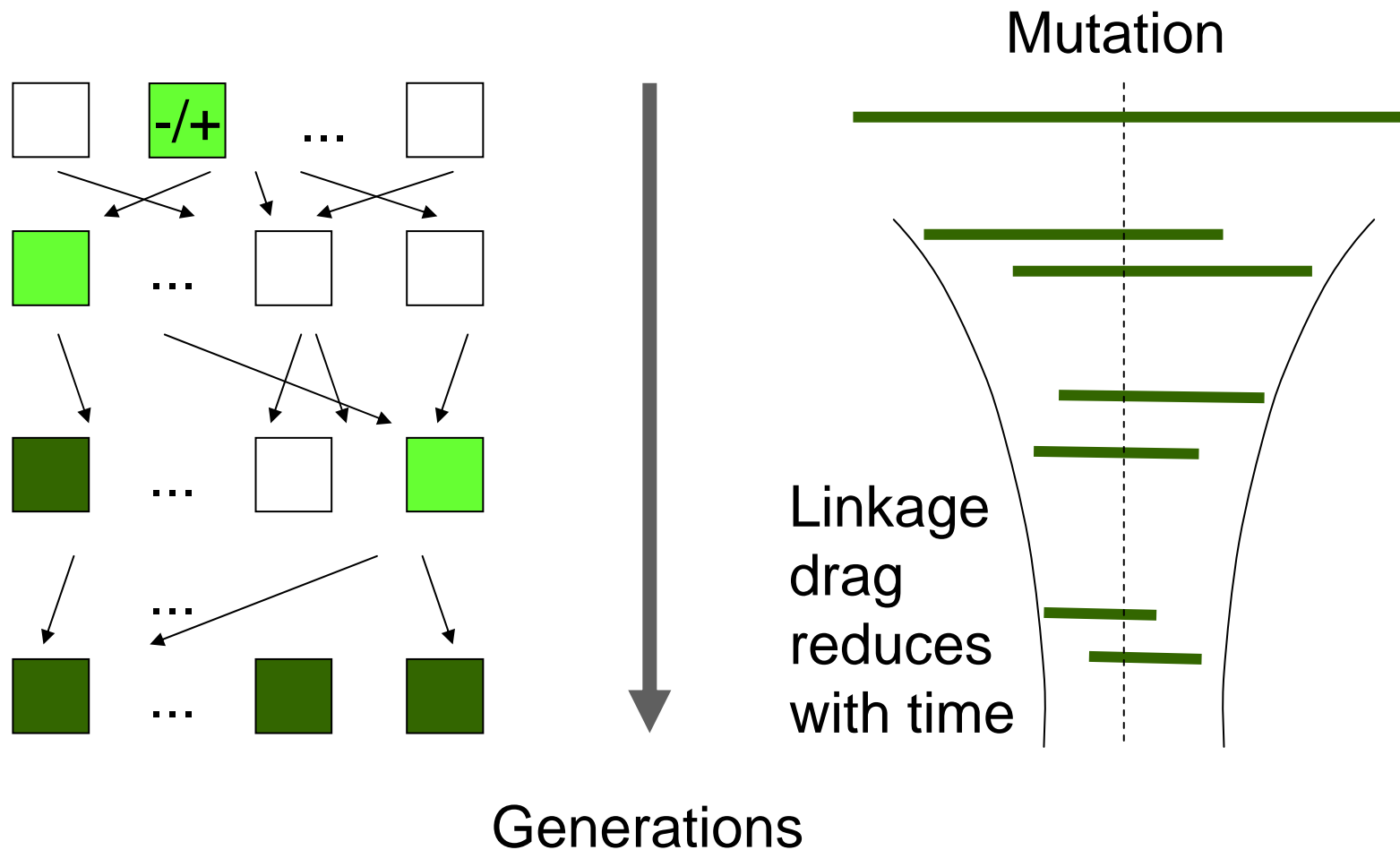
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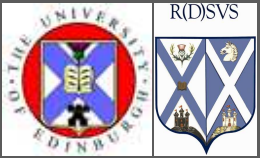


Recombination among chromosomes with and without mutation

Generations

What is a Selection Sweep?



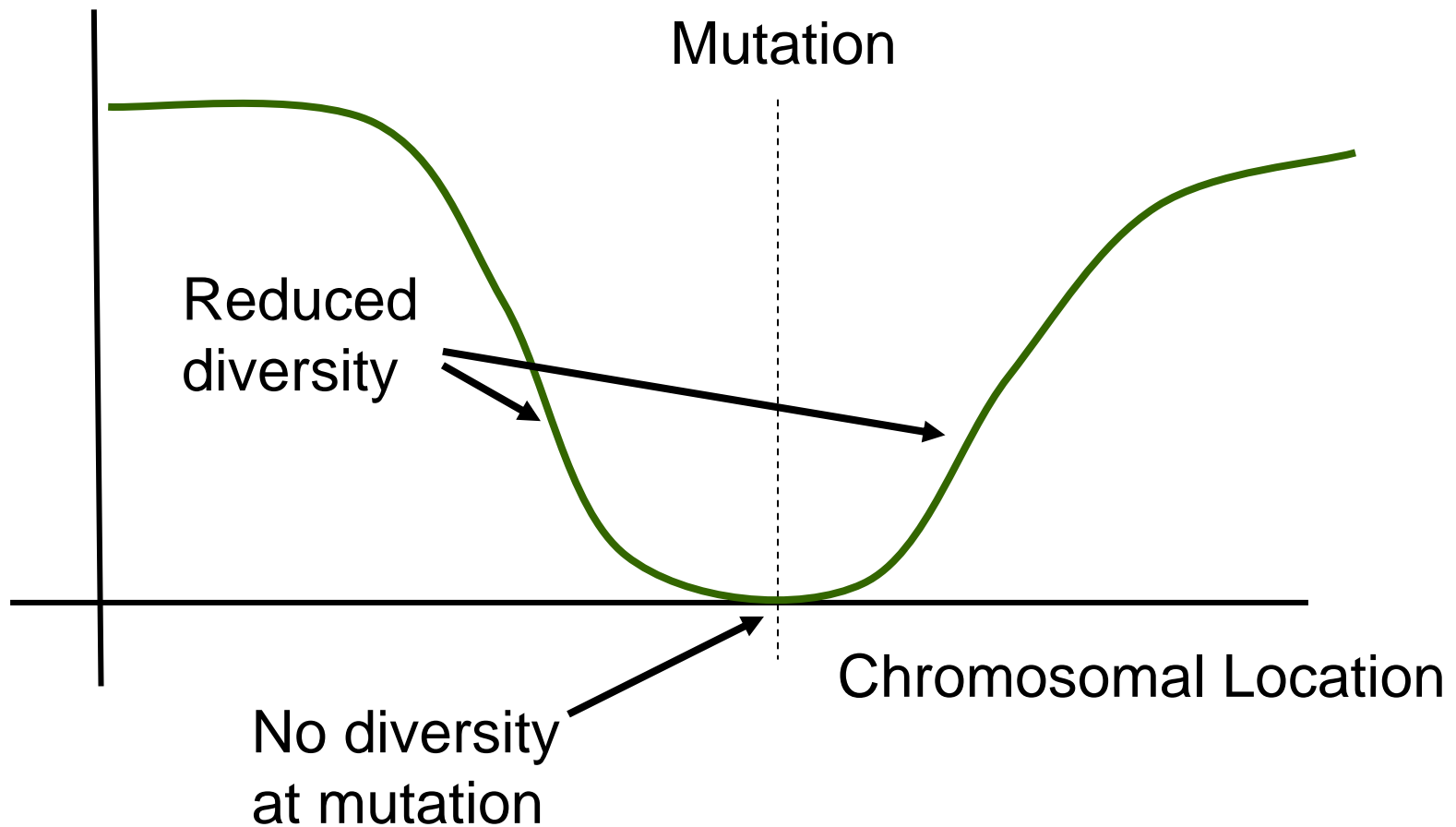


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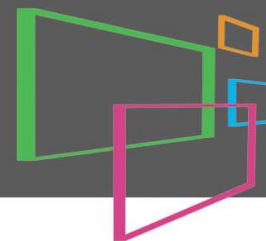
What is a Selection Sweep?

Molecular Diversity





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What is a Selection Sweep?

- Called a 'signature' or 'footprint'
 - » related to 'hitchhiking'
- Longer, steeper footprint when:
 - » more rapidly fixed
 - » lower 'genomic N_e ' at mutation
 - » lower population N_e & higher selection advantage
- Becomes degraded
 - » over evolutionary time by new mutations
 - » introgression from other populations

What is a Selection Sweep?

- Not every region of homozygosity will be due to a selection sweep
 - » although selective sweeps may be expected to be larger than chance
- Identifying possible sweeps requires very dense markers
 - » sweeps may be fractions of Mbases
 - » **so require modern genome tools**



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Selective Sweeps in Conservation

- Examine selective sweeps among breeds
 - » breeds valued on distinctiveness of diversity pattern within the genome
 - » not for how alike or similar they are on average
- Hypothesis: for adapted breeds, some of the sweeps observed will be caused by mutations relevant to their adaptation
 - » does not require individual phenotypes for ‘adaptation’



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Selective Sweeps in Conservation

- BUT need to identify footprints relevant to adaptations not an anonymous footprint!
 - » correlate presence/absence of footprint to the desired adaptation
 - » preferably multiple breeds per adaptation
 - » emphasises the need to secure breed diversity
 - » use bioinformatics to explore candidate footprints
 - » sequence candidate loci in breeds +/- adaptations
 - » seek mutations correlating with adaptation within footprint



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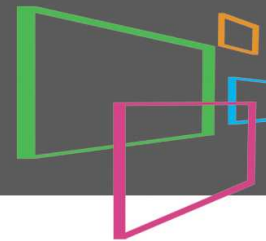


Selective Sweeps in Conservation

- **Caveats**
 - » do breeds share the same mutations?
 - » can enough breeds be collected for good inference?
- Potential benefit is to identify specific breeds as having specific adaptive mutations
 - » not just 'having an adapted phenotype'
 - » closing the genotype-phenotype gap in conservation



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Summary

- Seeking selection footprints may help close the genotype phenotype gap
- Knowing genes will help focus conservation efforts
- More effective use of breed variation



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3. Examples of Conservation Benefits from Genome Revolution

Part 1: Local Perspective



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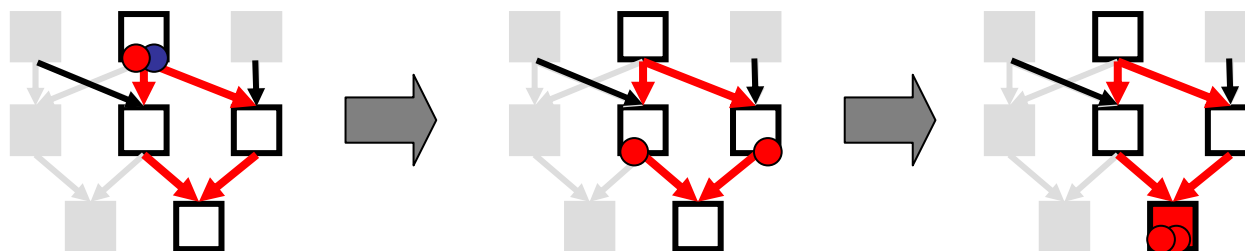


Curse of the Recessive Disease

- Common problem for vulnerable breeds
- Small numbers give small N_e
 - » large random drift of allele frequencies
 - » rare allele can reach significant frequencies
 - » such an allele may be defective & harmful when in homozygous form
 - » e.g. BLAD, CVM in Holsteins

Curse of the Recessive Disease

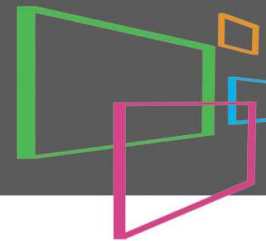
- Disease appears 2+ generations after mutation



- Selection against allele is small
 - » homozygotes rare, heterozygote carriers normal
 - » disease unrecognised for what it is
 - » secrecy due to fear of publicity
- Defective allele disperses into population



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Curse of the Recessive Disease

- How to identify the 'carriers' of defect?
 - » particularly if normal phenotype
- DNA has potential to do this!



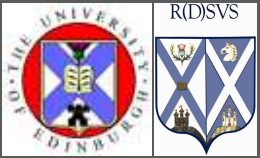
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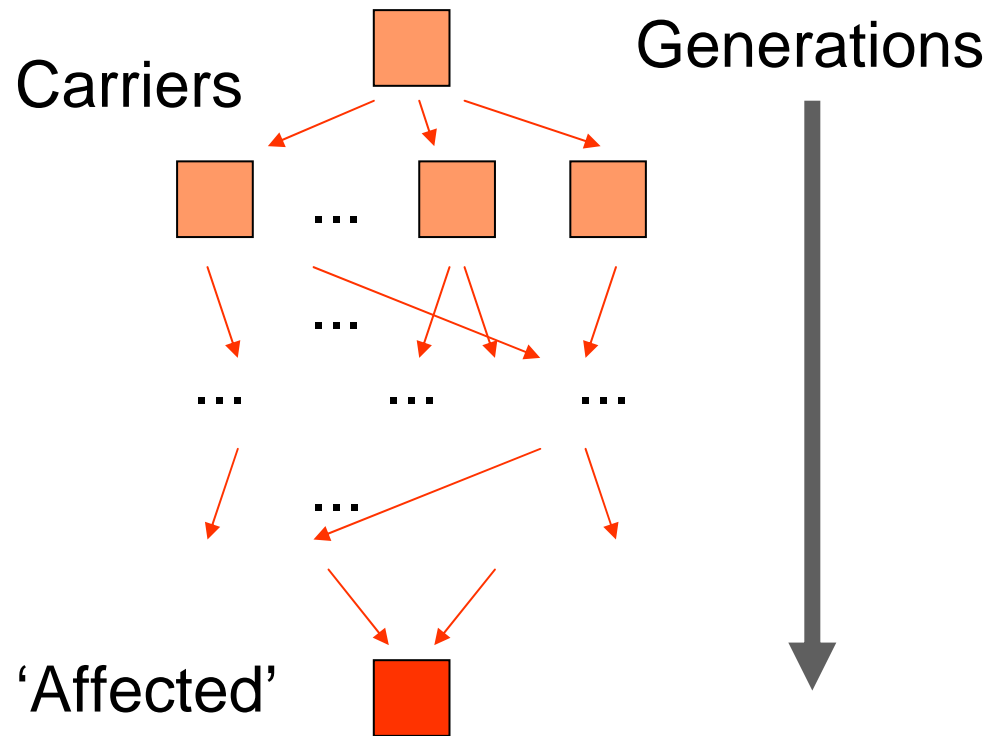
- Effective method is identity-by-descent mapping
 - » or more recent extension 'homozygosity mapping'



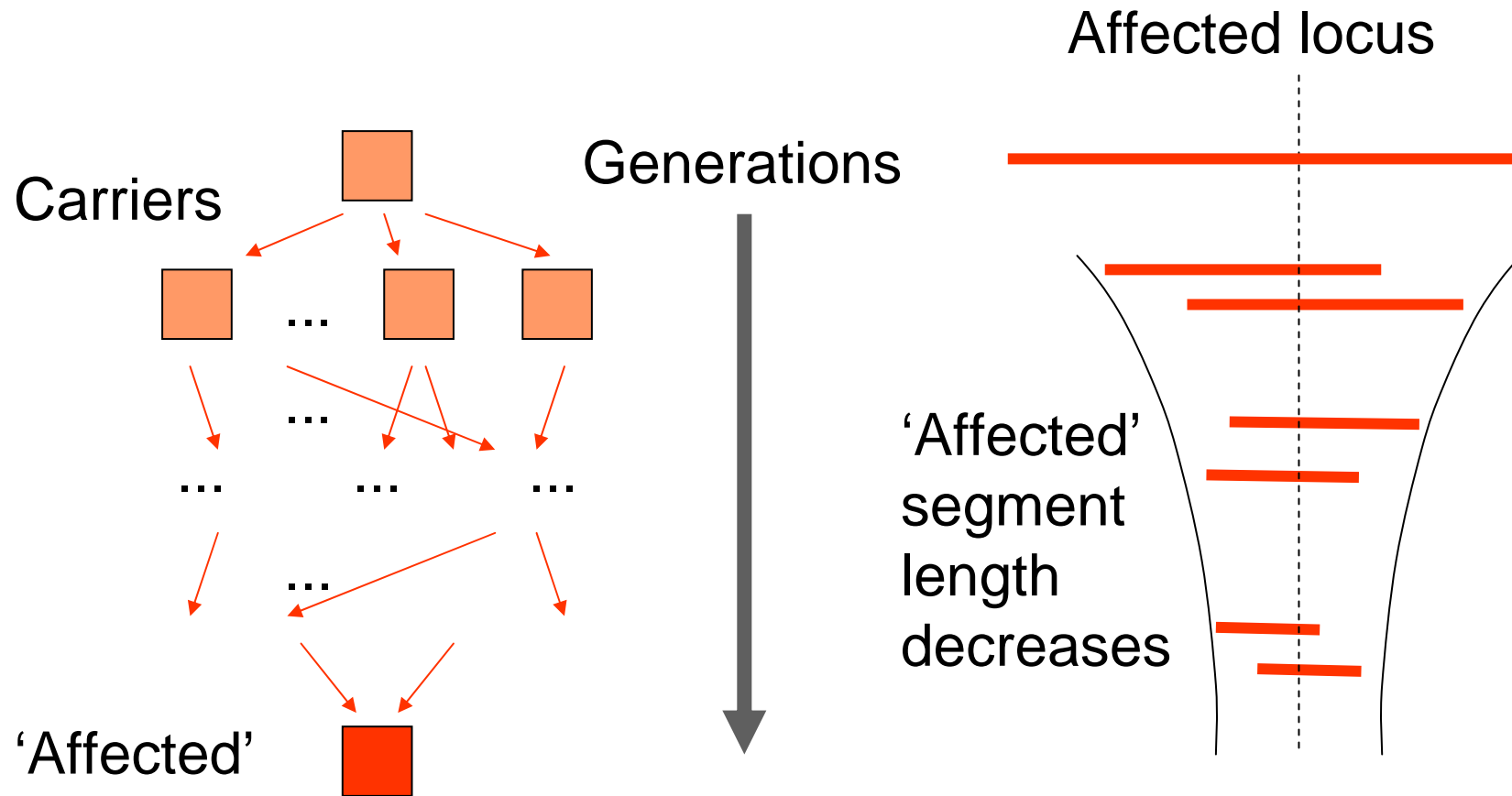
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Homozygosity Mapping



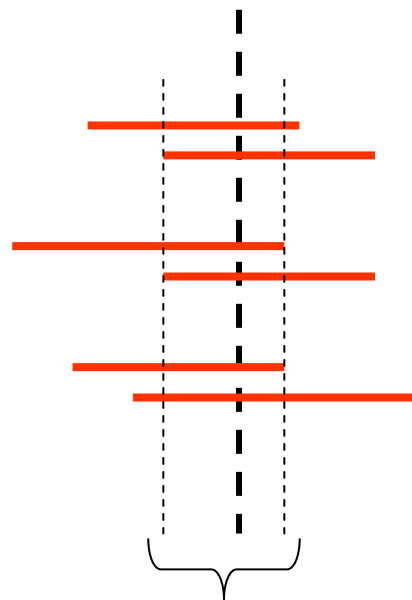
Homozygosity Mapping



Homozygosity Mapping

- By comparing genomes of 'affected' individuals

'Affected' locus

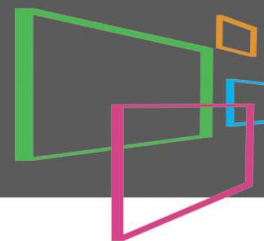


Chromosome
pairs from
'Affected'

Know locus must be here



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Homozygosity Mapping

- Finding a common homozygous segment has high probability of identifying segment with defect
- BUT segment can be small
 - » need to identify true homozygosity across the genome
 - » dense markers
 - » high throughput
 - » **value of dense SNP technology**
 - » Charlier et al. 2008. Nature Genetics 40: 449-454



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Homozygosity Mapping

Defect	CMD1	CMD2	IF	CTS	RL
# Scans	26	31	12	22	30
# Cases	12	7	3	8	6
Interval Mb	2.12	3.61	11.78	2.42	0.87
Mutation?	Yes	Yes	Yes	No	No

- » Few animals required to be scanned
- » Few cases
- » Bio-informatics identify candidate loci, re-sequencing identifies mutation
- » Intervals vary in length, some long!



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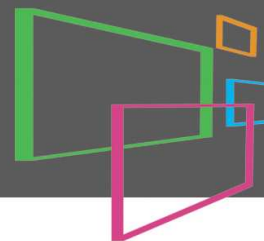


Homozygosity Mapping

- Find defective allele by
 - » use of dense SNPs to find homozygous segment(s)
 - » bio-informatics to locate candidate loci in segment
 - » re-sequence to find all mutations for candidate
 - » technology makes this easier and cheaper
 - » ideally, find mutation that correlates appropriately
 - » homozygote if and only if 'affected'



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Homozygosity Mapping

- **Caveats**

- » can remove disease without finding mutation if interval small
- » very recent mutations may have long intervals
- » diseases are not always simple recessives
- » depends upon pro-active approach of breeders



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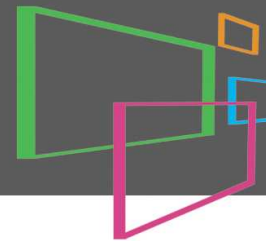


Summary

- New genomic tools greatly help removal of inherited diseases from populations



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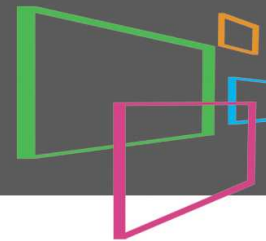


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5. Conclusions



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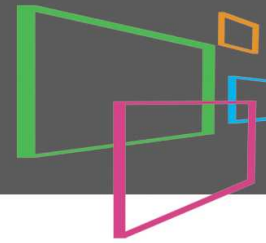
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Conclusions

- Breed variation is being selectively lost
 - » high input & outputs favoured over adapted & low inputs
 - » need for global breed conservation strategy now



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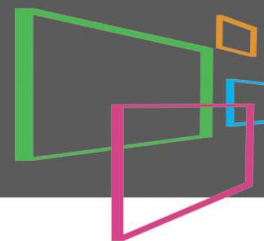
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- Animal genome revolution is a revolution!



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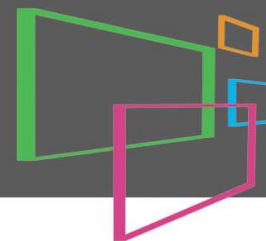
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 - » need for global breed conservation strategy now
- Animal genome revolution is a revolution!
- Genomic footprints may substantiate now what adapted breeds have to offer
 - » better valorisation, more efficient utilisation



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Conclusions

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 - » high input & outputs favoured over adapted & low inputs
 - » need for global breed conservation strategy now
- Animal genome revolution is a revolution!
- Genomic footprints may substantiate now what adapted breeds have to offer
 - » better valorisation, more efficient utilisation
- **Genomics will end curse of the recessive disease**



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Conclusions

- Breed variation is being selectively lost
 - » high input & outputs favoured over adapted & low inputs
 - » need for global breed conservation strategy now
- Animal genome revolution is a revolution!
- Genomic footprints may substantiate now what adapted breeds have to offer
 - » better valorisation, more efficient utilisation
- Genomics will end curse of the recessive disease