Introduction

Summar

General mode

## On the theory of two-locus clines on the real line

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• A cline describes a gradual change in genotypic or phenotypic frequency as a function of spatial location.



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- Examples: The frequency of the  $Adh^F$  allele in *D. melanogaster* increases from south to north along Eastern North America; in Australia, it increases as one goes south.



- A cline describes a gradual change in genotypic or phenotypic frequency as a function of spatial location.
- Examples: The frequency of the  $Adh^F$  allele in *D. melanogaster* increases from south to north along Eastern North America; in Australia, it increases as one goes south.
- Clines are frequently caused by the interaction of geographically variable selection and migration in a spatially distributed population.



- When does a cline, a spatially nonuniform, stationary solution, exist?
- How do existence and properties (e.g. shape) of a cline depend on migration, selection, dominance, recombination, etc.?
- What inferences about dispersal and selection intensity can be drawn from empirical observations, i.e., measurements of the cline?



- The diploid species inhabits the continuous, unidimensional habitat Ω = ℝ, in which it migrates.
- Migration is modeled by diffusion.
- The fitness of individuals (genotypes) depends on the position *x*, but is time- and density-independent.
- First, we consider a single *gene* (*locus*) with two *alleles*, *A* and *a*.



## **One-locus PDE model for migration and selection**

• p(x,t) is the frequency of allele A at location x and time t. Then p(x,t) evolves according to<sup>1</sup>

$$\begin{split} &\frac{\partial p}{\partial t} = p'' + \lambda \alpha(x) f(p) \quad \text{in } \ \mathbb{R} \times (0,\infty) \,, \\ &0 < p(x,0) < 1 \qquad \qquad \text{in } \ \mathbb{R} \,, \end{split}$$

where 
$$p'' = \frac{\partial^2 p}{\partial x^2}$$
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<sup>&</sup>lt;sup>1</sup>Haldane (1948), Fleming (1975). For the derivation of a much more general model, see Nagylaki (1975, 1989).



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- $\lambda \propto s/\sigma^2$  measures the strength of selection relative to diffusion.
- *α*(*x*) describes the spatial dependence of the fitnesses of the alleles.

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- $\lambda \propto s/\sigma^2$  measures the strength of selection relative to diffusion.
- $\alpha(x)$  describes the spatial dependence of the fitnesses of the alleles.
- f(p) = p(1-p)(1+h-2hp) describes selection.

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• The step environment approximates an abruptly changing environment:

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$$\alpha(x) = \begin{cases} \alpha_+ & \text{ if } x \ge 0, \\ -\alpha_- & \text{ if } x < 0, \end{cases}$$

where  $\alpha_+, \alpha_- > 0$ .

• Haldane (1948) calculated the one-locus cline in terms of hyperbolic functions for no dominance and for complete dominance.<sup>2</sup>

<sup>&</sup>lt;sup>2</sup>Slatkin (1973) and Nagylaki (1975, 1976) extended his work to include environmental pockets, barriers, etc.

































## A single locus with dominance (or linear frequency dependence)

We assume a spatially independent, intermediate degree of dominance:

$$f(p) = p(1-p)(1+h-2hp)$$
, where  $-1 \le h \le 1$ .

Then the cline is the  $C^1$  solution P(x) of

$$P'' + \lambda \alpha(x)P(1-P)(1+h-2hP) = 0$$

that satisfies 0 < P(x) < 1,  $P(-\infty) = 0$ , and  $P(\infty) = 1$ .



# Separating variables and integrating, we eventually find the slope of the cline in the center,

$$P'(0) = \frac{\sqrt{\lambda}}{\sqrt{3}} \sqrt{\frac{\alpha_+ \alpha_-}{\alpha_+ + \alpha_-}}$$

- Therefore, the slope P'(0) is independent of the degree of dominance.<sup>3</sup>
- An estimate of the dispersal variance is sufficient to infer the selection intensity ( $\lambda \propto 1/\sigma^2$ ), and vice versa.

<sup>&</sup>lt;sup>3</sup>See Lenormand et al. (1998), who concluded that dominance does not have an important effect on the estimation of migration variance in a study of clines in the mosquito *Culex pipiens*.

Introduction One locus Two loci Strong recombination Summary General mod

## The single-locus cline can be computed explicitly

There exists a unique cline solution P(x). For  $x \ge 0$ , it is given by

$$P(x) = \begin{cases} 1 - \frac{6(1-h)}{Z_+ + 2(1-3h) + (1+3h)Z_+^{-1}} & \text{if } h < 1 \,, \\ \\ 1 - \frac{12}{9 + 4(x\lambda\alpha_+ + A_+)^2} & \text{if } h = 1 \,, \end{cases}$$

where

$$Z_+(x)=A_+e^{X_+}\,,$$
 
$$X_+=x\lambda\alpha_+\sqrt{1-h}\quad (\text{if }h<1) \ \text{ and }\ A_+=F_+(a_0,h)\,.$$

An analogous result holds for x < 0.



One locus

wo loci

Strong recombination

Summary

General mode

#### Dominance and the shape of the cline



The single-locus cline P(x) as a function of x for different values of the dominance parameter h. The other parameters are such that  $\lambda \alpha_+ = \lambda \alpha_- = 1$ .



- Most traits are determined by more than one locus.
- Recombination, occurring at the (scaled) rate  $\rho \ge 0$ , and linkage disequilibrium have to be taken into account.



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- Recombination, occurring at the (scaled) rate  $\rho \ge 0$ , and linkage disequilibrium have to be taken into account.

Alleles: A a B b  
Fitnesses: 
$$\frac{1}{2}\alpha(x) - \frac{1}{2}\alpha(x) \frac{1}{2}\beta(x) - \frac{1}{2}\beta(x)$$

- We now have two step function,  $\alpha(x)$  and  $\beta(x)$ , which change sign at the same point (w.l.o.g. at x = 0).
- We assume additive fitnesses.<sup>4</sup>

<sup>&</sup>lt;sup>4</sup>On the expense of considerable technical complications, the analysis below can be performed for intermediate dominance.

Introduction

General mode

## Allele frequencies and linkage disequilibrium

- We use the following coordinates:
  - $p_A \dots$ frequency of A $p_B \dots$ frequency of B $D \dots$ linkage disequilibrium





· After rescaling time, the dynamics is given by

$$\begin{aligned} \frac{\partial p_A}{\partial t} &= p''_A + \lambda \alpha(x) p_A (1 - p_A) + \lambda \beta(x) D, \\ \frac{\partial p_B}{\partial t} &= p''_B + \lambda \beta(x) p_B (1 - p_B) + \lambda \alpha(x) D, \\ \frac{\partial D}{\partial t} &= D'' + 2 p'_A p'_B \\ &+ \lambda [\alpha(x)(1 - 2p_A) + \beta(x)(1 - 2p_B)] D - \rho D \end{aligned}$$

• with zero-flux boundary conditions,  $0 < p_A < 1$ ,  $0 < p_B < 1$ , and the natural constraints on *D*.

Introduction One locus Two loci Strong recombination Summary General model Independent loci (D = 0)

- If loci are independent, as is expected if  $\rho \to \infty,$  the dynamics becomes

$$\begin{aligned} \frac{\partial p_A}{\partial t} &= p_A'' + \lambda \alpha(x) p_A (1 - p_A) + \lambda \beta(x) D, \\ \frac{\partial p_B}{\partial t} &= p_B'' + \lambda \beta(x) p_B (1 - p_B) + \lambda \alpha(x) D, \\ \frac{\partial D}{\partial t} &= D'' + 2 p_A' p_B' \\ &+ \lambda [\alpha(x)(1 - 2p_A) + \beta(x)(1 - 2p_B)] D - \rho D \end{aligned}$$

• If D(x,t) is forced to be 0, then two decoupled one-locus systems are obtained.



- The system is uncoupled and has an internal equilibrium because both one-locus systems have a nontrivial equilibrium (cline).
- The internal equilibrium, being a Cartesian product, is globally asymptotically stable.

Introduction One locus Two loci Strong recombination

Summary

General mode

## The two-locus model with strong recombination

We fix  $\lambda$  and assume

$$\epsilon = 1/\rho \ll 1 \,.$$

| Introduction | One locus | Two loci | Strong recombination | Summary | General model |
|--------------|-----------|----------|----------------------|---------|---------------|
|              |           |          |                      |         |               |

## The two-locus model with strong recombination

We fix  $\lambda$  and assume

$$\epsilon = 1/\rho \ll 1 \,.$$

Rescaling time yields

$$\begin{aligned} \frac{\partial p_A}{\partial t} &= \epsilon \left[ p''_A + \lambda \alpha(x) p_A (1 - p_A) + \lambda \beta(x) D \right], \\ \frac{\partial p_B}{\partial t} &= \epsilon \left[ p''_B + \lambda \beta(x) p_B (1 - p_B) + \lambda \alpha(x) D \right], \\ \frac{\partial D}{\partial t} &= \epsilon \left[ D'' + 2 p'_A p'_B + \lambda [\alpha(x)(1 - 2p_A) + \beta(x)(1 - 2p_B)] D \right] \\ &- D. \end{aligned}$$

The limit  $\epsilon \to 0$  is degenerate: Every  $(p_A, p_B, 0)$  is an equilibrium and this (noncompact) manifold (D = 0) is globally attracting.

• We apply a singular perturbation approach to derive the cline by assuming

$$p_A = P + \epsilon p + O(\epsilon^2), \quad p_B = Q + \epsilon q + O(\epsilon^2),$$
  
 $D = O(\epsilon),$ 

where P and Q are the single-locus clines.

<sup>&</sup>lt;sup>5</sup>For a more general multilocus approach, see Barton and Shpak (2000).

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 $D = O(\epsilon),$ 

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It is not difficult to show that

$$D = 2\epsilon P'Q' + O(\epsilon^2).^5$$

 $<sup>^5\</sup>mathrm{For}$  a more general multilocus approach, see Barton and Shpak (2000).

• Eventually, we find that p(x) is the unique solution of the linear inhomogeneous second-order equation

$$\mathbf{p}'' + \lambda \alpha(x)[1 - 2P(x)]\mathbf{p} + 2\lambda\beta(x)P'(x)Q'(x) = 0.$$

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Variation of constants yields

$$p(x) = P'(x)k(x) \,,$$

where k(x) is obtained by integration of expressions such as  $[P'(y)]^2Q'(y)$ .

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Variation of constants yields

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• Explicit expressions can be derived if  $\alpha = \beta$ ; then P = Q.

Introduction One locus Two loci Strong recombination Summary General mode An important property of p(x) and  $p_A(x)$ 

$$p'(0) = \frac{2\sqrt{3}\lambda[\alpha_{-}^{2}\beta_{+}^{2}I_{+}(0) + \alpha_{+}^{2}\beta_{-}^{2}I_{-}(0)]}{\alpha_{+}\alpha_{-}\sqrt{\alpha_{+}^{2} + \alpha_{-}^{2}}} > 0.6$$

• Therefore, the cline

$$p_A = P + \epsilon p + O(\epsilon^2)$$

gets steeper in its center as  $\epsilon$  increases from 0, i.e., as linkage between the two loci gets tighter.

<sup>&</sup>lt;sup>6</sup>If, more generally,  $h \neq 0$  is admitted, then p'(0) depends on h (in contrast to P'(0)!).

Introduction

Strong recombination

Summary

General mode

## p(x) and the 'true' (numerical) solution











 $(\lambda = 1, \, \alpha_{+} = 0.2, \, \alpha_{-} = 0.4, \, \beta_{+} = 1, \, \beta_{-} = 0.8)$ 





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• Linkage (smaller *ρ*) steepens the cline in the center<sup>7</sup> but affects the asymptotics only weakly.

see also Slatkin 1975, Barton 1983

<sup>&</sup>lt;sup>8</sup>For a detailed treatment, see Bürger R., Two-locus clines on the real line with a step environment. Theor. Popul. Biol. 117, 1-22 (2017).



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- Therefore, the two loci 'reinforce' each other.

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- Linkage (smaller ρ) steepens the cline in the center<sup>7</sup> but affects the asymptotics only weakly.
- Therefore, the two loci 'reinforce' each other.
- Dominance does not (for two loci, almost not) affect the slope in the center, but strongly influences the asymptotics.

see also Slatkin 1975, Barton 1983

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Now we consider

- A bounded, open domain  $\Omega \subset \mathbb{R}^n$  (with smooth boundary);
- 'General' functions α(x) and β(x) which change sign at least once;
- Neumann boundary conditions.

<sup>&</sup>lt;sup>9</sup>This is based on joint work in progress with Linlin Su, SUSTC, Shenzhen; but see Oberwolfach Report No. 28/2017; DOI: 10.4171/OWR/2017/28



Then the dynamics is given by

$$\begin{aligned} \frac{\partial p_A}{\partial t} &= \Delta p_A + \lambda \alpha(x) p_A (1 - p_A) + \lambda \beta(x) D, \\ \frac{\partial p_B}{\partial t} &= \Delta p_B + \lambda \beta(x) p_B (1 - p_B) + \lambda \alpha(x) D, \\ \frac{\partial D}{\partial t} &= \Delta D + 2 \nabla p_A \cdot \nabla p_B \\ &+ \lambda [\alpha(x)(1 - 2p_A) + \beta(x)(1 - 2p_B)] D - \rho D. \end{aligned}$$

The Laplace operator  $\Delta$  can be replaced by a second-order elliptic operator (then it models rather general migration).

Introduction One locus Two loci Strong recombination Summary General model

## The two-locus PDE model for strong recombination

As before, we fix  $\lambda$  and assume  $\epsilon=1/\rho\ll 1.$  Rescaling time yields

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The limit  $\epsilon \to 0$  is degenerate: Every  $(p_A, p_B, 0)$  is an equilibrium and this manifold (D = 0) is globally attracting.



#### Assume

$$\label{eq:p_A_basis} \hat{p}_A^{(\epsilon)} = P + O(\epsilon), \ \hat{p}_B^{(\epsilon)} = Q + O(\epsilon), \ \hat{D}^{(\epsilon)} = O(\epsilon) \,,$$

where P and Q are the one-locus clines at loci A and B.

Then

$$\hat{D}^{(\epsilon)} = 2\epsilon \nabla P \cdot \nabla Q + O(\epsilon^2).$$



## Approximating the two-locus cline if $\epsilon = 1/\rho \ll 1$

• We set 
$$\hat{p}_A^{(\epsilon)} = P + \epsilon \mathbf{p} + o(\epsilon)$$
.

• Then p(x) is the unique solution of

$$\Delta \mathbf{p} + \lambda \alpha(x) [1 - 2P(x)] \mathbf{p} + 2\lambda \beta(x) \nabla P(x) \cdot \nabla Q(x) = 0.$$

(Because *P* is a globally asymptotically stable equilibrium of the one-locus problem,  $\Delta + \lambda \alpha(x)[1 - 2P]$  is invertible.)



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• The above expansions ( $\hat{p}_A^{(\epsilon)} = P + \epsilon p + o(\epsilon)$ , etc.) essentially require the implicit function theorem.



### If $\epsilon > 0$ , every equilibrium of

$$\begin{aligned} \frac{\partial p_A}{\partial t} &= \epsilon \left[ \Delta p_A + \lambda \alpha(x) p_A (1 - p_A) + \lambda \beta(x) D \right], \\ \frac{\partial p_B}{\partial t} &= \epsilon \left[ \Delta p_B + \lambda \beta(x) p_B (1 - p_B) + \lambda \alpha(x) D \right], \\ \frac{\partial D}{\partial t} &= \epsilon \left[ \Delta D + 2 \nabla p_A \cdot \nabla p_B + \lambda [\alpha(x)(1 - 2p_A) + \beta(x)(1 - 2p_B)] D \right] \\ &- D. \end{aligned}$$

is a solution of

 $F(p_A, p_B, D, \epsilon) = 0,$ 

where F denotes the right-hand side.

<sup>&</sup>lt;sup>10</sup> In the meantime, Adrian (K.Y.) Lam has suggested a solution.



For small  $\epsilon,$  we want to show existence and uniqueness of solutions  $(p_A,p_B,D)$  of

$$F(p_A, p_B, D, \epsilon) = 0,$$

where

$$F: X^3 \times \mathbb{R} \to Y^3$$
,

and

$$\begin{split} X &:= \left\{ u \in C^{2+\gamma}(\bar{\Omega}) : \frac{\partial u}{\partial \nu} = 0 \text{ on } \partial \Omega \right\}, \\ Y &:= C^{\gamma}(\bar{\Omega}) \quad \text{for some } \gamma \in (0,1) \,. \end{split}$$

## **Open problem**

• We need the eigenvalues of the linearization of F with respect to  $(p_A, p_B, D)$  evaluated at (P, Q, 0):

$$\begin{split} -\mu\phi_1 &= \Delta\phi_1 + \lambda\alpha(x)(1-2P)\phi_1 + \lambda\beta(x)\phi_3 &\text{in }\Omega\,,\\ -\mu\phi_2 &= \Delta\phi_2 + \lambda\beta(x)(1-2Q)\phi_2 + \lambda\alpha(x)\phi_3 &\text{in }\Omega\,,\\ -\mu\phi_3 &= -\phi_3 &\text{in }\Omega\,,\\ \frac{\partial\phi_i}{\partial\nu} &= 0 &\text{on }\partial\Omega \text{ for }i = 1,2,3\,. \end{split}$$

## One locus Two loci Strong recombination Summary

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General model

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• Because *P* and *Q* are globally asymptotically stable in their respective 1-locus problems, all eigenvalues are positive.

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- Because *P* and *Q* are globally asymptotically stable in their respective 1-locus problems, all eigenvalues are positive.
- Therefore, the linearization of *F* is one-to-one.
- However, it is not onto, as is required for applying the IFT in infinitely many dimensions.



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