Dynamics and Equilibrium Structure of Migration-Selection Models

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## Outline

1. A semilinear parabolic system pertaining to selection and migration

2. Theory of two-allele migration-selection models

3. The complexity of the complete dominance case

4. Various extensions of migration-selection models

1. A semilinear parabolic system pertaining to selection and migration

## Diploid Population at Single Locus



Alleles  $A_1, A_2, \ldots, A_n$ ; genotypes  $A_iA_j$  (= $A_jA_i$ ) E.g., At ABO locus for human blood type, there are 3 major alleles A, B, O; and 6 genotypes AA, AB, AO, BO, BB, OO

$$\frac{dp_i}{dt} = p_i[r_i(p) - \bar{r}(p)] \tag{S}$$

 $p_i(t)$ : frequency of allele  $A_i$  at time  $t,\,1\leqslant i\leqslant n$ 

 $p = (p_1, p_2, \ldots, p_n)$ : gene freq. vector;

 $p \in \Delta_n = \{ p \in \mathbb{R}^n : 0 \leqslant p_i \leqslant 1, \sum_i p_i = 1 \}$  (n-simplex)

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•  $d\bar{r}/dt = 2\sum_i p_i (r_i - \bar{r})^2 \ge 0$ , "=" holds iff at equilibrium

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Sir Ronald Aylmer Fisher (17 Feb 1890 – 29 Jul 1962) British statistician and geneticist

#### Fisher's Fundamental Theorem of Natural Selection (1930)

"The rate of increase in fitness of any organism at any time is equal to its genetic variance at that time."



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This integrates the principles of Mendelian genetics with Darwinian natural selection.

#### Selection with Spatial Structure

 $\Omega$ : smooth bounded domain in  $\mathbb{R}^N$ , habitat.

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$$\frac{\partial p_i}{\partial t} = \Delta p_i + \lambda p_i [r_i(x, p) - \bar{r}(x, p)], \quad x \in \Omega, \ t > 0$$
 (MS)

#### with zero Neumann b.c.

- $\lambda > 0$  is ratio of selection intensity s to migration rate d
- ▶  $p = (p_1, ..., p_n)$ ,  $r_i(x, p) = \sum_j r_{ij}(x)p_j$ ,  $\bar{r}(x, p) = \sum_i r_i p_i$

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**Core questions**: protection/elimination of certain allele(s); existence, uniqueness, multiplicity of pos. equilibriums; stability of equilibriums; global dynamics, etc.

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(Lou, Nagylaki 2002, 2004, 2006 JDE; Lou, Nagylaki, Ni 2013 DCDS; Hofbauer, Su 2016 SIAP) 2. Theory of two-allele migration-selection models

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 $p_1 = u(x,t)$ : freq. of allele  $A_1$  at location  $x \in \Omega \subset \mathbb{R}^N$  and time t,  $p_2 = 1 - u$ : freq. of allele  $A_2$ .

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Fitness of genotype  $A_iA_j$ :  $r_{ij}(x) = c_{ij}g(x)$ , where

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• h = 0:  $f_h(u) = u(1 - u)$ , no dominance (as in Fisher's eq.)

► h = -1:  $f_h(u) = 2u^2(1-u)$ ,  $A_1$  recessive (or  $A_2$  completely dominant to  $A_1$ )

► 
$$h = 1$$
:  $f_h(u) = 2u(1-u)^2$ ,  $A_2$  recessive

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$$u_t = \Delta u + \lambda g(x) f(u), \quad x \in \Omega, \ t > 0$$
 (MS<sub>2</sub>)

with zero Neumann b.c.

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 $f(0) = f(1) = 0; \ f(u) > 0, \ u \in (0,1); \ f \in C^1([0,1])$ (cf.,  $f_h(u) = u(1-u)[1+h-2hu]$ )

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- ►  $0 = \int_{\Omega} [\Delta u + \lambda g f(u)] dx = \int_{\Omega} \lambda g f(u) dx$  $\Rightarrow \exists$  nontrivial equil. only if g(x) changes sign
- ▶ By strong maximum principle, every nontrivial equil.  $u(x) \in (0,1)$  in  $\overline{\Omega}$  $u(x,0) \in [0,1], \neq 0, \neq 1 \Rightarrow u(x,t) \in (0,1), \forall x \in \overline{\Omega}, t > 0$

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Without migration  $u_t = \lambda g(x) f(u)$ :

$$\begin{array}{l} g(x)>0 \Rightarrow u(x,t) \rightarrow 1 \text{ as } t \rightarrow \infty;\\ g(x)<0 \Rightarrow u(x,t) \rightarrow 0 \text{ as } t \rightarrow \infty. \end{array}$$

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**Theorem.** Assume f'(0) > 0, f'(1) < 0 (e.g.,  $f_h$  with |h| < 1). (i) If  $\int_{\Omega} g(x) dx = 0$ , then a nontrivial equil. always exists with migration.

(ii) If  $\int_{\Omega} g(x) dx \neq 0$ , then a nontrivial equil. exists if migration is not too strong (compared to selection), i.e.,  $\lambda > \lambda^*$ .

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- Fleming 1975 JMB ( $\Delta$ ): variational approach
- Hess & Senn 1982 Math. Ann. (elliptic L): indefinite-weight eigenvalue problem with principal eigenvalue λ\* (Lφ + λm(x)φ = 0)
- Senn 1983 CPDE (elliptic L): linearization at u = 0, 1, upper and lower solutions, global bifurcation w.r.t. λ

## Uniqueness of Nontrivial Equilibrium

**Theorem.** If f''(u) < 0 in (0,1) (e.g.,  $f_h$  with  $|h| \leq 1/3$ ), then nontrivial equil. (if  $\exists$ ) is unique and globally asymptotically stable.

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► Henry 1981 (△)

Lou and Nagylaki 2002 (elliptic L)





Nontrivial Equilibrium near Bifurcation.I

**Theorem.** (i) If  $\int_{\Omega} g(x) dx = 0$  and f'(0) > 0, f'(1) < 0, then max. (min.) points of f lead to stable (unstable) branches



• Brown and Lin 1981 ( $\Delta$  with stability); Senn 1983 (elliptic L)

(a)

## Nontrivial Equilibrium near Bifurcation.II

**Theorem.** (ii) If  $\int_{\Omega} g(x) dx < 0$  and f'(0) > 0, then



Fleming 1975 ( $\Delta$ ), Senn 1983 (elliptic L)

## Nontrivial Equilibrium near Bifurcation.II

**Theorem.** (ii) If  $\int_{\Omega} g(x) dx < 0$  and f'(0) > 0, then



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(iii) The case  $\int_{\Omega} g(x) \ dx > 0$  and f'(1) < 0 is similar.

3. The complexity of the complete dominance case

# The Complete Dominance Case

When allele  $A_2$  is completely dominant to allele  $A_1$ , h = -1 and

$$f_h(u) = u(1-u)[1+h-2hu] = 2u^2(1-u).$$

Thus, (MS<sub>2</sub>) becomes

$$u_t = \Delta u + \lambda g(x)u^2(1-u), \quad x \in \Omega, \quad t > 0$$
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- degeneracy: f'(0) = 0
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Conjecture of Lou-Nagylaki (2002 JDE, 2008 Tutorials in mathematical biosciences IV):



## Positive Answers to LN Conjecture



- Existence: Nakashima, Ni, Su 2010 DCDS; Lou, Ni, Su 2010 DCDS
- ▶ Uniqueness for  $\int g \ge 0$ :  $\Omega = (-1, 1)$ , large  $\lambda$ ,  $g(x) \ge b_1(x)$ , Nakashima 2016, 2018 JDE

For  $\Omega = (-1, 1)$  and large  $\lambda$ ,

▶  $\int g < 0$ : Nakashima 2020 JDE ( $\exists g \text{ with } 2 \text{ pos. nodal domains, } g(x) < b_2(x), \exists 8 \text{ equils. }$ )

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- ▶ For  $\lambda g^+ \mu g^-$ , g has m pos. domains,  $\lambda > \lambda$ ,  $\mu > \tilde{\mu}(\lambda)$ , then  $\exists (3^m - 1)$  equils. Feltrin, Sovrano 2018 Nonlinearity; Boscaggin, Feltrin, Sovrano 2020 Adv. Nonlinear Stud.

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- For λg<sup>+</sup> − μg<sup>−</sup>, g has m pos. domains, λ > λ̃, μ > μ̃(λ), then ∃ (3<sup>m</sup> − 1) equils. Feltrin, Sovrano 2018 Nonlinearity; Boscaggin, Feltrin, Sovrano 2020 Adv. Nonlinear Stud.



Fig. 1 in F-S 2018,  $\lambda = 20$ ,  $\mu = 500$ ,  $g = \sin(\pi t)$ ,  $\Omega = (0,3)$   $\int g \ge 0$ : Nakashima, Su 2020 JDE ( $\exists g \text{ with } 2 \text{ pos. domains,}$  $g(x) < b_3(x)$ , 3 equils.)

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## Some Open Problems

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- ► Equilibrium structure of (SM<sub>2</sub>) when f is not concave in (0,1) and not degenerate at 0 and 1 (e.g., |h| < 1)?</p>

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- For the complete dominance case  $f(u) = u^2(1-u)$ , when  $\Omega = (-1, 1)$  and q(x) changes sign only once, does LN Conjecture hold?
- Equilibrium structure of  $(SM_2)$  when f is not concave in (0,1)and not degenerate at 0 and 1 (e.g., |h| < 1)?
- Dynamics and eugil. structure of system (SM) for multiple alleles?

(Many open problems in Lou-Nagylaki-Ni 2013 DCDS)

4. Various extensions of migration-selection models

# (MS) + Long-Distance Migration



In Nagylaki 2012a TPB, long-distance migration was approximated by panmixia:

$$\frac{\partial p_i}{\partial t} = \Delta p_i + p_i [r_i(x, p) - \bar{r}(x, p)] + \frac{b[\bar{p}_i(t) - p_i]}{b[\bar{p}_i(t) - p_i]}, \quad x \in \Omega, \ t > 0$$

with zero Neumann b.c., where

 $\bar{p}_i(t) = \frac{1}{|\Omega|} \int_{\Omega} p_i(x,t) \ dx$ , b > 0 rescaled panmictic rate.

# (MS) + Long-Distance Migration



In Nagylaki 2012a TPB, long-distance migration was approximated by panmixia:

$$\frac{\partial p_i}{\partial t} = \Delta p_i + p_i [r_i(x, p) - \bar{r}(x, p)] + \frac{b[\bar{p}_i(t) - p_i]}{b[\bar{p}_i(t) - p_i]}, \quad x \in \Omega, \ t > 0$$

with zero Neumann b.c., where

 $\bar{p}_i(t) = \frac{1}{|\Omega|} \int_{\Omega} p_i(x,t) \, dx, \quad b > 0$  rescaled panmictic rate.

(Nagylaki 2012b TPB; Lou, Nagylaki, Su 2013 JDE; Su, Nagylaki 2015 DCDS; Li, Nakashima, Ni 2017 Eur. J. Appl. Math., etc.)



#### Nagylaki (2016 TPB) proposed

$$\frac{\partial p_i}{\partial t} = \Delta p_i + p_i [r_i(x, p) - \bar{r}(x, p)] + \frac{b[\bar{p}_i(t) - p_i]}{b[\bar{p}_i(t) - p_i]}, \quad x \in \Omega, \ t > 0$$

with zero Neumann b.c. on  $\partial\Omega$  and transition condition

$$abla_{\nu} p_i(x\pm,t) = \gamma_{\pm} [p_i(x+,t) - p_i(x-,t)], \quad x \in \Gamma, \ t > 0.$$
 (TC)

Here  $\Gamma$  barrier,  $\Omega = \Omega_{-} \cup \Gamma \cup \Omega_{+}$ ,  $\Omega_{-} \cap \Omega_{+} = \emptyset$ ,  $\nu$  unit normal vector along  $\Gamma$  from  $\Omega_{-}$  to  $\Omega_{+}$ ,  $x \pm$  limit of x as  $x \to \Gamma$  from  $\Omega_{\pm}$ ,  $\gamma_{+}$  and  $\gamma_{-}$  rescaled rightward and leftward transmissivities.

#### $abla_{\nu} p_i(x\pm,t) = \gamma_{\pm} [p_i(x+,t) - p_i(x-,t)], \quad x \in \Gamma, \ t > 0$ (TC)

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- Question: Can (TC) be derived by the method of effective boundary conditions? Yes, if γ<sub>+</sub> = γ<sub>-</sub> (Li and Wang 2017 Nonlinearity).

Locus A: alleles A, a; locus B: alleles B, b4 types of gametes: AB, Ab, aB, abRecombination of two loci during meiosis



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Freqs. of gametes  $p = (p_1, \ldots, p_4) \in \Delta_4$  and obey

 $\partial_t p_i = d\Delta p_i + \lambda S_i(x, p) - \eta_i \rho D, \quad x \in \Omega, \ t > 0$  (MS+R)

with zero Neumann b.c. Here  $\rho$  rescaled recombination rate,

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## Thank you for your attention!

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- Thomas Nagylaki<sup>†</sup>, The Univ. of Chicago
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