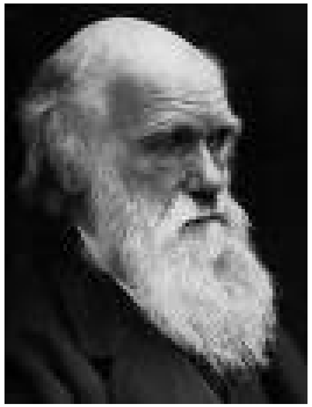
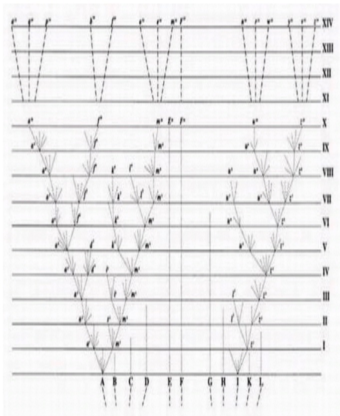
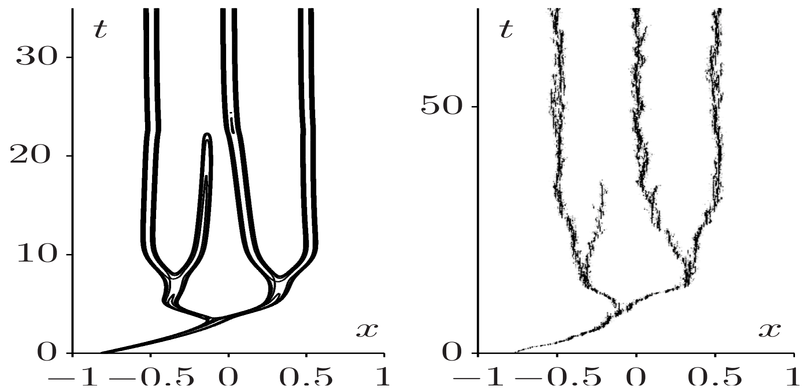
Adaptation, selection, mutation : a mathematical view of evolution

Benoît Perthame, METE 2018







Population formalism

$$\underbrace{\frac{\partial}{\partial t} n(x,t)}_{\text{variation of number of individuals}} = \overbrace{\int b(y) M(x,y) n(y,t) dy}^{\text{birth with mutations}} + n(x,t) \underbrace{R\big(x, I(t)\big)}_{\text{growth rate}}$$

- $n(x,t) =$ number of indivuduals with trait x
- $x =$ phenotypical trait
- $I(t) = (I_1(t), ...I_J(t)) =$ environmental unknowns
- $R(x,I)$ of Lotka-Volterra type, can be negative
- Standard : Calsina, Cuadrado, Desvillettes, Raoul, Jabin, Mirrahimi, ...

Population formalism

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- interplay between population and environment

Population formalism

A variant is

$$\underbrace{\frac{\partial}{\partial t} n(x,t)}_{\text{variation of number of individuals}} = \overbrace{\Delta n(y,t)}^{\text{neutral mutations}} + n(x,t) \underbrace{R\Big(x, I(t)\Big)}_{\text{growth rate}}$$

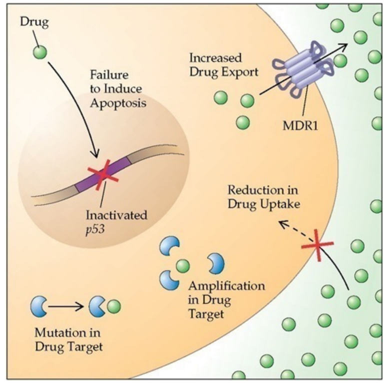
Motivation

The variable x can be

- Size of the adult individuals (adaptation to foraging)
- Cannibalism rate (and evolutionary suicide)
- Cooperative behaviour
- Dispersal rate

Motivation

But adaptation can be seen on shorter times scales



- Resistance of tumor cells to chemotherapy

- Resistance to insecticides

Rescaling

$$\varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t) = \int b(y) M_\varepsilon(x,y) n_\varepsilon(y,t) dy + n_\varepsilon(x,t) R\Big(x, I_\varepsilon(t)\Big),$$

- $M_\varepsilon(x,y)$ means mutations are rare/have small effect

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- $M_\varepsilon(x,y) = \frac{1}{\varepsilon^d} M\left(\frac{x-y}{\varepsilon}\right)$

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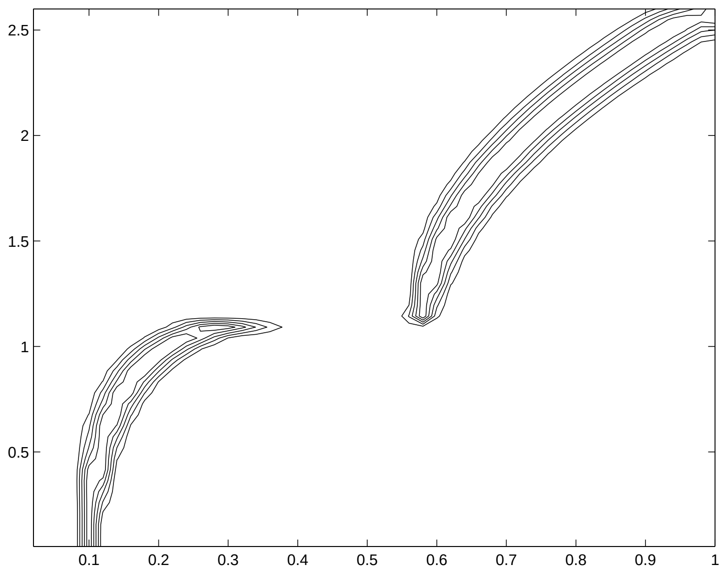
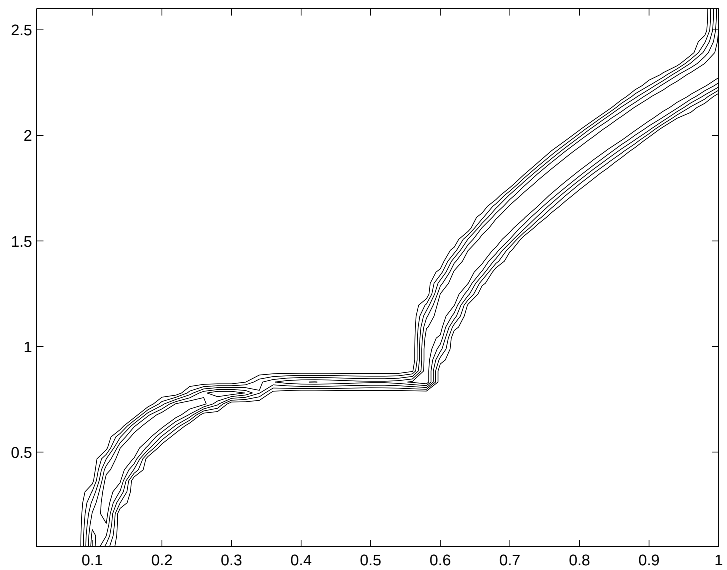
- $M_\varepsilon(x,y)$ means mutations are rare/have small effect
- $\varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t)$ means we consider a long time scale
- $M_\varepsilon(x,y) = \frac{1}{\varepsilon^d} M\left(\frac{x-y}{\varepsilon}\right)$
- Concentrations occur $n_\varepsilon(x,t) \approx e^{-|x-\bar{x}(t)|^2/\varepsilon}$

Examples of behaviors

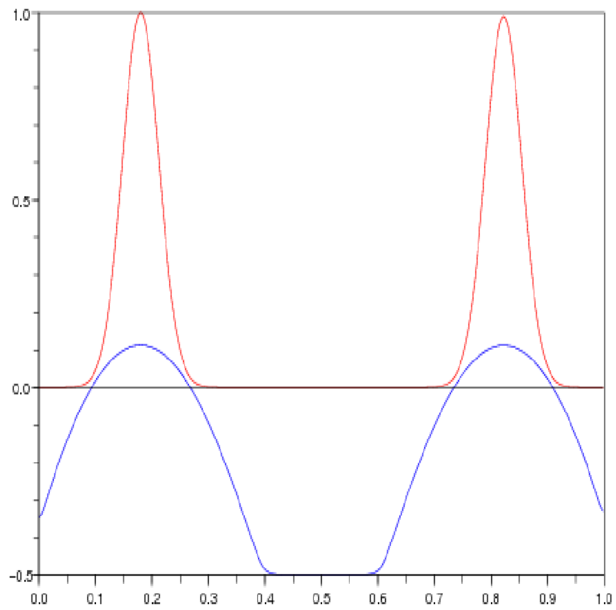


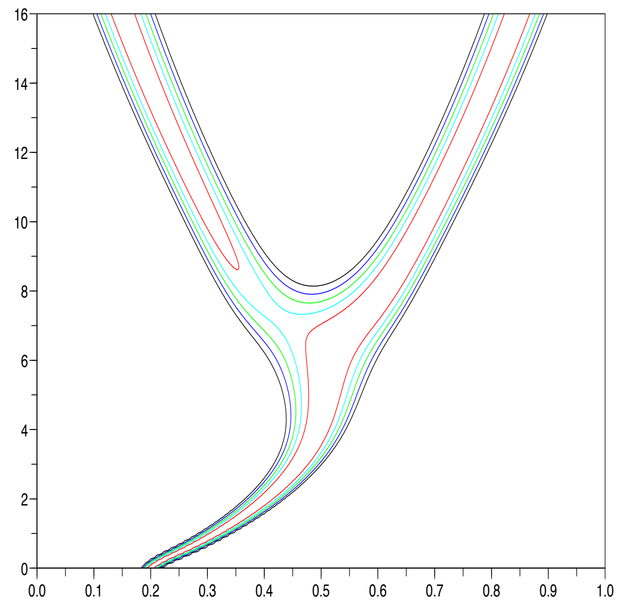
Direct simulation (1500 points)



H.-J. solution (200 points)

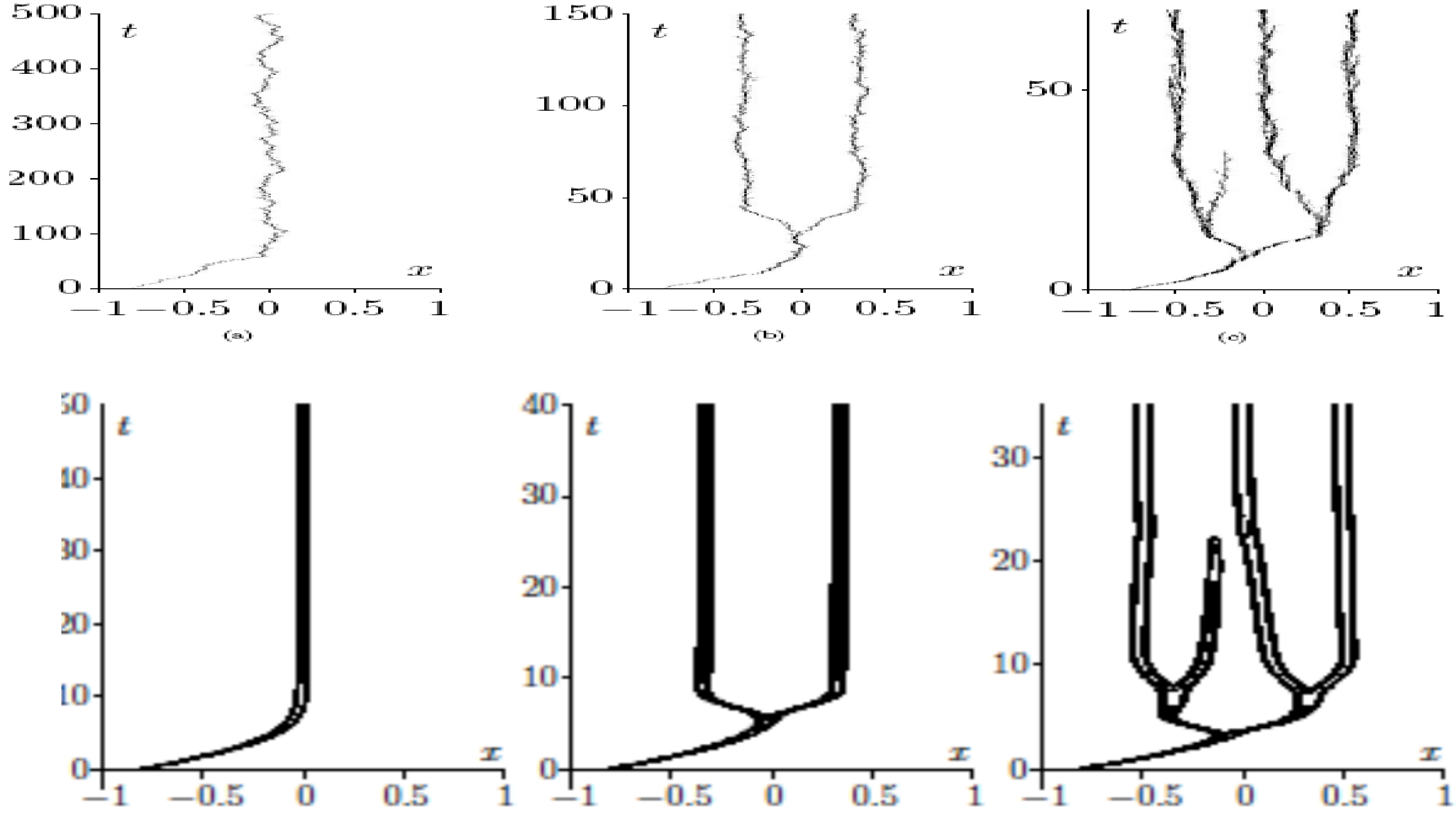
Examples of behaviors





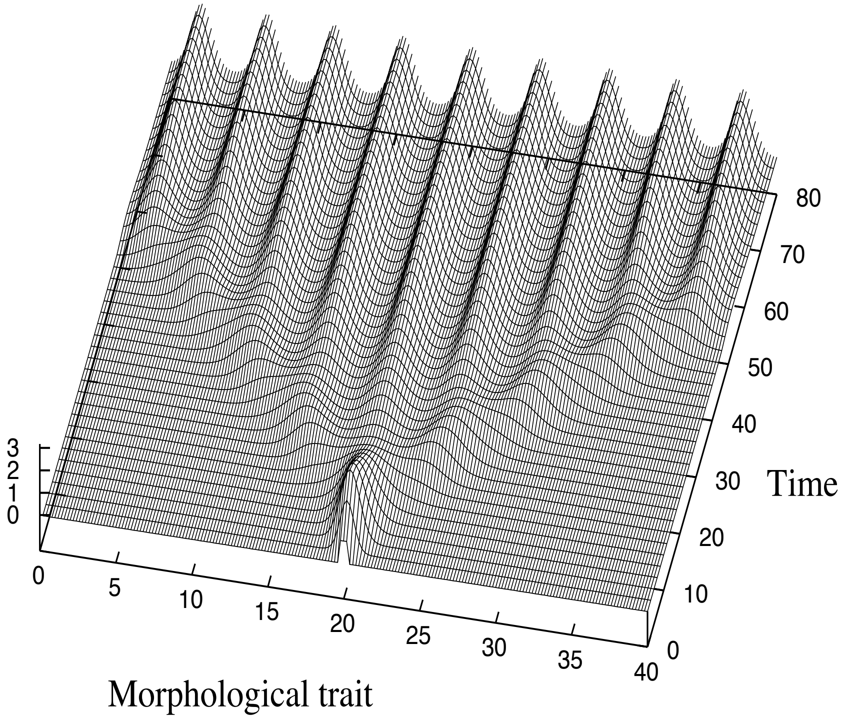
Branching can occur for more general right hand sides (convolution)

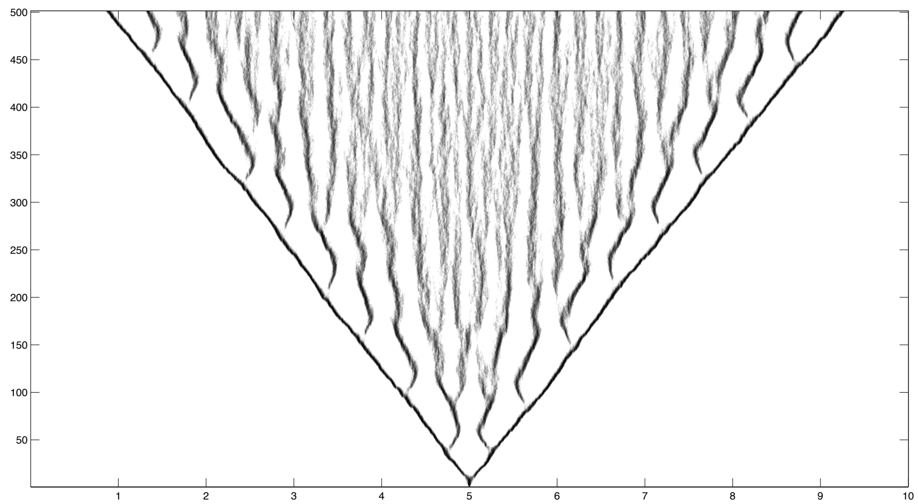
Examples of behaviors



Branching for a Gaussian convolution

Examples of behaviors





Branching for a non-Gaussian convolution

Rescaling

$$\varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t) = \int b(y) M_\varepsilon(x,y) n_\varepsilon(y,t) dy + n_\varepsilon(x,t) R\Big(x, I_\varepsilon(t)\Big),$$

- $M_\varepsilon(x,y)$ means mutations are rare/have small effect
- $\varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t)$ means we consider a long time scale
- Simple case $I_\varepsilon(t)$ is reduced to the knowledge of

$$\varrho_\varepsilon(t) = \int_{\mathbb{R}^d} n_\varepsilon(x,t) dx$$

Concentration phenomena

$$\begin{cases} \varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t) - \varepsilon^2 \Delta n_\varepsilon = n_\varepsilon(x,t) R\Big(x, \varrho_\varepsilon(t)\Big), & x \in \mathbb{R}, \\ \varrho_\varepsilon(t) = \int_{\mathbb{R}^d} n_\varepsilon(x,t)\,dx. \end{cases}$$

- $\exists \varrho_M > 0$ s.t. $\max_x R(x, \varrho_M) = 0$
- $R_\varrho < 0$
- $R_x > 0$

Theorem (d=1, monotone) For well-prepared initial data, we have

$$n_\varepsilon(x,t) \underset{\varepsilon_k \to 0}{\longrightarrow} \bar{\varrho}(t)\delta(x = \bar{x}(t)), \qquad \bar{x}(t),\ \bar{\varrho}(t) \in BV_{\text{loc}}(0,\infty)$$

$$R\Big(\bar{x}(t), \bar{\varrho}(t)\Big) = 0 \qquad \text{for a.e. } t > 0$$

$\bar{x}(t)$ is the fittest trait

Concentration phenomena

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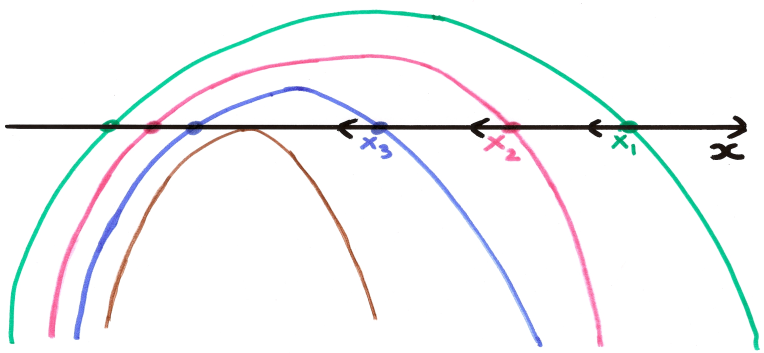
as $t \to \infty$ $$R\big(\bar{x}_\infty, \bar{\varrho}_\infty\big) = 0 = \max_x R\big(x, \bar{\varrho}_\infty\big)$$

Concentration phenomena, $d \geq 1$

$$\begin{cases} \varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t) - \varepsilon^2 \Delta n_\varepsilon = n_\varepsilon(x,t) R\Big(x, \varrho_\varepsilon(t)\Big), \qquad x \in \mathbb{R}^d \\ \varrho_\varepsilon(t) = \int_{\mathbb{R}^d} n_\varepsilon(x,t)\,dx. \end{cases}$$



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as $t \to \infty$ $\qquad R\Big(\bar x_\infty, \bar\varrho_\infty\Big) = 0 = \min_\rho \max_x R\Big(x, \varrho\Big)$

Concentration phenomena

Why is mathematics interesting ?

- Nonlocal nonlinearity drastically changes the picture
- Control in L^1 only
- Constrained Hamilton-Jacobi eq.
- Is there a simple rule for the dynamics of $\bar{x}(t)$?

Related approaches

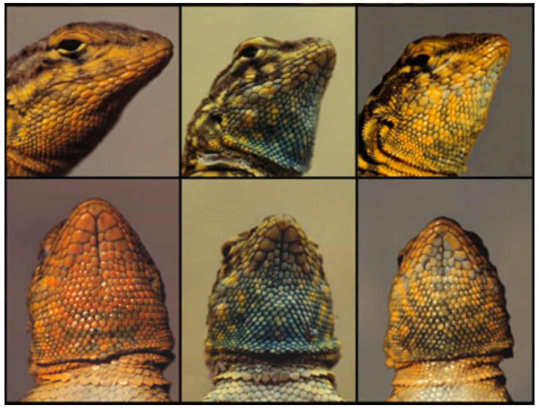
- **Evolutionary game theory**

Blue (stronger),

Orange (middle size),

Yellow (smaller)

compensate by mating **strategies**



from B. Sinervo. *http : //bio.research.ucsc.edu/barrylab*

NATURE VOL. 246 NOVEMBER 2 1973

The Logic of Animal Conflict

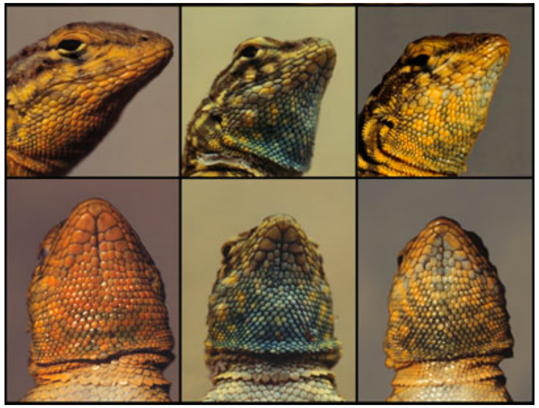
J. MAYNARD SMITH
School of Biological Sciences, University of Sussex, Falmer, Sussex BN1 9QG

G. R. PRICE
Galton Laboratory, University College London, 4 Stephenson Way, London NW1 2HE

J. Hofbauer- M. Nowak- K. Sigmund

Related approaches

• Evolutionary game theory



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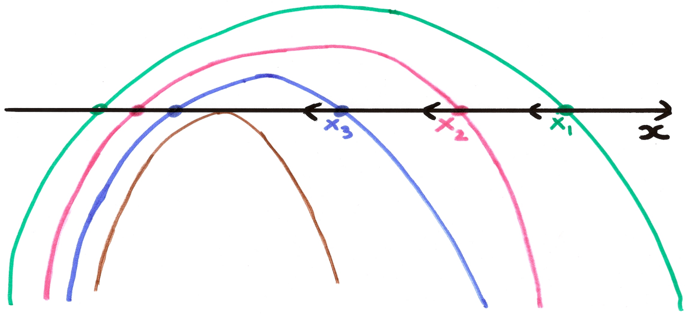
The relation can be seen by

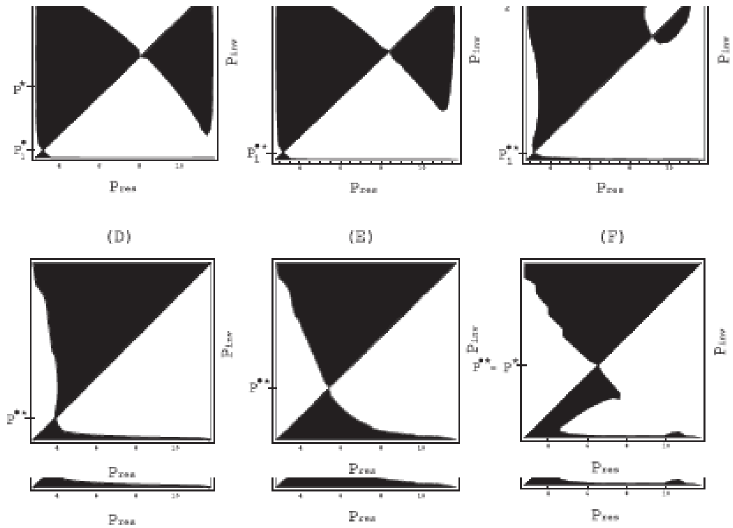


$$\max_{S} R(x, \bar{\varrho}_\infty) = 0 = R(\bar{x}_\infty, \bar{\varrho}_\infty)$$

$$\min_{\varrho} \max_{S} R(x, \varrho) = 0 = R(\bar{x}_\infty, \bar{\rho}_\infty)$$

Related approaches

- **Dynamical systems**



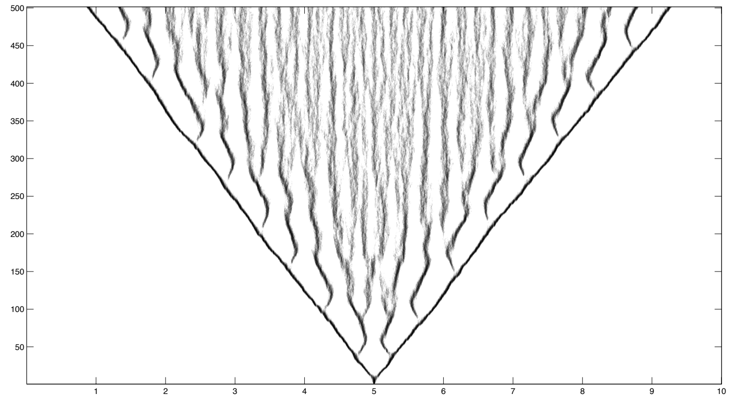
H. Metz, S. Geritz, G. Meszena, S. Kisdi, **O. Diekmann**

Can a mutant invade the resident population ?

Related approaches

• Stochastic models, Individual Based Models : N individuals,

rescale mutation, birth, death rates



U. Dieckmann-R. Law, R. Ferriere

S. Billard, N. Champagnat

S. Méléard, V. C Tran

Related approaches

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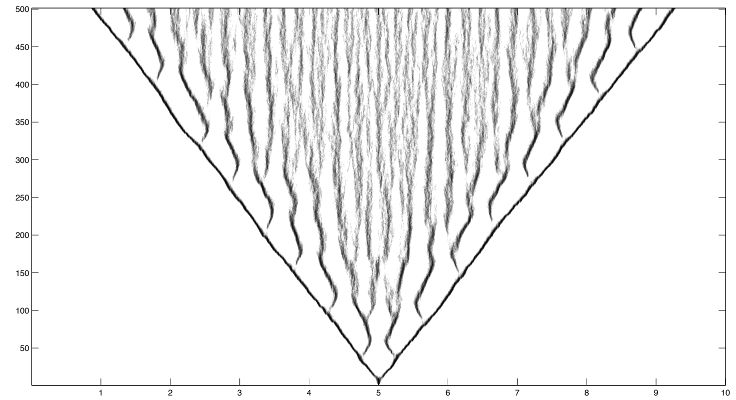


R. Ferriere, N. Champagnat
S. Méléard, V. C Tran

As $N \to \infty$, they establish both

$$\varepsilon \frac{\partial}{\partial t} n_\varepsilon(t,x) - \varepsilon^2 \Delta n_\varepsilon = n_\varepsilon(t,x) R\big(x, \varrho_\varepsilon(t)\big)$$

$$\varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t) = \int b(y) \frac{1}{\varepsilon^d} M\Big(\frac{x-y}{\varepsilon}\Big) n_\varepsilon(y,t)\,dy + n_\varepsilon(x,t) R\big(x, I_\varepsilon(t)\big),$$

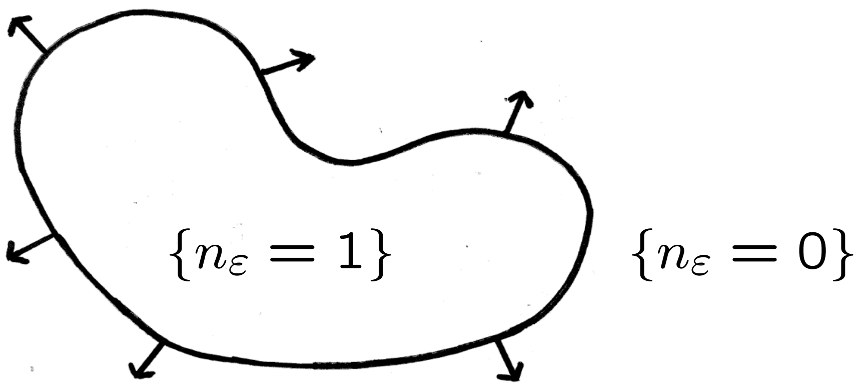
Asymptotics with mutations

$$\begin{cases} \varepsilon \frac{\partial}{\partial t} n_\varepsilon(t,x) - \varepsilon^2 \Delta n_\varepsilon = n_\varepsilon(t,x) R\Big(x, \varrho_\varepsilon(t)\Big), \\ \\ \varrho_\varepsilon(t) = \int_{\mathbb{R}^d} n_\varepsilon(t,x)\,dx. \end{cases}$$

Asymptotics with mutations

This is not far from Fisher/KPP equation for invasion fronts/chemical reaction

$$\varepsilon \frac{\partial}{\partial t} n_\varepsilon(t,x) - \varepsilon^2 \Delta n_\varepsilon = n_\varepsilon(t,x)\Big(1 - n_\varepsilon(t,x)\Big),$$



WKB, large deviations, level sets, geometric motion

G. Barles, L. C. Evans, W. Fleming, P. E. Souganidis, Mete

Asymptotics with mutations

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In the limit one can expect

$$0 = n(t,x)R\Big(x, \varrho(t)\Big),$$

$$n(t,x) = \rho \delta_{\Gamma(t)}, \qquad \Gamma(t) \subset \Big\{ R(\cdot, \rho(t)) = 0 \Big\}.$$

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Which points are selected in this hypersurface ?

Asymptotics with mutations

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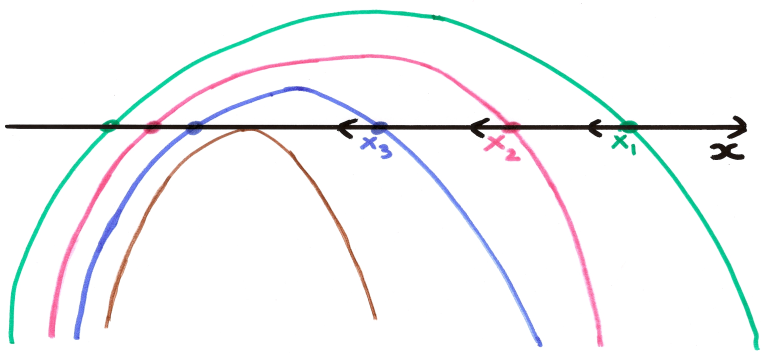
In dimension $d = 1$, R monotone, there is a single point.

$$\bar{x}(t) \Longleftrightarrow \bar{\varrho}(t)$$

Concentration phenomena, $d \geq 1$

$$\begin{cases} \varepsilon \frac{\partial}{\partial t} n_\varepsilon(x,t) - \varepsilon^2 \Delta n_\varepsilon = n_\varepsilon(x,t) R\Big(x, \varrho_\varepsilon(t)\Big), \quad x \in \mathbb{R}^d \\ \varrho_\varepsilon(t) = \int_{\mathbb{R}^d} n_\varepsilon(x,t)dx. \end{cases}$$



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Proof

Step 1. $\varrho_\varepsilon(t) \in_{\text{b}} L^\infty, \qquad n_\varepsilon \in_{\text{b}} L^\infty_t(L^1_x)$

Step 2. A BV estimate

Step 3. Represent

$$n_\varepsilon(t,x) = \exp \frac{\varphi_\varepsilon(t,x)}{\varepsilon}$$

the 'fittest' trait $\bar{x}(t)$ is characterised by the Eikonal equation with constraints

$$\begin{cases} \frac{\partial}{\partial t}\varphi(t,x) = R\Big(x, \bar{\varrho}(t)\Big) + |\nabla\varphi(t,x)\Big)|^2 \\ \max_x \varphi(t,x) = 0 \qquad \Big(= \varphi(t, \bar{x}(t)) \Big). \end{cases}$$

Proof

In the viscosity sense

$$\begin{cases} \frac{\partial}{\partial t}\varphi(t,x) = R\Big(x, \bar{\varrho}(t)\Big) + |\nabla\varphi(t,x)\Big)|^2 \\ \max_x \varphi(t,x) = 0 \qquad \Big(= \varphi(t,\bar{x}(t))\ \Big). \end{cases}$$

$\varphi(t,x)$ is Lipschitz

This is not an obstacle problem.

$\bar{\varrho}(t)$ is a Langrange multiplier !

Proof

In the viscosity sense

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Uniqueness

- $R(x,\varrho) = b(x)a(\varrho) - d(x)$ (G. Barles and BP)
- J.-M. Roquejoffre et S. Mirrahimi
- V. Calvez, A. Lam Work in preparation

Proof

$$\begin{cases} \frac{\partial}{\partial t}\varphi(t,x) = R\Big(x, \bar{\varrho}(t)\Big) + |\nabla\varphi(t,x)\Big)|^2 \\ \max_x \varphi(t,x) = 0 \qquad \Big(= \varphi(t, \bar{x}(t)) \Big). \end{cases}$$

Step 4. Any concentration point $x_i(t)$ will satisfy

$$R\Big(\bar{x}_i(t), \bar{I}(t)\Big) = 0$$

Thanks to semi-concavity property of $\varphi(t,x)$

$$-\nu Id \leq D^2\varphi.$$

Canonical equation

Step 5. The concave case leaves place for a regularity regime, if

$$D^2 R \le -\nu Id, \qquad D^2 \varphi^0 \le -\nu Id,$$

then

$$D^2 \varphi \le -\nu Id.$$

Canonical equation

Any concentration point $x_i(t)$ will satisfy

(i) $$R\Big(\bar{x}_i(t), \bar{I}(t)\Big) = 0$$

(ii) $$\frac{d}{dt}\bar{x}_i(t) = \Big(-D^2\varphi(\bar{x}_i(t), t)\Big)^{-1}.\nabla R\Big(\bar{x}_i(t), \bar{I}(t)\Big)$$

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Conclusions :

- The competitive exclusion principle (single Dirac mass for a single nutrient)

For two nutrients $R\Big(\bar{x}_i(t), \bar{I}_1(t), I_2(t)\Big) = 0$
one has four unknows $\bar{I}_1(t), I_2(t), \bar{x}_1(t), x_2(t)$

$R(x, I_1, I_2)$ should have 1 or 2 roots (Champagnat, Jabin, Méléard)

Canonical equation

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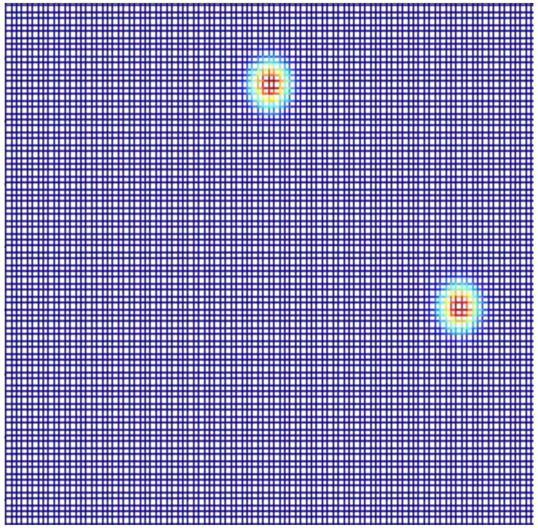
Conclusions :

- The competitive exclusion principle (single Dirac mass)
- $n_\varepsilon = \exp(\varphi/\varepsilon)$ the shape of φ plays a role

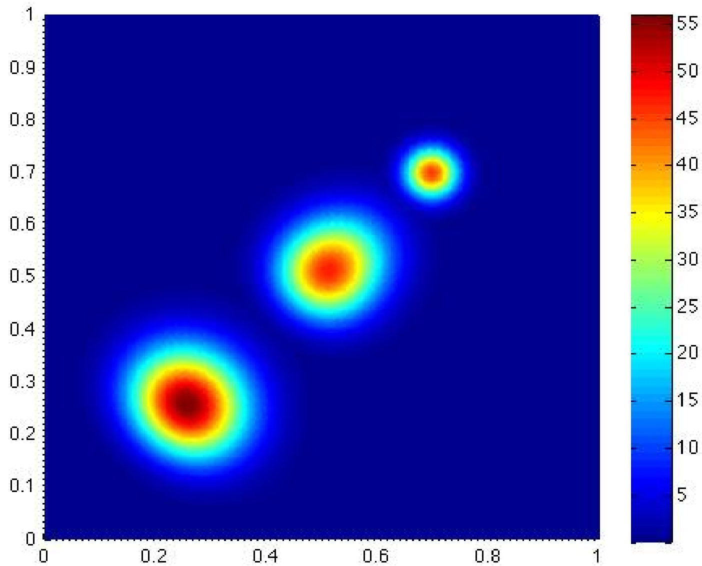
Canonical equation

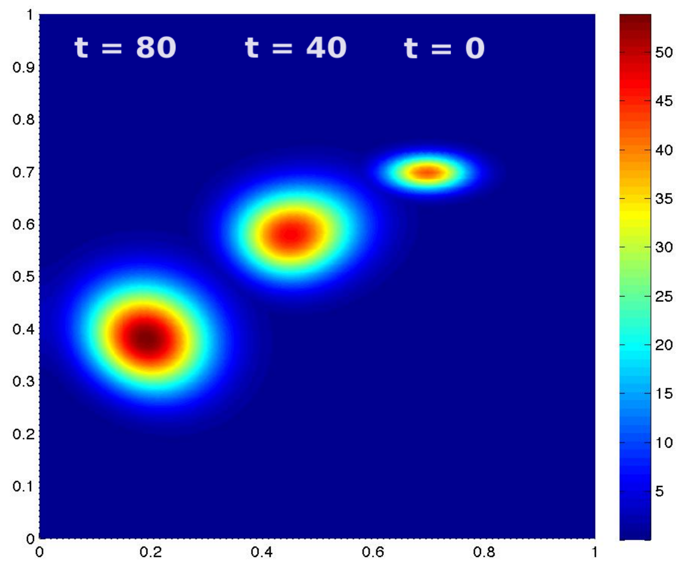


Canonical equation

$$\frac{d}{dt}\bar{x}(t) = \Big(- D^2\varphi(\bar{x}(t),t)\Big)^{-1}.\nabla R\big(\bar{x}(t), \bar{\varrho}(t)\big)$$

Effect of the matrix $\Big(- D^2\varphi(\bar{x}(t),t)\Big)$ (microstructure of the Dirac)





Challenges today

- Explain diversity/heterogeneity with space
- Selection without a proliferating advantage

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- Selection without a proliferating advantage

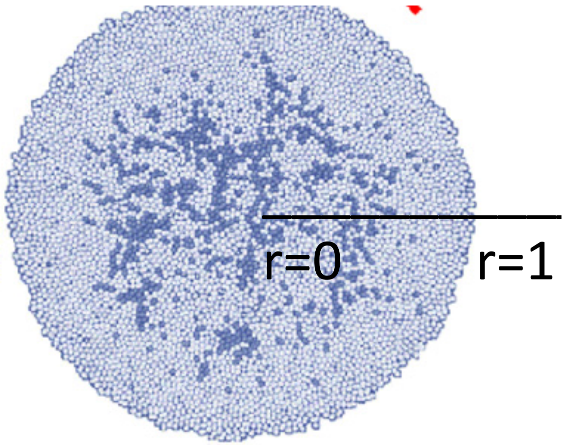
Examples are

- Local selection of a trait with a space variable
- Selection of the fittest age/size
- Selection of dispersal

Space-trait concentration

Let $y \in \mathbb{R}$ the space variable, $x \in \mathbb{R}$ trait variable

$$\begin{cases} \varepsilon \partial_t n_\varepsilon(y,x,t) = \Big[r(x) c_\varepsilon(y,t) - d(x) \varrho_\varepsilon(y,t) - \mu(x)\Big] n_\varepsilon(y,x,t) \\ -\Delta_y c_\varepsilon(y,t) + \Big[\varrho_\varepsilon(y,t) + \lambda\Big] c_\varepsilon(y,t) = \lambda c_B, \\ \varrho_\varepsilon(y,t) = \int n_\varepsilon(y,x,t) dx \end{cases}$$



Interpetation

- Nutrients/drugs are diffused and consumed by cells
- Local conditions select space-dependent traits

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Theorem : For well-prepared initial data, as $\varepsilon_k \to 0$, we have

$$n_\varepsilon(y,x,t) \to \overline{\rho}(y,t) \delta\Big(x - \overline{X}(y,t) \Big)$$

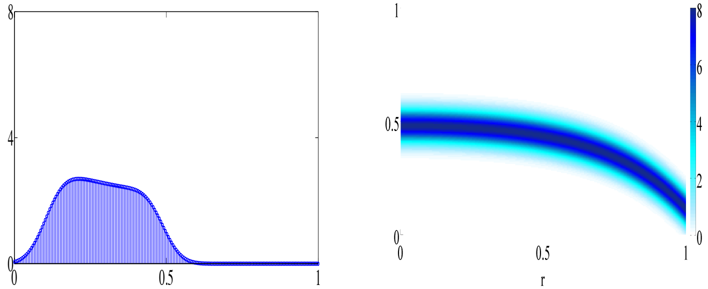
Difficulty : Space works well with L^∞. Traits with L^1

Outcome : Explains heterogeneity

Space–trait concentration

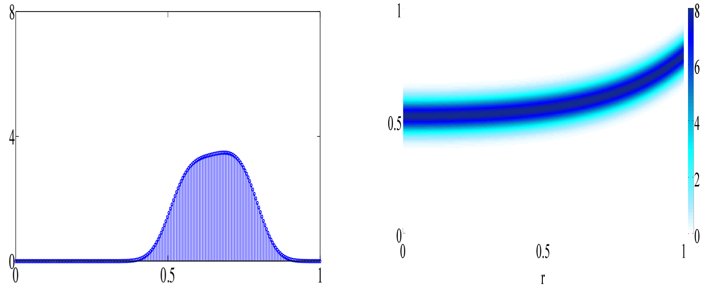
Let $y \in \mathbb{R}$ the space variable, $x \in \mathbb{R}$ trait variable

$$\begin{cases} \varepsilon \partial_t n_\varepsilon(y,x,t) = \Big[r(x) c_\varepsilon(y,t) - d(x) \varrho_\varepsilon(y,t) - \mu(x) \Big] n_\varepsilon(y,x,t) \\ -\Delta_y c_\varepsilon(y,t) + \Big[\varrho_\varepsilon(y,t) + \lambda \Big] \, c_\varepsilon(y,t) = \lambda c_B, \\ \varrho_\varepsilon(y,t) = \int n_\varepsilon(y,x,t) dx \end{cases}$$



Without cytotoxic drug

High heterogeneity



With cytotoxic drug

Lower heterogeneity

Selection of age

A second example (viral load, age when cancer occurs)

$$
\begin{cases}
\varepsilon \partial_t n_\varepsilon(y,x,t) + \partial_y [A(x,y) n_\varepsilon(y,x,t)] + \Big[d(x,y) + \varrho_\varepsilon(t) \Big] n_\varepsilon(y,x,t) = 0 \\
A(x, y=0) n_\varepsilon(y=0,x,t) = \int b(x,y') M_\varepsilon(y,y') n_\varepsilon(y',x,t) dy' dx \\
\varrho_\varepsilon(t) = \int_{y=0}^{\infty} \int_x n_\varepsilon(y,x,t) dx dy
\end{cases}
$$

How to describe the concentration effect ?

Selection of age

Consider the eigenvalue problem x by x

$$\begin{cases} \partial_y[A(x,y)N(y,x)] + d(x,y)N(y,x) = \Lambda(x,\eta) \\ A(x,y=0)N(y=0,x) = \eta \int b(x,y)N(y,x)dydx \\ N(y,x) > 0 \end{cases}$$

The dynamics of concentration is described by

$$\begin{cases} \partial_t\varphi(x,t) + \bar{\varrho}(t) + \Lambda\Big(x, \int M(z)e^{z.\nabla\varphi(x,t)}dz\Big) = 0 \\ \max_x \varphi(x,t) = 0. \end{cases}$$

Selection of age

$$n_\varepsilon(y,x,t) \approx \bar{\varrho}(t)\, e^{\varphi_\varepsilon(x,t)/\varepsilon}\, N_\varepsilon(x,y,t)$$

$$\approx \bar{\varrho}(t)\, \delta(x-\bar{x}(t))\, N(y,t)$$

The strategy of proof is to use $\varphi_\varepsilon(x,t)$ and handle the other corrections by entropy methods for $N_\varepsilon(x,y,t)$

Selection of age

$$n_\varepsilon(y,x,t) \approx \bar{\varrho}(t)\, e^{\varphi_\varepsilon(x,t)/\varepsilon}\, N_\varepsilon(y,x,t)$$

$$\approx \bar{\varrho}(t)\, \delta(x-\bar{x}(t))\, N(y,t)$$

The canonical equation is

$$\frac{d}{dt}\bar{x}(t) = \left(-D^2\varphi(\bar{x}(t),t)\right)^{-1}\left[\nabla_x\Lambda(x,1) + \frac{\partial\Lambda(x,1)}{\partial\eta} D^2\varphi(\bar{x}(t),t).M_1\right]$$

$$M_1 = \int zM(z)dz$$

$M_1 = 0$ for symmetric mutation kernels

Evolution of dispersal

Selection without a proliferative advantage ?

- motility/dispersal of individuals is subject to variability
- no advantage regarding their reproductive rate

- $R(x, \rho) =$ Operator acting on the space variable

Hastings, *Theor. Popul. Biol.* 1983

Evolution of dispersal

We model it for $y \in \Omega$ + Neuman BC, $x =$ dispersal (trait)

$$\partial_t n(t,x,y) \overbrace{= D(x)\partial^2_{yy} n(t,x,y)}^{\text{dispersion/motility}} + \underbrace{\overbrace{n(t,x,y)\,(K(y) - \rho(t,y))}^{\text{reproduction}}}_{=R(x,\cdot)} \overbrace{+\varepsilon^2 \partial^2_{xx} n(t,x,y)}^{\text{mutations on motility}}$$

$$\rho(t,y) = \int_0^\infty n(t,x,y)\,dx$$

$K(y)$ is not constant.

Evolution of dispersal

$$\partial_t n(t,x,y) \overbrace{= D(x)\partial^2_{yy} n(t,x,y)}^{\text{dispersion/motility}} + \overbrace{n(t,x,y)\,(K(y)-\rho(t,y))}^{\text{reproduction}} \overbrace{+\varepsilon^2 \partial^2_{xx} n(t,x,y)}^{\text{mutations on motility}}$$

$$\rho(t,y) = \int_0^\infty n(t,x,y)\,dy$$

Theorem (P. E. Souganidis, BP and K. Y. Lam, Y. Lou) The ESS are of the form

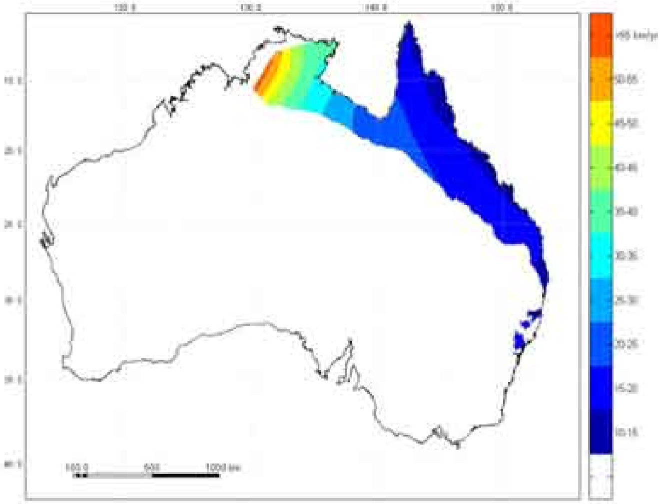
$$n(t,x,y) \approx \bar\rho_\infty(y)\delta\Big(x=\bar x\Big), \qquad D(\bar x) = \min D(x)$$

and the constrained H.-J. eq.

$$\begin{cases} \frac{\partial}{\partial t}\varphi(x,t) = \Lambda(x,\bar\varrho(\cdot,t)) + |\nabla\varphi|^2 \\ \max_x \varphi(x,t) = 0 = \varphi(\bar x(t),t), \end{cases}$$

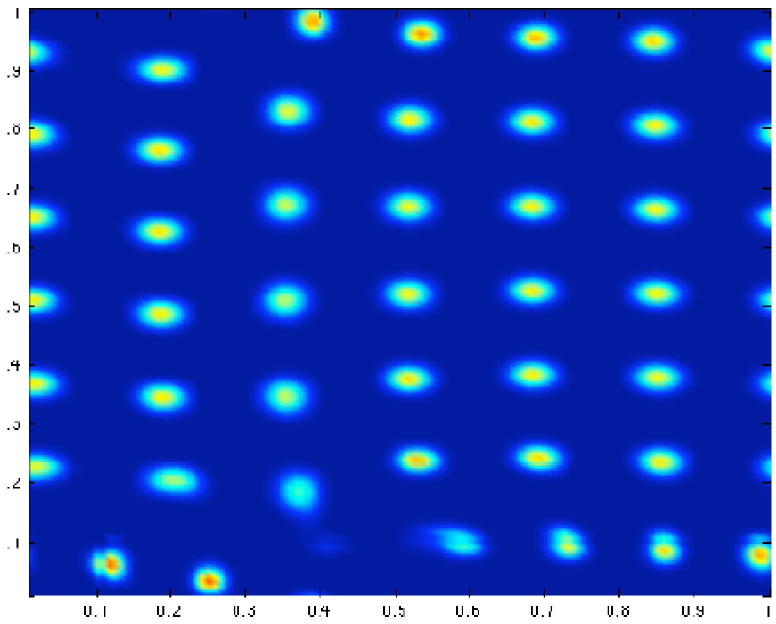
Evolution of dispersal

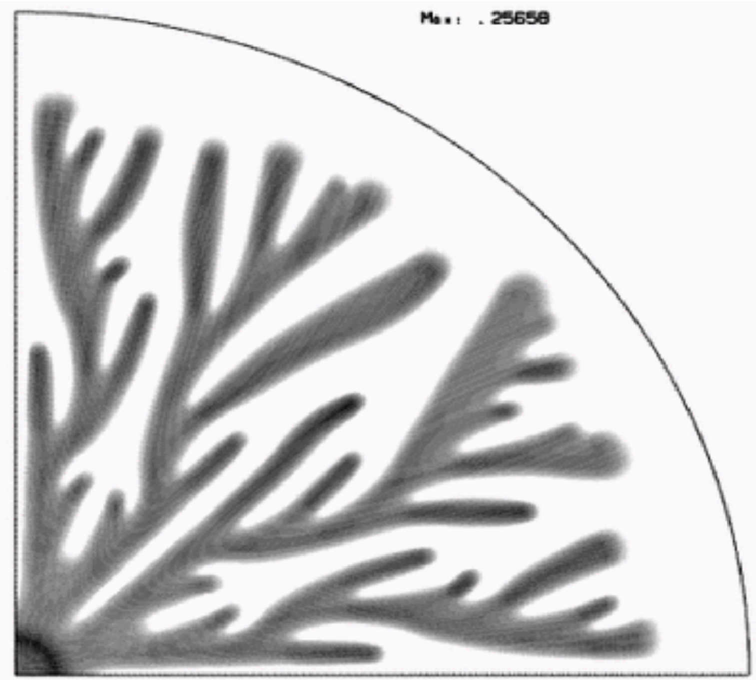
- Same question for traveling waves
- Accelerating waves
- Example cane toads invasion in Australia



J. Berestycki, E. Bouin, V. Calvez, C. Mouhot, G. Raoul, L. Ryzhik., C. Henderson

Turing (dentritic) patterns





Thanks to my collaborators

O. Diekmann, P.-E. Jabin, S. Mischler,

M. Gauduchon, J. Clairambault, A. Escargueil,

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Happy birthday Mete