Cross-diffusion models in biology

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Mainly joint work with Li Chen (Tsinghua University, Beijing)

- Introduction: (cross-diffusion) population model
- Existence of global-in-time solutions
- Long-time behavior of solutions
- Other cross-diffusion models in biology

Population dynamics

Classical Lotka-Volterra equations: (Volterra 1929)

$$\partial_t u_i = f_i(u_1, u_2), \quad i = 1, 2$$

$$f_i(u_1, u_2) = (a_i - b_i u_1 - c_i u_2) u_i$$

- u_i population densities
- $f_i(u_1, u_2)$ describes birth-death processes
- Interest: analyze long-time behavior

Two scenarios: one of the species dies out or $(u_1(t), u_2(t))$ converges to stable steady state:

$$(u_1^*, u_2^*) = \left(\frac{a_1 c_2 - a_2 c_1}{b_1 c_2 - b_2 c_1}, \frac{b_1 a_2 - b_2 a_1}{b_1 c_2 - b_2 c_1} \right)$$

Lotka-Volterra diffusion system: (Lou, Mimura, Ni etc.)

$$\partial_t u_i - d_i \Delta u_i = f_i(u_1, u_2) = (a_i - b_i u_1 - c_i u_2) u_i$$

Set $A = a_1/a_2$, $B = b_1/b_2$, $C = c_1/c_2$

Three scenarios:

- $A > \max\{B, C\}$ or $A < \min\{B, C\}$:
  one of the species dies out, convergence to steady states $s_1 = (a_1/b_1, 0)$, $s_2 = (0, a_2/c_2, 0)$ resp.
- Weak competition $B > A > C$: as $t \to \infty$,
  $$(u_1(t), u_2(t)) \to (u_1^*, u_2^*) = \left(\frac{a_1 c_2 - a_2 c_1}{b_1 c_2 - b_2 c_1}, \frac{b_1 a_2 - b_2 a_1}{b_1 c_2 - b_2 c_1}\right)$$
- Strong competition $B < A < C$: s_i locally stable, (u_1^*, u_2^*) unstable

Lotka-Volterra cross-diffusion system:

(Shigesada, Kawasaki, Teramoto 1979)

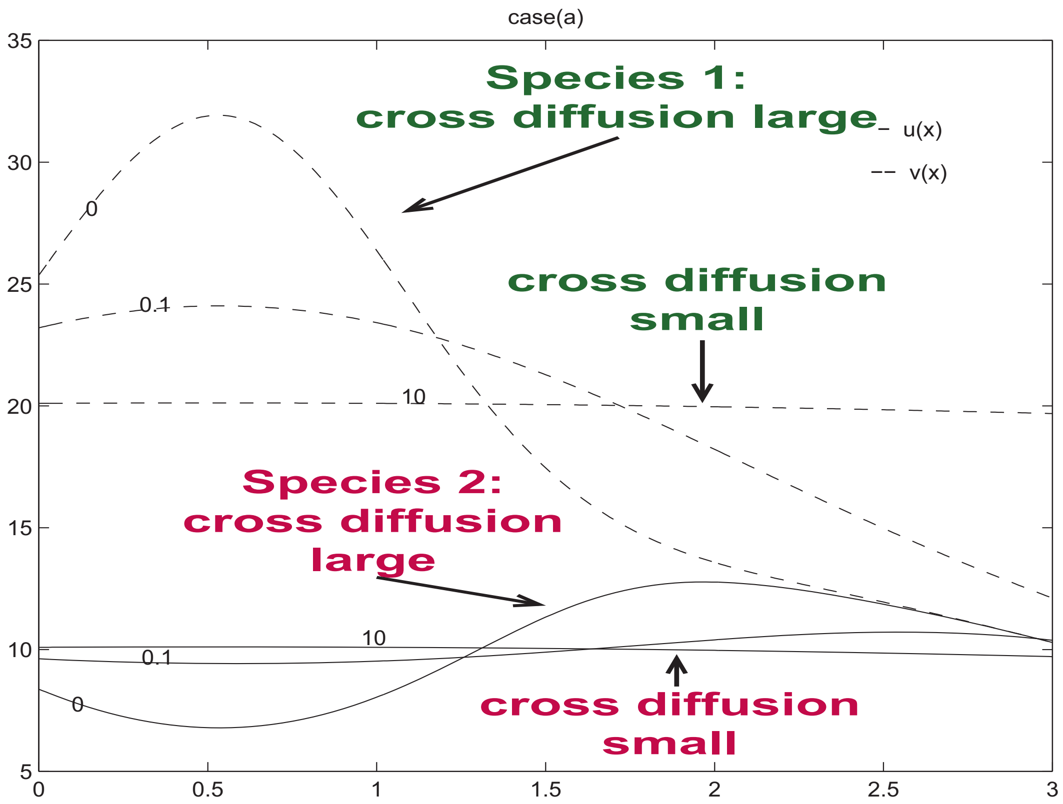
$$\partial_t u_i - \mathrm{div}\, J_i = f_i(u_1, u_2), \quad i = 1, 2$$

$$J_i = \alpha_i \nabla u_i + \beta_i \nabla(u_i^2) + \gamma_i \nabla(u_1 u_2) - d_i u_i \nabla \phi$$

$$\nabla u_i \cdot \nu = 0 \quad \text{on } \partial\Omega, \quad u_i(\cdot, 0) = u_{0i} \quad \text{in } \Omega \subset \mathbb{R}^d$$

- $\nabla(u_i^2)$: self-diffusion
- $\nabla(u_1 u_2)$: cross-diffusion
- $\phi(x)$: environmental potential

Figure: steady states



Lotka-Volterra cross-diffusion system:

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$$\nabla u_i \cdot \nu = 0 \quad \text{on } \partial\Omega, \quad u_i(\cdot, 0) = u_{0i} \quad \text{in } \Omega \subset \mathbb{R}^d$$

Previous results:

- Nonconstant steady state exists if α_i “small” (Lou/Ni 1996)
- Local existence of solutions (Amann 1990)
- Global existence if $\gamma_1 = 0$ and 2-D (Lou/Ni/Wu 1998)
- Global existence if $\alpha_1 = \alpha_2$ and 1-D (Kim 1984) or if $8\beta_i > \gamma_i$, $\gamma_1 = \gamma_2$, and 2-D (Yagi 1993)

Objective: Global existence without restrictions, $t \to \infty$

Mathematical analysis

$$\partial_t u_i - \operatorname{div} J_i = f_i(u_1, u_2), \quad i = 1, 2$$

$$J_i = \alpha_i \nabla u_i + \beta_i \nabla(u_i^2) + \gamma_i \nabla(u_1 u_2) - d_i u_i \nabla \phi$$

Difficulties:

- No maximum principle: how to derive a priori estimates?
- How to prove nonnegativity of u_i?
- Diffusion matrix generally not symmetric positive def.:

$$\partial_t u - \operatorname{div}\left(A(u)\nabla u\right) = f(u), \quad u = \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}$$

$$A(u) = \begin{pmatrix} \alpha_1 + 2\beta_1 u_1 + \gamma_1 u_2 & \gamma_1 u_1 \\ \gamma_2 u_2 & \alpha_2 + 2\beta_2 u_1 + \gamma_2 u_1 \end{pmatrix}$$

Main idea: introduce $u_i = e^{w_i}$

Advantage: gives automatically nonnegativity of u_i

Transformed problem:

$$\partial_t \begin{pmatrix} e^{w_1} \\ e^{w_2} \end{pmatrix} - \operatorname{div}\left(B(w)\nabla w\right) = f(w), \quad w = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}$$

$$B = \begin{pmatrix} (\alpha_1 + 2\beta_1 e^{w_1} + \gamma_1 e^{w_2})e^{w_1} & e^{w_1+w_2} \\ e^{w_1+w_2} & (\alpha_2 + 2\beta_2 e^{w_2} + \gamma_2 e^{w_1})e^{w_2} \end{pmatrix}$$

- New diffusion matrix symmetric positive definite
- Problem "symmetrizable" iff there exists an entropy $H = \int_\Omega h dx$ with density h (Kawashima/Shuzita 1988)
- New variables: $w_i = \partial h/\partial u_i$, entropy:

$$H = \int_\Omega h dx = \int_\Omega (u_1(\log u_i - 1) + u_2(\log u_2 - 1))dx$$

- Relation to thermodynamics: u_i intensive variables, w_i extensive variables

Existence of global solutions

$$\partial_t \begin{pmatrix} e^{w_1} \\ e^{w_2} \end{pmatrix} - \operatorname{div}(B(w)\nabla w) = f(w), \quad w = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}$$

$$B = \begin{pmatrix} (\alpha_1 + 2\beta_1 e^{w_1} + \gamma_1 e^{w_2})e^{w_1} & e^{w_1+w_2} \\ e^{w_1+w_2} & (\alpha_2 + 2\beta_2 e^{w_2} + \gamma_2 e^{w_1})e^{w_2} \end{pmatrix}$$

- Entropy–entropy dissipation inequality:

$$H = \int_\Omega (u_1(\log u_i - 1) + u_2(\log u_2 - 1))dx$$

$$\frac{dH}{dt} + \sum_{i=1}^{2} \int_\Omega (2\alpha_i |\nabla \sqrt{u_i}|^2 + \beta_i |\nabla u_i|^2)dx$$

$$+ 2\sqrt{\gamma_1 \gamma_2} \int_\Omega |\nabla \sqrt{u_1 u_2}|^2 dx \le \text{const.}$$

- A priori estimates: $u_i \in L^\infty(0,T;L^1(\Omega)) \cap L^2(0,T;H^1(\Omega))$ if $\beta_i > 0$

Existence of global solutions

$$\partial_t u_i - \operatorname{div} J_i = f_i(u_1, u_2), \quad i = 1, 2$$
$$J_i = \alpha_i \nabla u_i + \beta_i \nabla(u_i^2) + \gamma_i \nabla(u_1 u_2) - d_i u_i \nabla \phi$$

Theorem 1: (Galiano/Garzón/A.J. 2003)

- One-dimensional, mixed Dirichlet-Neumann boundary
- $T > 0$, α_i, $\beta_i > 0$, f_i: Lotka-Volterra fct., $u_{0i} \in L^\infty(\Omega)$

$\Rightarrow$ $\exists$ nonnegative weak solution $(u_1, u_2) \in L^2(0, T; H^1(\Omega))$

Ideas of Proof:

- New entropy estimate: $\alpha = 2\min\{\alpha_1, \alpha_2\}$, $u_i = e^{w_i}$

$$H_2 = \sum_{i=1}^{2} \int_\Omega u_i(\log u_i - 1)dx + \alpha \sum_{i=1}^{2} \int_\Omega (u_i - \log u_i)dx$$

- Entropy–entropy dissipation inequality: $(u_i = e^{w_i})$

$$\frac{dH_2}{dt} + \sum_{i=1}^{2} \int_\Omega \left(\frac{\alpha^2}{4}|w_{i,x}|^2 + \alpha|(\sqrt{u_i})_x|^2 + \beta_i |u_{i,x}|^2 \right) dx \le C$$

Existence of global solutions

$$\partial_t u_i - \mathrm{div}\, J_i = f_i(u_1, u_2), \quad i = 1, 2$$

$$J_i = \alpha_i \nabla u_i + \beta_i \nabla(u_i^2) + \gamma_i \nabla(u_1 u_2) - d_i u_i \nabla \phi$$

Theorem 2: (Chen/A.J. 2004)

- Multi-dimensional, homogeneous Neumann boundary
- $T > 0$, $\beta_i > 0$, f_i: Lotka-Volterra, $u_{0i} \in L^1 \log L^1(\Omega)$

$\Rightarrow$ $\exists$ nonnegative weak solution $u_i \in L^2(0, T; H^1(\Omega))$

Ideas of proof:

- Local existence: finite differences for cross-diffusion term $D^{-h}(\chi_h u_1 u_2 D^h(\log(u_1 u_2)))$, χ_h cut-off close to $\partial\Omega$
- Show semi-discrete entropy–entropy production inequality

$$\frac{dH}{dt} + \sum_{i=1}^{2} \int_\Omega (\beta_i |\nabla u_i|^2 + C u_1 u_2 |D^h \log(u_1 u_2)|^2) dx \le C$$

Existence of global solutions

$$\frac{dH}{dt} + \sum_{i=1}^{2} \int_\Omega (\beta_i |\nabla u_i|^2 + C u_1 u_2 |D^h \log(u_1 u_2)|^2) dx \le C$$

Ideas of proof:

- Problem: $\log(u_1 u_2)$ only defined if $u_i > 0$
- Solution: consider $\log((u_1^+ + \delta)(u_2^+ + \delta))$ with $u_i^+ = \max\{0, u_i\}$, $\delta > 0$
- Two more approximations: time-discrete problem $\tau > 0$, bounded coefficients $\nu > 0$
- Global existence: Leray-Schauder fixed point and approximation parameters $\tau, \delta, \nu, h \to 0$

Existence of global solutions

$$\partial_t u_i - \operatorname{div} J_i = f_i(u_1, u_2), \quad i = 1, 2$$

$$J_i = \alpha_i \nabla u_i + \beta_i \nabla(u_i^2) + \gamma_i \nabla(u_1 u_2) - d_i u_i \nabla \phi$$

Theorem 3: (Chen/A.J. 2006)

- Multi-dimensional, homogeneous Neumann boundary
- $T > 0$, $\beta_i \geq 0$, f_i: Lotka-Volterra, $u_{0i} \in L^1 \log L^1(\Omega)$

$\Rightarrow$ $\exists$ nonnegative weak solution $u_i \in L^2(0, T; W^{1,4/3}(\Omega))$

Ideas of proof:

- Since $\beta_1 = 0$ allowed, we have only $\sqrt{u_i} \in H^1(\Omega)$ from entropy estimates
- Diffusion matrix not uniform elliptic: add $\varepsilon \Delta w_i$
- Time discretization τ, Galerkin method N, Leray-Schauder, limits $N \to \infty$, $\tau \to 0$, $\varepsilon \to 0$

Existence of global solutions

$$\partial_t u_i - \Delta(\varepsilon u_i - u_1 u_2) = 0, \quad i = 1, 2, \ \varepsilon > 0$$

Theorem 4: (Chen/A.J. 2009, work in progress)

- Multi-dimensional, homogeneous Neumann boundary
- $T > 0$, no self-diffusion, u_{0i} smooth

$\Rightarrow \exists$ positive weak solution $u_i \in L^2(0,T;H^1(\Omega))$

Ideas of proof:

- $u_1 - u_2$ smooth since $\partial_t(u_1 - u_2) - \varepsilon\Delta(u_1 - u_2) = 0$
- Approximation:

$$\partial_t u_i - \varepsilon\Delta u_i - \operatorname{div}\left(\frac{(u_1^+ + u_2^+ + \eta)\nabla u_i}{1+\gamma(u_1^+ + u_2^+ + \eta)}\right) = -\operatorname{div}\left(\frac{(u_i^+ + \eta)\nabla(u_1 - u_2)}{1+\gamma(u_1^+ + u_2^+ + \eta)}\right)$$

- Standard a priori estimates and maximum principle:

$$\|(u_i - m)^-\|_{L^2}^2 \le C\eta, \quad i = 1, 2$$

$\longrightarrow$ Positive lower bound only in the limit $\eta \to 0$

- Perform limit η, $\gamma \to 0$

Long-time behavior of solutions

$$\partial_t u_i - \operatorname{div} J_i = f_i(u_1, u_2), \quad i = 1, 2$$

$$J_i = \alpha_i \nabla u_i + \beta_i \nabla(u_i^2) + \gamma_i \nabla(u_1 u_2) - d_i u_i \nabla \phi$$

Theorem: (Lou/Ni 1996)

- Diffusion or self-diffusion large $\Rightarrow$ only constant steady states (no segregation)
- Weak competition case and if self-diffusion or cross-diffusion weaker than diffusion $\Rightarrow$ only constant steady states
- Weak or strong competition case and one cross-diffusion term "large" $\Rightarrow$ exists nonconstant steady state

Question: $\gamma_1 = O(\gamma_2)$ "large" $\Rightarrow$ do exist nonconstant steady states?

Long-time behavior of solutions

$$\partial_t u_i - \operatorname{div} J_i = f_i(u_1, u_2) = (a_i - b_i u_1 - c_i u_2) u_i$$

Question: $\gamma_1 = O(\gamma_2)$ "large" $\Rightarrow$ exist nonconstant steady states?

Partial answer: No, if inter-specific competition vanishes

$$H_{\mathrm{rel}}(u_1, u_2) = \sum_{i=1}^{2} \int_\Omega u_i \left(\log\left(\frac{u_i}{U_i}\right) - 1 \right) dx$$

$$U_i = (\text{meas}(\Omega))^{-1} \int_\Omega u_i dx$$

Theorem: (Chen/A.J. 2006)

If $b_2 = c_1 = 0$ then, with $\lambda = \min\{\alpha_1, \alpha_2\}$,

$$H_{\mathrm{rel}}(u_1(t), u_2(t)) \le H_{\mathrm{rel}}(u_1(0), u_2(0)) e^{-\lambda t}$$

and there exist only constant steady states

Other examples of cross-diffusion in biology

Keller-Segel model of chemotaxis:

$$\partial_t n - \operatorname{div}(\varepsilon\nabla n - n\chi(n)\nabla S) = 0$$

$$\partial_t S - \Delta S - \delta\nabla n = r(n,S), \quad r(n,S) = n - S$$

- Variables: density of cells n, chemoattractant S
- $\delta = 0$: finite-time blow up possible
- $\delta > 0$: interpret (n,S) as approximate Keller-Segel solutions
- Cross diffusion $\delta\nabla n$ allows for new estimate:

$$\frac{d}{dt}\int_\Omega \Big(n(\log n - 1) + \frac{1}{2\delta}S^2\Big)dx + \int_\Omega \big(4|\nabla\sqrt{n}|^2 + |\nabla S|^2\big)dx \le C(\delta)$$

- Hope for global existence of solutions for any $\delta > 0$ (work in progress), may be useful for numerical approx.

Tumor-growth model: (Jackson/Byrne 2002)

$$\partial_t c - \big((1-c)(c^2)_x - c(m^2(1+\theta c))_x\big)_x = R_c$$
$$\partial_t m - \big((1-m)(m^2(1+\theta c))_x - m(c^2)_x\big)_x = R_m$$

- Variables: volume fractions of tumor cells c and of extra-cellular matrix (ECM) m
- Consumption-production rates R_c, R_m
- $\theta \geq 0$ measures strength of ECM pressure increase due to tumor cell pressure
- Entropy estimate for $\theta = 0$:

$$E = \int_\Omega \big(c(\log c - 1) + m(\log m - 1)\big)dx$$
$$\frac{dE}{dt} + \int_\Omega \big(|((1-c)^{3/2})_x|^2 + |((1-m)^{3/2})_x|^2\big)dx \leq C$$

- Existence of global solutions: work in progress

Summary

Population cross-diffusion model:

- Global existence of weak solutions
- Nonexistence of nonconstant steady states for arbitrarily large cross-diffusion (no inter-specific competition)

Entropy variable method:

- Existence of entropy (Lyapunov functional) equivalent to "symmetrizing" variable transformation (entropy variables)
  $\Rightarrow$ symm. pos. definite diffusion matrix & a priori estimates
  $\Rightarrow$ global existence and long-time behavior of solutions
- Physical entropy $h(u) = u(\log u - 1)$
  $\Rightarrow$ entropy variable $w = \log u$
  $\Rightarrow$ allows for proof of nonnegativity of solutions

$\longrightarrow$ Seems to be applicable to other cross-diffusion in biology