Analysis of cross-diffusion models for multi-species systems: How entropy can help

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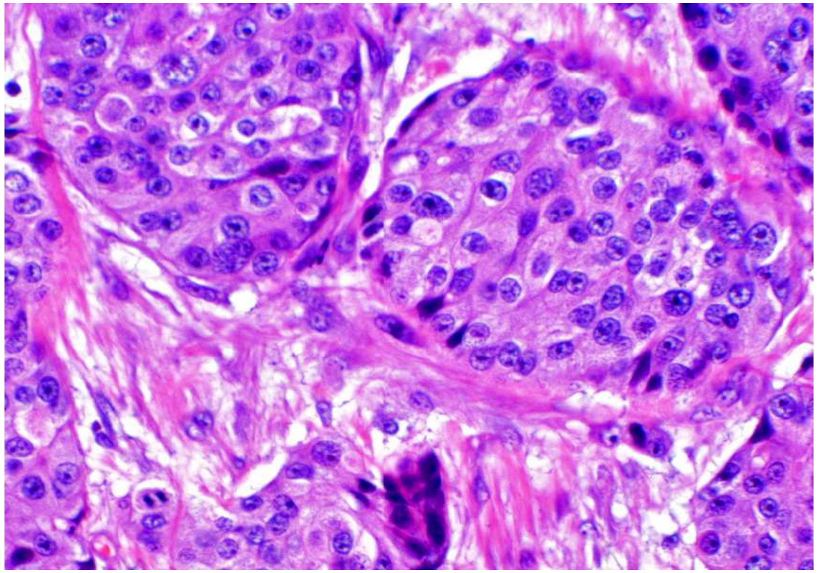
- Introduction
- Boundedness-by-entropy principle
- Examples from biology/chemistry



Tumor cells in breast tissue

Introduction

Many biological problems can be written as reaction-diffusion systems for particle densities $u \in \mathbb{R}^{N+1}$:

$$\partial_t u - \operatorname{div}(A(u)\nabla u) = f(u), \quad x \in \Omega, \ t > 0$$

$J = A(u)\nabla u \in \mathbb{R}^n$ particle flux, $f(u)$ reaction term

Example ①: Population dynamics

$$A(u) = \begin{pmatrix} d_1 + 2\alpha_1 u_1 + u_2 & u_1 \\ u_2 & d_2 + 2\alpha_2 u_2 + u_1 \end{pmatrix}$$

- Shigesada-Kawasaki-Teramoto 1979
- Derivation from random walk on lattice
- Population densities: u_1, u_2,
  Lotka-Volterra term: $f(u)$
- Cross-diffusion induces segregation

$\rightarrow A(u)$ generally not symm. pos. definite

Introduction

$$\partial_t u - \operatorname{div}\left(A(u)\nabla u\right) = f(u), \quad x \in \Omega,\ t > 0$$

Example ②: Tumor growth

$$A(u) = \begin{pmatrix} 2u_1(1-u_1) - \beta\theta u_1 u_2^2 & -2\beta u_1 u_2 (1+\theta u_1) \\ -2u_1 u_2 + \beta\theta u_2^2 (1-u_2) & 2\beta u_2 (1-u_2)(1+\theta u_1) \end{pmatrix}$$

- Derived by Jackson-Byrne 2002
- Derivation from mass balance and force balance equations (avascular growth)
- Volume fractions of tumor cells u_1, extracellular matrix (ECM) u_2, water $u_3 = 1 - u_1 - u_2$
- Symmetry assumption: $x \in \Omega = (0,1)$
- Pressure parameters: $\beta \geq 0$, $\theta \geq 0$

$\rightarrow$ $A(u)$ gener. not pos. definite! Expect that $0 \leq u_1, u_2 \leq 1$

Introduction

$$\partial_t u - \operatorname{div}\left(A(u)\nabla u\right) = f(u), \quad x \in \Omega,\ t > 0$$

Example ③: Multicomponent gas mixtures

$$(A(u)\nabla u)_i = J_i, \quad \nabla u_i = \sum_{j \neq i} d_{ij}(u_j J_i - u_i J_j)$$

- Proposed by Maxwell 1866 & Stefan 1871
- Derivation from Boltzmann eq. for simple mixtures: Boudin-Grec-Salvarani 2013
- Ideal mixture of $N+1$ gas components
- Molar fractions $u = (u_1, \ldots, u_{N+1})$ with total molar fraction $\sum_{i=1}^{N+1} u_i = 1$

→ (d_{ij}) generally not positive definite, inversion $\nabla u_i \leftrightarrow J_i$ necessary (and nontrivial); expect that $0 \leq u_i \leq 1$

Introduction

$$\partial_t u - \mathrm{div}\,(A(u)\nabla u) = f(u), \quad x \in \Omega,\ t > 0$$

Main features:

- Cross-diffusion: Diffusion matrix $A(u)$ non-diagonal
- Matrix $A(u)$ may be neither symmetric nor pos. definite
- Variables u_i expected to be bounded from below/above

Objectives:

- Global-in-time existence of weak solutions
- Positivity and boundedness of solution if physically expected
- Large-time behavior, design of stable numerical schemes

Mathematical difficulties:

- No general theory for diffusion systems
- Generally no maximum principle, no regularity theory
- Lack of positive definiteness $\Rightarrow$ Local existence nontrivial

Introduction

$$\partial_t u - \operatorname{div}(A(u)\nabla u) = f(u), \quad x \in \Omega,\ t > 0$$

Some previous results: Global existence if ...

- Growth conditions on nonlinearities (Ladyženskaya ... 1988)
- Control on L^∞ and Hölder norms (Amann 1989)
- Invariance principle holds (Redlinger 1989, Küfner 1996)
- Positivity, mass control, diagonal $A(u)$ (Pierre-Schmitt '97)

Unexpected behavior:

- Finite-time blow-up of bounded solutions (John-Stará 1995)
- Weak solutions may exist after L^∞ blow-up (Pierre 2003)
- Cross-diffusion may lead to pattern formation (instability) or may avoid finite-time blow-up (Hittmeir-A.J. 2011)

Special structure needed for global existence theory (boundedness-by-entropy principle)

Overview

- Introduction
- Boundedness-by-entropy principle
- Examples from biology and chemistry

Boundedness-by-entropy principle

Main assumption: $\partial_t u - \operatorname{div}(A(u)\nabla u) = f(u)$ possesses formal gradient-flow structure

$$\partial_t u - \operatorname{div}\left(B\nabla\frac{\delta H}{\delta u}\right) = f(u),$$

where B positive semi-definite, $H(u) = \int_\Omega h(u)dx$ entropy

Equivalent formulation: $\frac{\delta H}{\delta u} \simeq \mathrm{D}h(u) =: w$ (entropy variable)

$$\partial_t u - \operatorname{div}(B\nabla w) = f(u), \quad B = A(u)\mathrm{D}^2h(u)^{-1}$$

Consequences:

- H is Lyapunov functional if $f = 0$:

$$\frac{dH}{dt} = \int_\Omega \partial_t u \cdot \underbrace{\mathrm{D}h(u)}_{=w} dx = -\int_\Omega \nabla w : B\nabla w dx \le 0$$

- L^∞ bounds for u: Let $\mathrm{D}h : D \to \mathbb{R}^n$ ($D \subset \mathbb{R}^n$) be invertible

$\Rightarrow u = (\mathrm{D}h)^{-1}(w) \in D$ (no maximum principle needed!)

Example ①: no volume filling

- Mass densities u_1, u_2 satisfying $u_i > 0$
- Entropy: $h(u) = \sum_{i=1}^{2} u_i(\log u_i - 1)$, $u \in D = (0,\infty)^2$
- Entropy variable: $w = \mathrm{D}h(u)$ or $u = (\mathrm{D}h)^{-1}(w)$

$$w_i = \frac{\partial h}{\partial u_i} = \log u_i, \qquad u_i = e^{w_i} > 0$$

Example ②: volume filling

- Mass fractions u_i satisfying $u_1 + u_2 + u_3 = 1$
- Entropy: $h(u) = \sum_{i=1}^{3} u_i(\log u_i - 1)$, $u_3 = 1 - u_1 - u_2$,
  $u \in D = \{(u_1, u_2) : u_1, u_2 > 0,\ u_1 + u_2 < 1\}$
- Entropy variable: $w = \mathrm{D}h(u)$ or $u = (\mathrm{D}h)^{-1}(w)$

$$w_i = \frac{\partial h}{\partial u_i} = \log \frac{u_i}{u_3}, \qquad u_i = \frac{e^{w_i}}{1 + e^{w_1} + e^{w_2}} \in (0,1)$$

Important: Range of $\mathrm{D}h$ equals $\mathbb{R}^2$

Boundedness-by-entropy principle

Relation to non-equilibrium thermodynamics:

- Physical entropy $s(u) = -h(u)$ versus math. entropy
- Entropy variable $w_i = \partial h/\partial u_i$ = chemical potential μ_i
- Mixture of ideal gas: $\mu_i = \mu_i^0 + \log u_i \Rightarrow$

$$w_i = -\frac{\partial s}{\partial u_i} = \mu_i^0 + \log u_i \quad \text{or} \quad u_i = e^{w_i - \mu_i^0} > 0$$

Relation to GENERIC: (Öttinger 1997, Mielke 2011ff.)

(General Equation for Non-Equilibrium Reversible-Irreversible Coupling)

- Onsager operator K, entropy $H(u) = \int_\Omega h(u)dx$

$$\partial_t u = -K(w)\mathrm{D}H(u), \quad K(w)\xi = -\mathrm{div}\,(B(w)\nabla\xi)$$

- Geometric structure (geodesic λ-convexity of H) unknown

General global existence result

$\partial_t u - \mathrm{div}\,(A(u)\nabla u) = f(u)$ in Ω, $\nabla u \cdot \nu|_{\partial\Omega} = 0$, $u(0) = u_0$

Entropy-dissipation inequality for entropy $H(u) = \int_\Omega h(u)dx$:

$$\frac{dH}{dt} + \int_\Omega \nabla u : (\mathrm{D}^2 h)A(u)\nabla u dx = \int_\Omega f(u) \cdot \mathrm{D}h(u)dx$$

Assumptions: Let D be bounded.

(H1) $\exists\ h \in C^2(D;[0,\infty))$ with invertible $\mathrm{D}h : D \to \mathbb{R}^n$

(H2) $\forall u$: $(\mathrm{D}^2 h)A(u) \geq \mathrm{diag}(a_i(u_i))$, where $a_i(u_i) \sim u_i^{2m_i-2}$ and $m_i \geq 0$ (yields $\nabla u : (\mathrm{D}^2 h)A\nabla u \sim \sum_i |\nabla u_i^{m_i}|^2$)

(H3) A continuous, $\forall u$: $\mathrm{D}h(u) \leq C(1 + h(u))$

Theorem: (A.J. 2014)

Let (H1)-(H3), $u_0 \in L^1 \cap D$. Then $\exists$ global weak solution $u(x,t) \in \overline{D}$, $u \in L^2_{\mathrm{loc}}(0,\infty;H^1)$, $\partial_t u \in L^2_{\mathrm{loc}}(0,\infty;(H^1)')$

Overview

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- Boundedness-by-entropy principle
- Examples from biology and chemistry

Example: Population dynamics model

$$\partial_t u - \operatorname{div}(A(u)\nabla u) = f(u) \quad + \text{ homog. Neumann b.c.}$$

$$A(u) = \begin{pmatrix} d_1 + 2\alpha_1 u_1 + u_2 & u_1 \\ u_2 & d_2 + 2\alpha_2 u_2 + u_1 \end{pmatrix}$$

(H1) Entropy functional:

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

$\to \mathrm{D}h(u) = (\log u_1, \log u_2)$ invertible on $D = (0,\infty)^2$

(H2) Entropy-dissipation inequality: Let $d_i > 0$, $\alpha_i \geq 0$

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

Theorem: (L. Chen-A.J., *SIMA* 2004)

$\exists$ global nonnegative weak solution $\sqrt{u_i} \in L^2_{\mathrm{loc}}(0,\infty;H^1)$

Example: Population dynamics model

$$\partial_t u - \mathrm{div}\,(A(u)\nabla u) = f(u) \quad + \text{homog. Neumann b.c.}$$

$$A(u) = \begin{pmatrix} d_1 + 2\alpha_1 u_1 + \beta_1 u_2 & \beta_1 u_1 \\ \beta_2 u_2 & d_2 + 2\alpha_2 u_2 + \beta_2 u_1 \end{pmatrix}$$

Lotka-Volterra terms:

$$f_i(u) = (b_{i0} - b_{i1}u_1 - b_{i2}u_2)u_i, \quad i = 1, 2$$

Question: Are the weak solutions bounded? Partial answer:

Theorem: (A.J.-Zamponi 2014)

- $\beta_1 = \alpha_2$, $\beta_2 = \alpha_1$, and $d_1 - d_2 = \alpha_1 - \alpha_2$
- $b_{i0} \le \min\{b_{i1}, b_{i2}\}$, $i = 1, 2$

Then the weak solution satisfies $0 \le u_1 + u_2 \le 1 \; \forall\, t > 0$

Idea of proof: Use entropy density

$$h(u) = u_1(\log u_1 - 1) + u_2(\log u_2 - 1) + (1 - u_1 - u_2)(\log(1 - u_1 - u_2) - 1)$$

and verify (H2) ($\mathrm{D}^2 h A(u) \ge \mathrm{diag}(a_i(u_i))$)

Generalizations

Macroscopic limit of random-walk on lattice:

$$A(u) = \begin{pmatrix} p_1(u) + u_1 \frac{\partial p_1}{\partial u_1}(u) & u_1 \frac{\partial p_1}{\partial u_2}(u) \\ u_2 \frac{\partial p_2}{\partial u_1}(u) & p_2(u) + u_2 \frac{\partial p_2}{\partial u_2}(u) \end{pmatrix}$$

- p_i linear: L. Chen-A.J. 2004
- p_i sublinear: Desvillettes-Lepoutre-Moussa 2014
- p_i superlinear: $p_i(u) = a_{i0} + a_{i1}u_1^s + a_{i2}u_2^s$ $(i = 1, 2)$,
  entropy density: $h(u) = a_{21}u_1^s + a_{12}u_2^s$

Theorem: (A.J. 2014)
Let $1 < s < 4$ and $(1 - \frac{1}{s})a_{12}a_{21} \le a_{11}a_{22}$, $H(u_0) < \infty$.
Then $\exists$ nonnegative weak solution $u_i^{s/2} \in L^2_{\mathrm{loc}}(0, \infty; H^1(\Omega))$

- More than two species: work in progress (Daus-A.J. 2014)

Example: Tumor-growth model

$$\partial_t u - \partial_x(A(u)\partial_x u) = f(u) \quad + \text{homog. Neumann b.c.}$$

$$A(u) = \begin{pmatrix} 2u_1(1-u_1) - \beta\theta u_1 u_2^2 & -2\beta u_1 u_2(1+\theta u_1) \\ -2u_1u_2 + \beta\theta u_2^2(1-u_2) & 2\beta u_2(1-u_2)(1+\theta u_1) \end{pmatrix}$$

(H1) Entropy functional: $u \in D = \{(u_1, u_2) \in (0,1) : u_1 + u_2 < 1\}$

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

$\to w_i = \partial h/\partial u_i$ or $u_i = e^{w_i}/(1 + e^{w_1} + e^{w_2}) \in D$

(H2) Entropy-dissipation inequality: if $\theta < 4/\sqrt{\beta}$ then

$$\frac{dH}{dt} + C_\theta \int_\Omega ((u_1)_x^2 + (u_2)_x^2)dx \leq \text{const.}$$

Theorem: (A.J.-Stelzer, *M3AS* 2012)

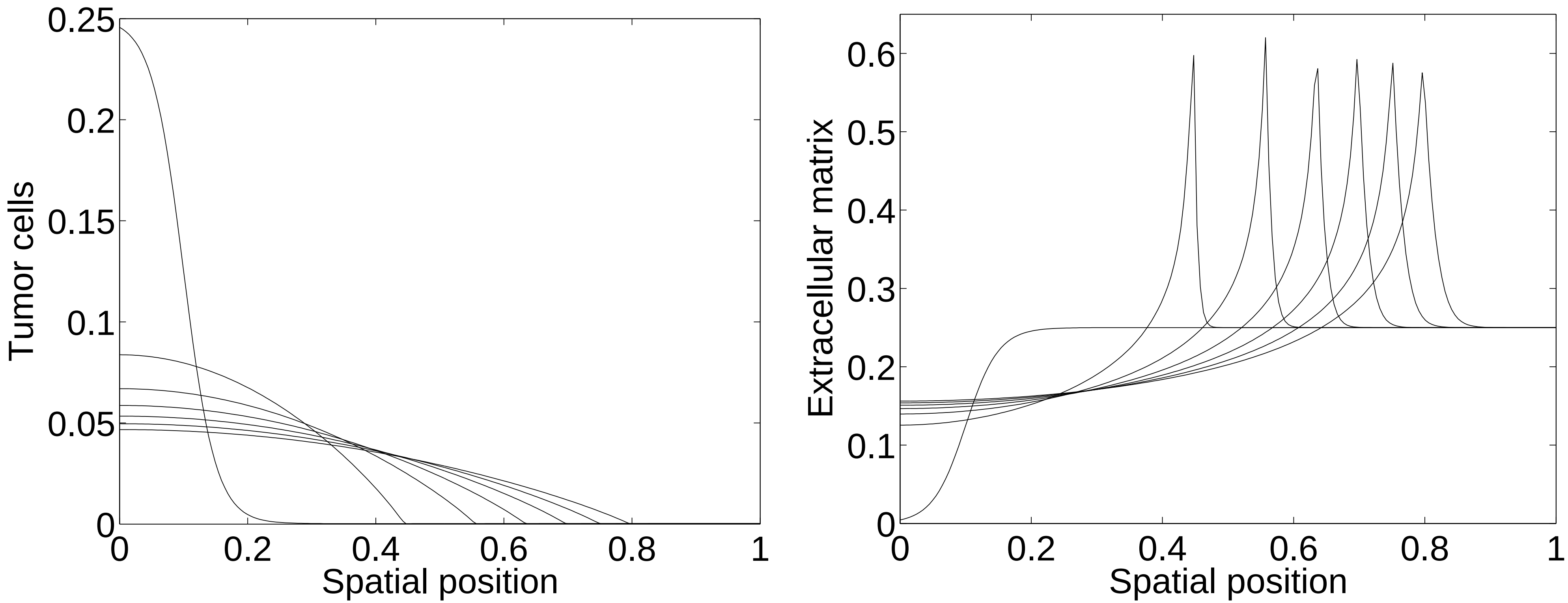
Let $\theta < 4/\sqrt{\beta}$, $H(u_0) < \infty \Rightarrow \exists$ weak solution $0 \leq u_i \leq 1$

Example: Tumor-growth model

Fact: global existence if $\theta < 4/\sqrt{\beta}$

Question: What happens for "large" θ?

Answer: Numerical results show "peaks" in ECM fraction



- Tumor front spreads from left to right (production $f = 0$)
- Tumor causes increase of ECM (encapsulation)

Example: Stefan-Maxwell model

- Mass balance equations: (mean velocity = 0, $\sum_{i=1}^{N+1} u_i = 1$)

  $\partial_t u_i - \operatorname{div} J_i = f_i(u)$ in Ω, $\nabla u_i \cdot \nu = 0$ on $\partial\Omega$, $u(0) = u_0$

- Force balance equations:

$$\nabla u_i = \sum_{j \neq i} d_{ij}(u_j J_i - u_i J_j) \quad \text{or} \quad \nabla u = A(u)J$$

Mathematical difficulties: ($u' = (u_1, \ldots, u_N)$ etc.)

① $\nabla u = A(u)J$ cannot be inverted! Replace u_{N+1}:
Is $A_0 \in \mathbb{R}^{N\times N}$ in $\nabla u' = A_0 J'$ invertible? Yes:
Apply Perron-Frobenius theory to $A \Rightarrow J' = A_0^{-1}\nabla u'$

② Entropy density $h(u')$, entropy variable $w = \mathrm{D}h(u')$
$\Rightarrow \nabla w = \mathrm{D}^2 h \nabla u'$, set $B(w) = A_0^{-1}(\mathrm{D}^2 h)^{-1}$

$$\partial_t u' - \operatorname{div}(B(w)\nabla w) = f(u), \quad B(w) \text{ pos.def.?}$$

Yes: Employ spectral properties of A_0 and B^{-1}

Example: Maxwell-Stefan models

$$\partial_t u_i - \operatorname{div} J_i = f_i(u), \quad \nabla u = A(u)J \in \mathbb{R}^{(N+1)\times(N+1)}$$

③ Gradient estimates: show that

$$\frac{d}{dt}\int_\Omega h(u')dx + C\sum_{i=1}^{N+1}\int_\Omega |\nabla\sqrt{u_i}|^2 dx \le 0$$

where $h(u') = \sum_{i=1}^{N+1} u_i(\log u_i - 1)$, $u_{N+1} = 1 - \sum_{i=1}^N u_i$

Theorem: (A.J.-Stelzer, *SIMA* 2014)

Assume (d_{ij}) symm., $\sum_{i=1}^{N+1} f_i(u)\log u_i \le 0$. Then

- $\exists$ global weak solution $\sqrt{u_i} \in L^2_{\rm loc}(0,\infty; H^1(\Omega))$, $0 \le u_i \le 1$ and $\sum_{i=1}^N u_i \le 1$ in Ω, $t > 0$
- $\exists$ $C > 0$, $\lambda > 0$:

$$\|u_i(\cdot,t) - \int_\Omega u_i^0 dx\|_{L^1(\Omega)} \le C(h(u^0))e^{-\lambda t}, \quad t \ge 0$$

Coupling with Navier-Stokes: X. Chen-A.J. 2013, Marion-Temam 2013, Mucha-Pokorný-Zatorska 2014

Summary

Global existence analysis of cross-diffusion systems

$$\partial_t u - \operatorname{div}\left(A(u)\nabla u\right) = f(u), \quad x \in \Omega,\ t > 0$$

Boundedness-by-entropy principle:

(H1) Given entropy variable $w = \mathrm{D}h(u)$, inverted relation

$u = (\mathrm{D}h)^{-1}(w)$ gives $u \in D \to L^\infty$ bounds possible

(H2) Entropy-dissipation ineq. gives gradient estimates

$\to$ global existence possible

Pros: General method, physical interpretation, applicable to many biological & chemical models

Work in progress:

- Characterize diffusion systems with bounded weak solutions
- Analyze discrete entropy structure (stable numer. methods)
- Develop entropy method for combined diffusion-reaction