

On volume-surface reaction-diffusion systems modeling asymmetric stem cell division: quasi-steady-state approximation and convergence to equilibrium

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1 Motivation: Asymmetric stem cell division

2 Linear models: Quasi-steady-state approximation

- Global existence of weak solutions
- Quasi-steady-state approximation

3 Nonlinear models: Convergence to equilibrium

- Existence of a unique global solution
- Convergence to equilibrium

4 Conclusion and further works

Section 1

Motivation: Asymmetric stem cell division

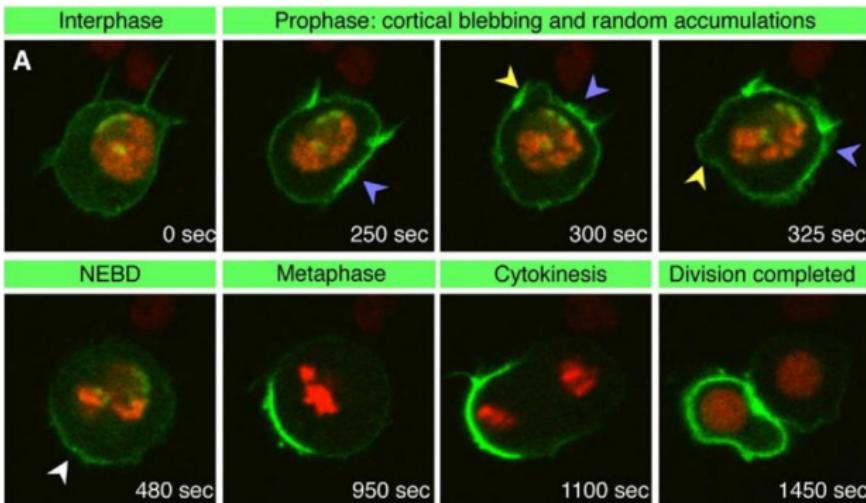


Figure: Asymmetric stem cell division.¹

¹Mayer et al., *Current Biology*, 15 (2005)

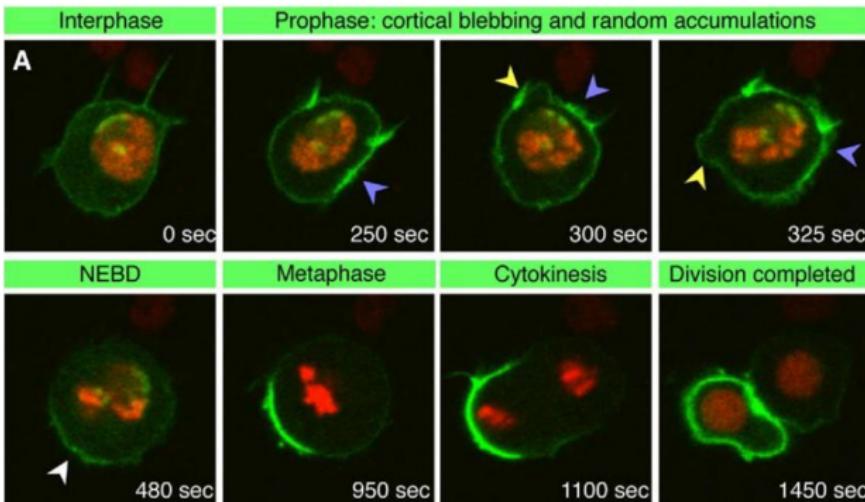


Figure: Asymmetric stem cell division.¹

Observed processes:

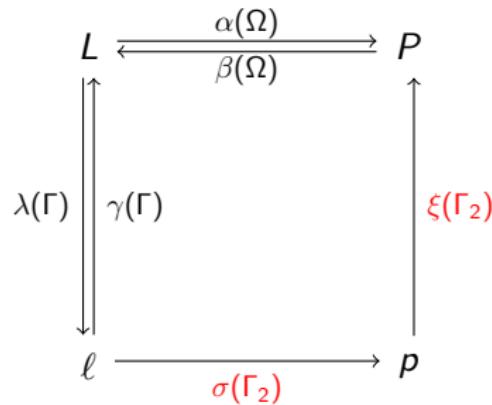
- Volume diffusions;
- Surface diffusions;
- Chemical reactions;

¹Mayer et al., *Current Biology*, 15 (2005)

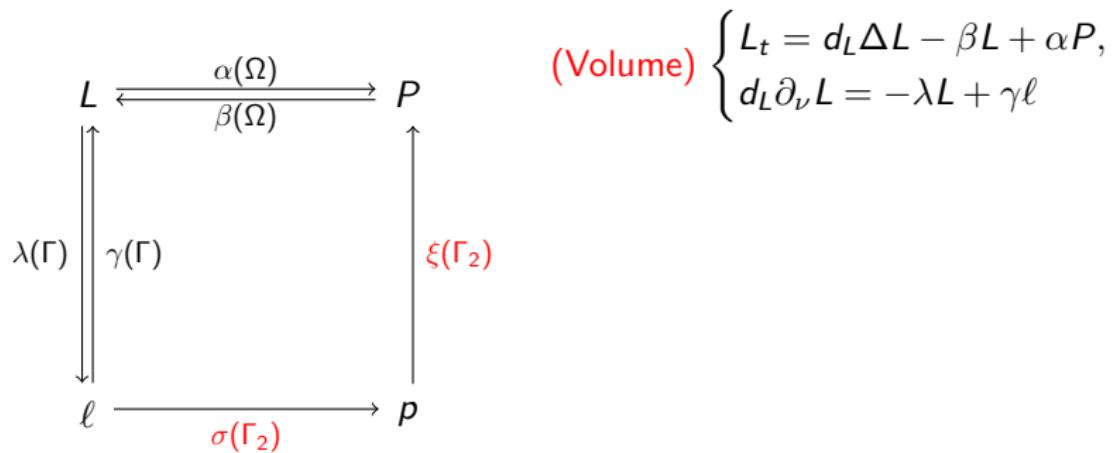
Section 2

Linear models: Quasi-steady-state approximation

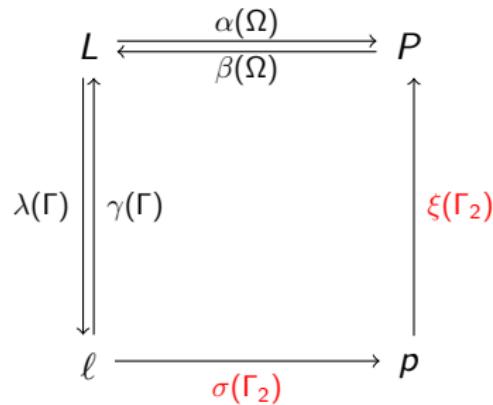
Reaction Dynamics and the System



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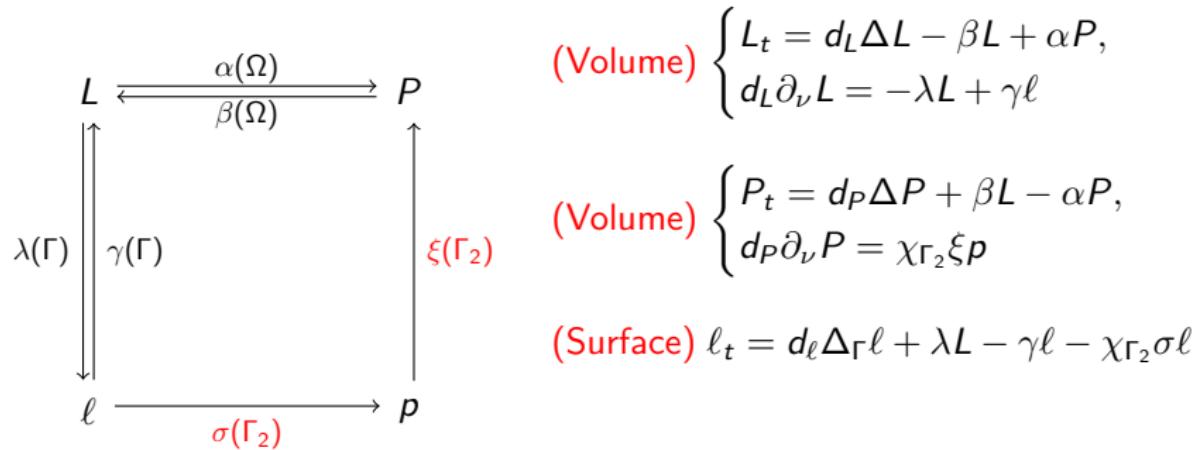
(Volume)

$$\begin{cases} L_t = d_L \Delta L - \beta L + \alpha P, \\ d_L \partial_\nu L = -\lambda L + \gamma \ell \end{cases}$$

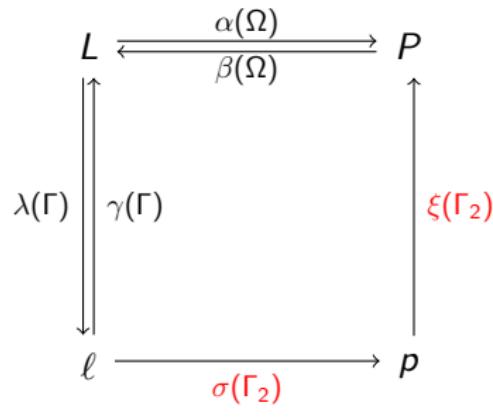
(Volume)

$$\begin{cases} P_t = d_P \Delta P + \beta L - \alpha P, \\ d_P \partial_\nu P = \chi_{\Gamma_2} \xi p \end{cases}$$

Reaction Dynamics and the System



Reaction Dynamics and the System



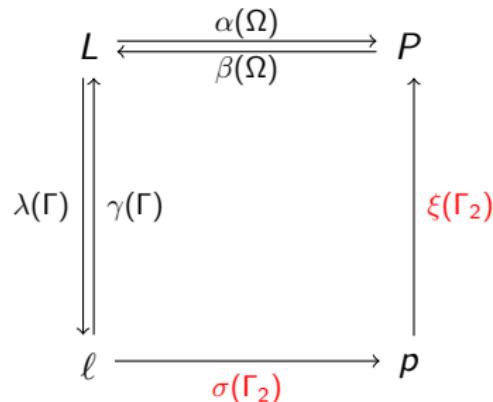
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(Surface) $\ell_t = d_\ell \Delta_\Gamma \ell + \lambda L - \gamma \ell - \chi_{\Gamma_2} \sigma \ell$

(Surface)
$$\begin{cases} p_t = d_p \Delta_{\Gamma_2} p - \xi p + \sigma \ell, \\ d_p \partial_\nu p = 0 \end{cases}$$

Reaction Dynamics and the System



(Volume) $\begin{cases} L_t = d_L \Delta L - \beta L + \alpha P, \\ d_L \partial_\nu L = -\lambda L + \gamma \ell \end{cases}$

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(Surface) $\ell_t = d_\ell \Delta_{\Gamma} \ell + \lambda L - \gamma \ell - \chi_{\Gamma_2} \sigma \ell$

(Surface) $\begin{cases} p_t = d_p \Delta_{\Gamma_2} p - \xi p + \sigma \ell, \\ d_p \partial_\nu p = 0 \end{cases}$

+ Non-negative initial data.

Goals:

1. Global existence of weak solutions
2. Asymptotic analysis (Quasi-steady-state approximation)

Subsection 1

Global existence of weak solutions

Localized method

$(L) \begin{cases} L_t = d_L \Delta L - \beta L + \alpha P, \\ d_L \partial_\nu L = -\lambda L + \gamma \ell \end{cases}$	$(P) \begin{cases} P_t = d_P \Delta P + \beta L - \alpha P, \\ d_P \partial_\nu P = \chi_{\Gamma_2} \xi p \end{cases}$
$(I) \ell_t = d_\ell \Delta_{\Gamma} \ell + \lambda L - \gamma \ell - \chi_{\Gamma_2} \sigma \ell$	$(p) \begin{cases} p_t = d_p \Delta_{\Gamma_2} p - \xi p + \sigma \ell, \\ d_p \partial_\nu p = 0 \end{cases}$

$$(\ell_1, p_1) \xrightarrow{\text{insert to } (L), (P)} (L_1, P_1) \xrightarrow{\text{insert to } (I), (p)} (\ell_2, p_2)$$

Localized method

Lemma

Let $\mathcal{A}(\ell_1, p_1) = (\ell_2, p_2)$. Then \mathcal{A} is a contraction mapping when T is small enough. As a corollary, the system $(L) - (P) - (I) - (p)$ has a unique **local weak solution**.

Proof. For all (ℓ, p) and (ℓ_1, p_1) , we have

$$\|\mathcal{A}(\ell, p) - \mathcal{A}(\ell_1, p_1)\| \leq \underbrace{\left(\frac{\lambda^2}{2\gamma} + \frac{\lambda^2 \sigma^2}{4\gamma\xi} T \right) \frac{2k}{\beta\lambda} T (2d_P T e^{2d_P T} + 1)}_{<1 \text{ when } T \text{ is small enough}} \|(\ell, p) - (\ell_1, p_1)\|$$

with $k = \max\{\beta\gamma^2/2\lambda, C_P\alpha\xi^2/4d_P\}$.

Theorem (K. Fellner, S. Rosenberger, T.)

For any $(L_0, P_0, \ell_0, p_0) \in L^2(\Omega) \times L^2(\Omega) \times L^2(\Gamma) \times L^2(\Gamma_2)$, there exists a unique **global weak solution** to the system (L)-(P)-(I)-(p). Moreover, if the initial data is non-negative then the weak solution is non-negative.

Proof: Some *a priori* estimates of an L^2 -functional.

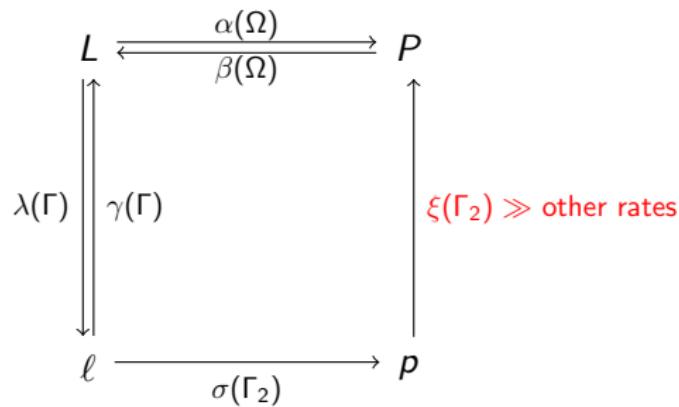
Remark:

- General initial data: The L^2 -growth of the solution is **exponentially bounded** in time;
- Non-negative initial data: The L^2 -growth of the solution is **uniformly bounded** in time;

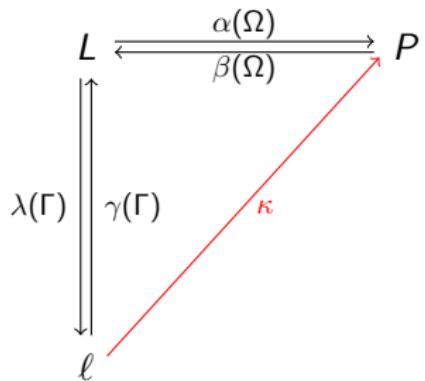
Subsection 2

Quasi-steady-state approximation

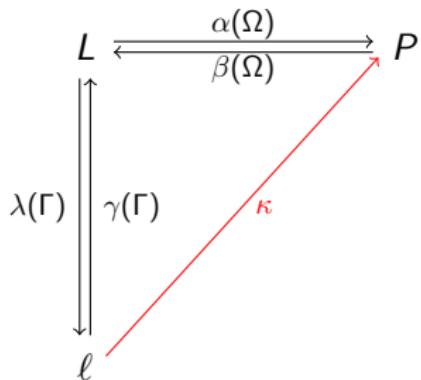
Due to biological data (Mayer *et al.* 2005)



Quasi-steady-state approximation?



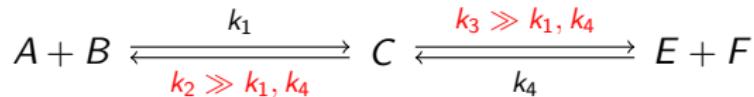
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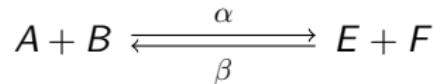
Yes when there is no surface diffusion $d_\ell = d_p = 0$ (**technical difficulty!!!**).

Some references:

- Enzymes reversible reaction:

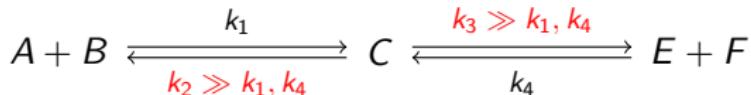


becomes

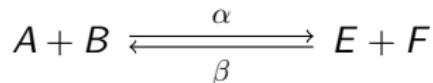


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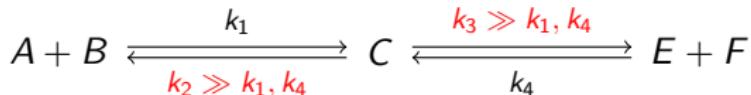
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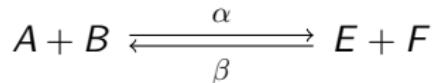
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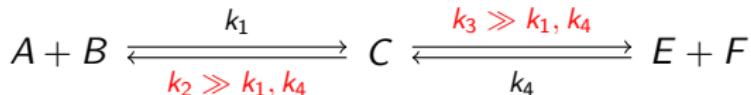
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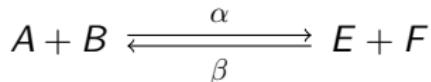
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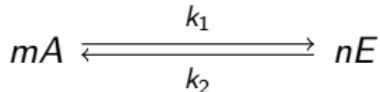
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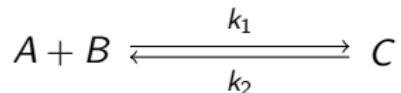


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- Bothe and Hilhorst (2003)



$\xrightarrow{k_1+k_2 \rightarrow +\infty}$ A **nonlinear diffusion** problem!

- Bothe and Pierre (2010)



$\xrightarrow{k_1+k_2 \rightarrow +\infty}$ A **cross diffusion** system!

Denote by $(L^\xi, P^\xi, \ell^\xi, p^\xi)$ the solution of the original system depending on ξ .

Theorem (K. Fellner, S. Rosenberger, T.)

Assume that $d_\ell = d_p = 0$. Let $\xi \rightarrow +\infty$. We have

$$(L^\xi, P^\xi, \ell^\xi, p^\xi) \longrightarrow (L, P, \ell, 0)$$

in $L^2([0, T] \times \Omega) \times (L^1([0, T] \times \Omega)) \times L^2([0, T] \times \Gamma) \times L^2([0, T] \times \Gamma_2)$, where (L, P, ℓ) is the solution to the QSSA.

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Proof.

- $\{L^\xi\}_{\xi>0}, \{P^\xi\}_\xi, \{\ell^\xi\}_{\xi>0}$ are bounded in $L^2([0, T] \times \Omega)$ (or $L^2([0, T] \times \Gamma)$) uniformly in ξ : **duality method** (extension of the method in Bothe and Pierre (2010));

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- $p^\xi \rightarrow 0$ in $L^2([0, T]; L^2(\Gamma_2))$ as $\xi \rightarrow +\infty$;
- $\{L^\xi\}_{\xi>0}$ is relatively compact in $L^2([0, T]; L^2(\Omega))$, thus $L^\xi \rightarrow L$;
- $\{\ell^\xi\}_{\xi>0}$ is relatively compact in $L^2([0, T]; L^2(\Gamma))$, thus $\ell^\xi \rightarrow \ell$;
- $\{P^\xi\}_{\xi>0}$ is relatively compact in $L^1([0, T]; L^1(\Omega))$, thus $P^\xi \rightarrow P$;

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- $\{P^\xi\}_{\xi>0}$ is relatively compact in $L^1([0, T]; L^1(\Omega))$, thus $P^\xi \rightarrow P$;
- Verify that (L, P, ℓ) is the solution to the QSSA.

Why does P^ξ only converges in $L^1([0, T]; L^1(\Omega))$?

Because of the singular boundary flux $d_P \partial_\nu P^\xi = \chi_{\Gamma_2} \xi p$!!!

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Improvements: We can get the convergence in $L^p([t_0, T]; L^2(\Omega))$ for any $1 \leq p < 2$ for a certain $t_0 > 0$.

Conjecture: We can get the convergence in $L^2(L^2)$ (at least for large time) if we know that the solution of the original system converges to the equilibrium!

This is non-trivial due to:

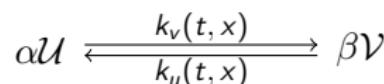
- Complexity of the reaction dynamics;
- The volume-surface coupling.

Section 3

Nonlinear models: Convergence to equilibrium

\mathcal{U} : volume substance; \mathcal{V} : surface substance.

\mathcal{U} and \mathcal{V} react on the boundary as

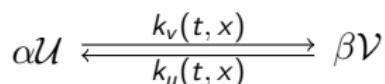


Denote by $u(t, x)$ and $v(t, x)$ the concentrations of \mathcal{U} and \mathcal{V} respectively. We have a **surface-volume reaction diffusion system**:

$$\begin{cases} u_t - \delta_u \Delta u = 0, & x \in \Omega, \\ \delta_u \partial_\nu u = -\alpha(k_u u^\alpha - k_v v^\beta), & x \in \partial\Omega, \\ v_t - \delta_v \Delta_{\partial\Omega} v = \beta(k_u u^\alpha - k_v v^\beta), & x \in \partial\Omega, \\ u(0, x) = u_0(x), \quad v(0, x) = v_0(x). \end{cases} \quad (1)$$

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Two goals:

1. Global existence of solutions.
2. Explicit convergence to equilibrium.

$$\begin{cases} u_t - \delta_u \Delta u = 0, & x \in \Omega, \\ \delta_u \partial_\nu u = -\alpha(k_u u^\alpha - k_v v^\beta), & x \in \partial\Omega, \\ v_t - \delta_v \Delta_{\partial\Omega} v = \beta(k_u u^\alpha - k_v v^\beta), & x \in \partial\Omega, \\ u(0, x) = u_0(x), \quad v(0, x) = v_0(x). \end{cases}$$

Assumptions:

- Stoichiometric coefficients $\alpha, \beta \geq 1$ (not necessarily integers);
- Reaction rates
 - Existence of solutions: $k_{\min} \leq k_u(t, x), k_v(t, x) \leq k_{\max}$.
 - Convergence to equilibrium: $k_u, k_v \equiv \text{constants}$.
- Non-negative initial data $u_0 \in L^\infty(\Omega)$ and $v_0 \in L^\infty(\partial\Omega)$.

Subsection 1

Existence of a unique global solution

Difficulties:

- General polynomial nonlinearities;
- Volume-surface coupling.

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Methods: Upper and lower solutions.

Consider a general PDEs:

$$\mathbf{u}_t = \mathbf{F}(\mathbf{u}), \quad \mathbf{u}(0) = \mathbf{u}_0. \quad (2)$$

- Upper solution $\bar{\mathbf{u}}$: $\bar{\mathbf{u}}_t \geq \mathbf{F}(\bar{\mathbf{u}})$ and $\bar{\mathbf{u}}(0) \geq \mathbf{u}_0$;
- Lower solution $\underline{\mathbf{u}}$: $\underline{\mathbf{u}}_t \leq \mathbf{F}(\underline{\mathbf{u}})$ and $\underline{\mathbf{u}}(0) \leq \mathbf{u}_0$.

Comparison principle for a couple of upper and lower solutions:

For any solution \mathbf{u} to (2):

$$\boxed{\bar{\mathbf{u}} \geq \mathbf{u} \geq \underline{\mathbf{u}}}.$$

General framework

$$\mathbf{u}_t = \mathbf{F}(\mathbf{u}), \quad \mathbf{u}(0) = \mathbf{u}_0. \quad (2)$$

Concept of the proof:

$$(\bar{\mathbf{u}}^{(0)}, \bar{\mathbf{v}}^{(0)})$$

$$(\bar{\mathbf{u}}^{(1)}, \bar{\mathbf{v}}^{(1)})$$

$$(\bar{\mathbf{u}}^{(2)}, \bar{\mathbf{v}}^{(2)})$$

...

$$(\mathbf{u}^*, \mathbf{v}^*)$$

$$(\underline{\mathbf{u}}^{(2)}, \underline{\mathbf{v}}^{(2)})$$

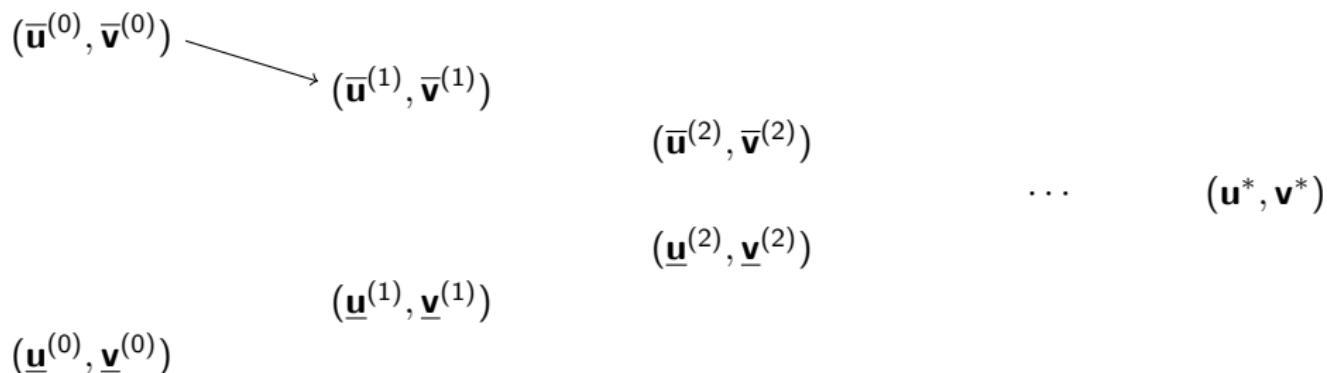
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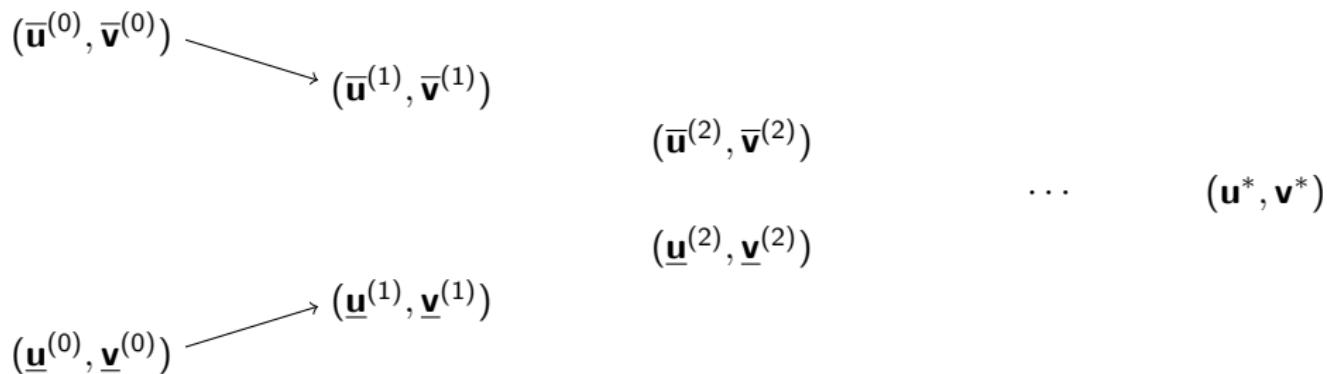
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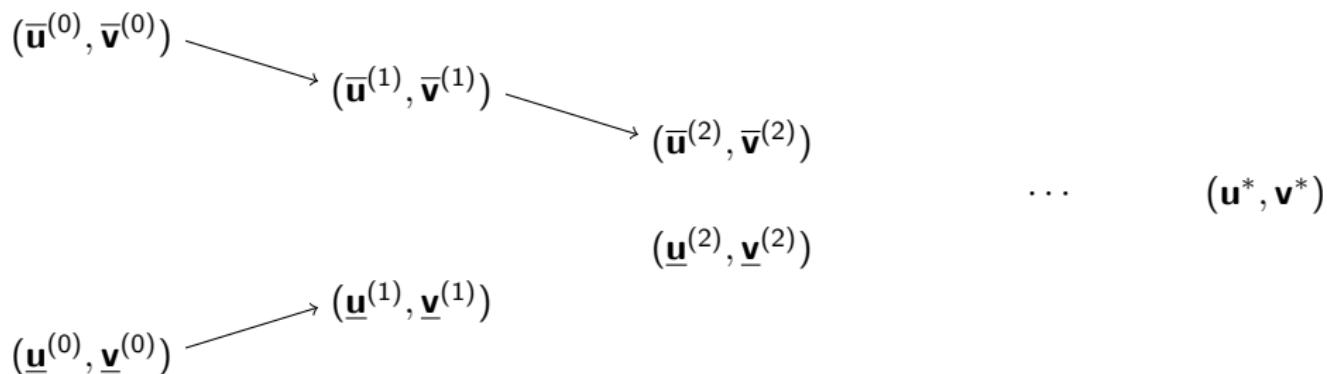
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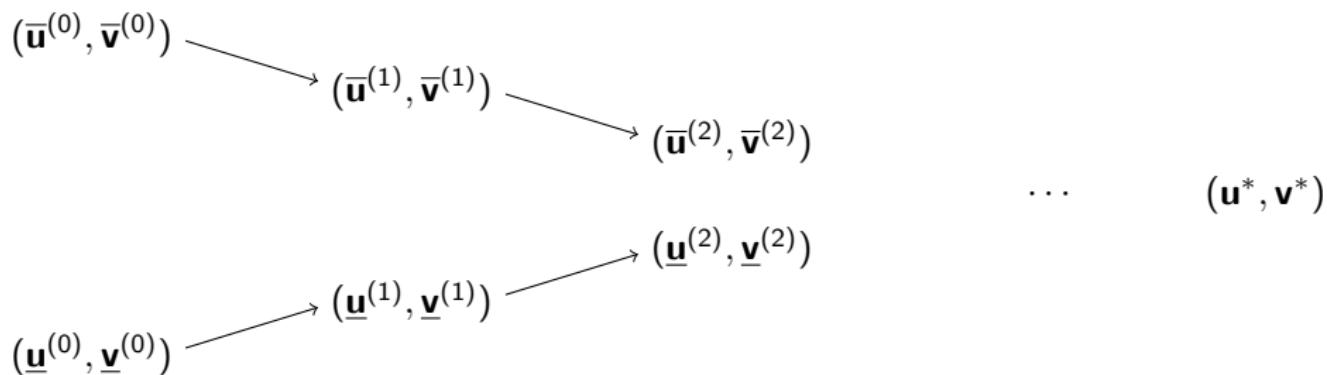
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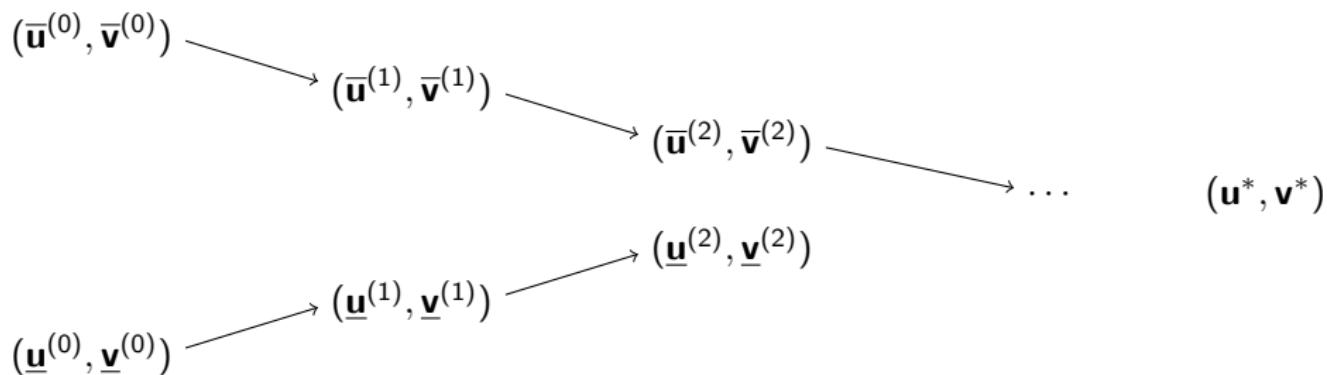
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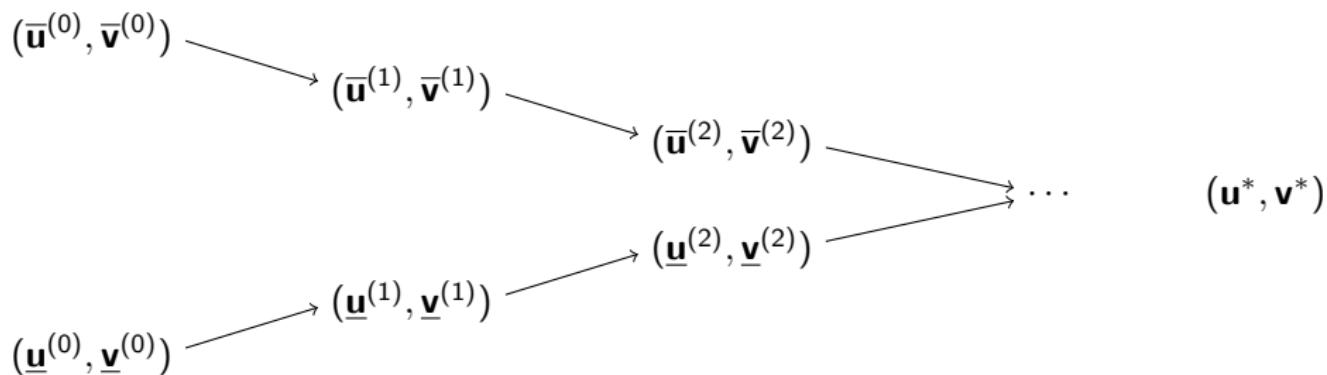
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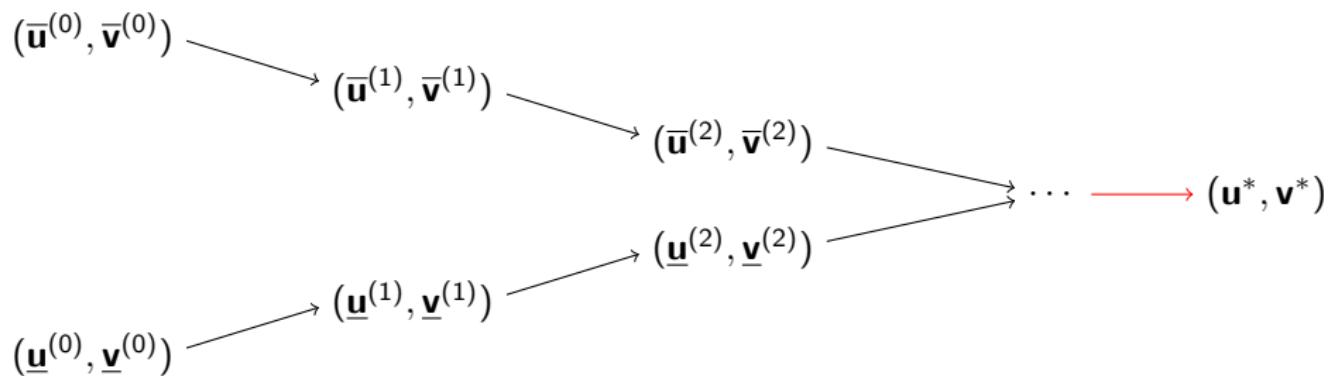
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Concept of the proof:



Theorem (K. Fellner, E. Latos, T.)

Assume that

- $\Omega \subset \mathbb{R}^n$ is a bounded domain with smooth boundary $\partial\Omega$ (e.g. $\partial\Omega \in C^{2+\epsilon}$);
- Stoichiometric coefficients $\alpha, \beta \geq 1$;
- Reaction rates are uniform bounded: $k_{min} \leq k_u(t, x), k_v(t, x) \leq k_{max}$;
- Non-negative initial data $u_0 \in L^\infty(\Omega)$ and $v_0 \in L^\infty(\partial\Omega)$.

Then the system

$$\begin{cases} u_t - \delta_u \Delta u = 0, & x \in \Omega, \\ \delta_u \partial_\nu u = -\alpha(k_u u^\alpha - k_v v^\beta), & x \in \partial\Omega, \\ v_t - \delta_v \Delta_{\partial\Omega} v = \beta(k_u u^\alpha - k_v v^\beta), & x \in \partial\Omega, \\ u(0, x) = u_0(x), \quad v(0, x) = v_0(x). \end{cases}$$

has a unique global weak solution.

Subsection 2

Convergence to equilibrium

When $k_u = k_v = 1$ (we write $\Gamma = \partial\Omega$)

$$\begin{cases} u_t - \delta_u \Delta u = 0, & x \in \Omega, \\ \delta_u \partial_\nu u = -\alpha(u^\alpha - v^\beta), & x \in \Gamma, \\ v_t - \delta_v \Delta_\Gamma v = \beta(u^\alpha - v^\beta), & x \in \Gamma, \\ u(0, x) = u_0(x), \quad v(0, x) = v_0(x). \end{cases}$$

Conservation of mass:

$$\begin{aligned} \beta \int_{\Omega} u(t, x) dx + \alpha \int_{\Gamma} v(t, x) dS \\ = \beta \int_{\Omega} u_0(x) dx + \alpha \int_{\Gamma} v_0(x) dS =: M \quad \text{for all } t > 0. \end{aligned}$$

Constant equilibrium: (u_∞, v_∞) satisfies

$$\begin{cases} u_\infty^\alpha = v_\infty^\beta & \text{(balance of reactions),} \\ \beta|\Omega|u_\infty + \alpha|\Gamma|v_\infty = M & \text{(conservation of mass).} \end{cases}$$

Convergence to equilibrium: $(u(t), v(t)) \rightarrow (u_\infty, v_\infty)$ as $t \rightarrow +\infty$?

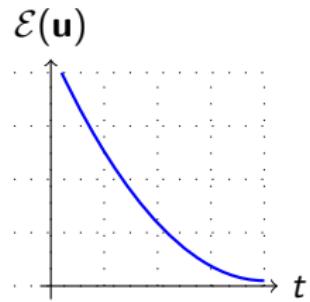
General framework

Consider a general flow $\mathbf{u}_t = \mathbf{F}(\mathbf{u}(t))$ with equilibrium \mathbf{u}_∞ satisfying $\mathbf{F}(\mathbf{u}_\infty) = 0$.

General framework

Consider a general flow $\mathbf{u}_t = \mathbf{F}(\mathbf{u}(t))$ with equilibrium \mathbf{u}_∞ satisfying $\mathbf{F}(\mathbf{u}_\infty) = 0$. A functional $\mathcal{E}(\mathbf{u})$ is called an **entropy** if:

$$\frac{d\mathcal{E}}{dt} \leq 0 \text{ or } \mathcal{D}(\mathbf{u}) = -\frac{d\mathcal{E}}{dt} \geq 0$$



$$\frac{d\mathcal{E}}{dt} = 0 + \text{conservation laws} \Leftrightarrow \mathbf{u} \equiv \mathbf{u}_\infty$$

$$\mathcal{E}(\mathbf{u})(t) \longrightarrow \mathcal{E}(\mathbf{u}_\infty)?$$

$$\mathcal{E}(\mathbf{u}) - \mathcal{E}(\mathbf{u}_\infty) \geq \kappa \|\mathbf{u} - \mathbf{u}_\infty\|$$

$$\mathcal{E}(\mathbf{u})(t) \longrightarrow \mathcal{E}(\mathbf{u}_\infty) \implies \mathbf{u}(t) \longrightarrow \mathbf{u}_\infty$$

General framework

If we have an *entropy – entropy dissipation estimate*

$$\mathcal{D}(\mathbf{u}) \geq \lambda(\mathcal{E}(\mathbf{u}) - \mathcal{E}(\mathbf{u}_\infty))$$

then

$$\underbrace{\frac{d}{dt}(\mathcal{E}(\mathbf{u}) - \mathcal{E}(\mathbf{u}_\infty))}_{y'(t)} = \frac{d}{dt}\mathcal{E}(\mathbf{u}) = \mathcal{D}(\mathbf{u}) \leq \underbrace{-\lambda(\mathcal{E}(\mathbf{u}) - \mathcal{E}(\mathbf{u}_\infty))}_{-\lambda y(t)},$$

thus

$$\mathcal{E}(\mathbf{u})(t) - \mathcal{E}(\mathbf{u}_\infty) \leq e^{-\lambda t}(\mathcal{E}(\mathbf{u})(0) - \mathcal{E}(\mathbf{u}_\infty)).$$

Advantages of the method

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- Explicit, computable rates of convergence;
- Rely on functional inequalities —→ robust to various problems;
- Obtain functional inequalities as by-product;

Explicit convergence to equilibrium for reaction-diffusion systems by entropy method

- In Fellner & Desvillettes (2006) (**first result on system!**)

$$2\mathcal{U} \rightleftharpoons \mathcal{W} \quad \text{and} \quad \mathcal{U} + \mathcal{V} \rightleftharpoons \mathcal{W}$$

- In Fellner & Desvillettes (2007)

$$2\mathcal{U} \rightleftharpoons \mathcal{W}$$

with degenerate diffusions.

- In Fellner & Desvillettes (2008)

$$\mathcal{U} + \mathcal{V} \rightleftharpoons \mathcal{W} + \mathcal{Z}$$

- In A. Mielke *et al.* (2013)

$$\sum_{i=1}^n \alpha_i \mathcal{A}_i \rightleftharpoons \sum_{j=1}^m \beta_j \mathcal{A}_j$$

This bases on a convex modification approach (**hard to compute explicit rate**) and is not applicable to surface-volume reaction-diffusion systems.

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We consider Boltzmann-type **entropy**

$$\mathcal{E}(u, v) = \int_{\Omega} (u \log u - u + 1) dx + \int_{\Gamma} (v \log v - v + 1) dS$$

and its **entropy dissipation**

$$\mathcal{D}(u, v) = \delta_u \int_{\Omega} \frac{|\nabla u|^2}{u} dx + \delta_v \int_{\Gamma} \frac{|\nabla_{\Gamma} v|^2}{v} dS + \int_{\Gamma} (u^\alpha - v^\beta) \log \frac{u^\alpha}{v^\beta} dS.$$

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Theorem (K. Fellner, E. Latos, T.)

There exists explicit constants $C_0 > 0$ and $\lambda > 0$ such that

$$\|u(t) - u_\infty\|_{L^1(\Omega)}^2 + \|v(t) - v_\infty\|_{L^1(\Gamma)}^2 \leq C_0 e^{-\lambda t}$$

for all $t \geq 0$.

Lemma

*There exists an **explicit** constant $\lambda = \lambda(\alpha, \beta, M, |\Omega|, |\Gamma|) > 0$ such that*

$$\mathcal{D}(u, v) \geq \lambda(\mathcal{E}(u, v) - \mathcal{E}(u_\infty, v_\infty)).$$

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Remarks:

- Global estimate;
- Fully nonlinear technique without any linearization.

$$\mathcal{D}(u, v) \geq \lambda(\mathcal{E}(u, v) - \mathcal{E}(u_\infty, v_\infty)).$$

Proof: Sorry, it is too long! (≈ 11 pages of calculation)

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$$\mathcal{D}(u, v) = \delta_u \int_{\Omega} \frac{|\nabla u|^2}{u} dx + \delta_v \int_{\Gamma} \frac{|\nabla_{\Gamma} v|^2}{v} dS + \int_{\Gamma} (u^\alpha - v^\beta) \log \frac{u^\alpha}{v^\beta} dS.$$

The proof is based on only **mass conservation**.

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The proof uses the L^∞ -bounds of solutions. Moreover, there exists $\kappa > 0$ such that

$$\|\nabla U\|_{\Omega}^2 + \|U^\alpha - V^\beta\|_{\Gamma}^2 \geq \kappa \|V - \bar{V}\|_{\Gamma}^2.$$

Diffusion of u + reaction of u and v \implies diffusion-effect of v

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Diffusion of u + reaction of u and v \implies diffusion-effect of v

Can we relax the use of the uniform bound of the solution in the degenerate case? **Yes**, if $\alpha = \beta = 1$ (linear case).

Our technique is extendable to a general elementary reversible reaction:

$$\sum_{i=1}^m \alpha_i \mathcal{A}_i \rightleftharpoons \sum_{j=1}^m \beta_j \mathcal{A}_j$$

Theorem (K. Fellner, T.)

For $i = 1, 2, \dots, m$, denote by $a_i(t, x)$ and $a_{i,\infty}$ the concentration and the equilibrium of the substance \mathcal{A}_i respectively. Then there exists explicit constants C_0 and λ such that

$$\sum_{i=1}^m \|a_i(t) - a_{i,\infty}\|_{L^1(\Omega)}^2 \leq C_0 e^{-\lambda t} \quad \text{for all } t \geq 0.$$

as well as enzymes reversible reaction



Section 4

Conclusion and further works

Conclusion

- Linear models: Existence and QSSA;
- Nonlinear models: Existence and convergence to equilibrium.

Conclusion

- Linear models: Existence and QSSA;
- Nonlinear models: Existence and convergence to equilibrium.

Further works

- Linear models: Convergence to equilibrium? (**Relative Entropy!**)
- Nonlinear models: QSSA?
- General chemical reaction systems?

THANK YOU VERY MUCH!