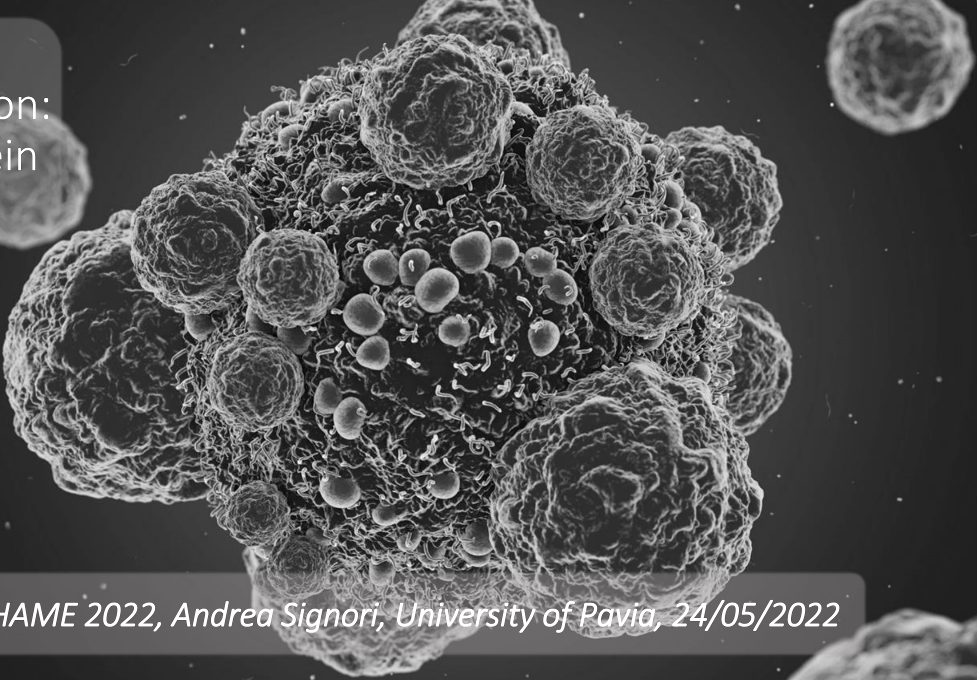
Cell's organisation: RNA-Protein dynamics



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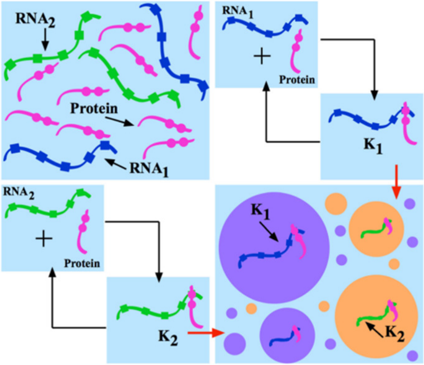
Modeling

Two species of RNA competing for a pool of shared protein. The φ_i complex, $i = 1, 2$, is formed when the RNA R_1 interacts with a free protein P. Both protein–RNA complexes are capable of driving phase separation and forming distinct droplets.



- Protein: P;
- RNA-species: R_1 and R_2;
- Protein-RNA complexes:
  $R_1 + P \rightsquigarrow \varphi_1, \quad R_2 + P \rightsquigarrow \varphi_2.$

- K. Gasior, M.G. Forest, A.S. Gladfelter and J.M. Newby. Modeling the mechanisms by which coexisting biomolecular RNA-Protein condensates form. *Bull. Math. Biol.* 82:153, 2020.
- K. Gasior, J. Zhao, G. McLaughlin, M.G. Forest, A.S. Gladfelter and J. Newby. Partial demixing of RNA-protein complexes leads to intradroplet patterning in phase-separated biological condensates. *Phys. Rev. E* 99:012411, 2019.

RNA-Protein model

Let $\Omega \subset \mathbb{R}^3$, bdd and smooth domain, and $T > 0$. We set

$$\boldsymbol{\varphi} := (\varphi_1, \varphi_2), \quad \boldsymbol{\mu} := (\mu_1, \mu_2), \quad \mathrm{R} := (R_1, R_2).$$

Then, the RNA-Protein system we are going to analyse reads as

$$\begin{aligned}
&\partial_t \boldsymbol{\varphi} - \Delta \boldsymbol{\mu} = \mathrm{S}_{\boldsymbol{\varphi}}(\boldsymbol{\varphi}, P, \mathrm{R}) && \text{in } Q := \Omega \times (0, T),\\
&\boldsymbol{\mu} = -\Delta \boldsymbol{\varphi} + \Psi_{\boldsymbol{\varphi}}(\boldsymbol{\varphi}) && \text{in } Q,\\
&\partial_t P - \Delta P = S_P(\boldsymbol{\varphi}, P, \mathrm{R}) && \text{in } Q,\\
&\partial_t \mathrm{R} - \Delta \mathrm{R} = \mathrm{S}_{\mathrm{R}}(\boldsymbol{\varphi}, P, \mathrm{R}) && \text{in } Q,\\
&\partial_{\mathbf{n}} \boldsymbol{\varphi} = \partial_{\mathbf{n}} \boldsymbol{\mu} = \partial_{\mathbf{n}} \mathrm{R} = 0, \quad \partial_{\mathbf{n}} P = 0 && \text{on } \Sigma := \partial\Omega \times (0, T),\\
&\boxed{\boldsymbol{\varphi}(0) = \mathbf{0},} \quad \mathrm{R}(0) = \left(\tfrac{1-P_0}{2}\right)\mathbf{1}, \quad P(0) = P_0 \in (0,1) && \text{in } \Omega,
\end{aligned}$$

being $\mathbf{0} = (0,0)$ and $\mathbf{1} = (1,1)$, $\Psi_{\boldsymbol{\varphi}} := \nabla \Psi$, and the source terms are defined by

$$\begin{aligned}
\mathrm{S}_{\boldsymbol{\varphi}}(\boldsymbol{\varphi}, P, \mathrm{R}) &= -\mathrm{S}_{\mathrm{R}}(\boldsymbol{\varphi}, P, \mathrm{R}) = (c_1 P R_1 - c_2 \varphi_1, c_3 P R_2 - c_4 \varphi_2),\\
S_P(\boldsymbol{\varphi}, P, \mathrm{R}) &= -c_1 P R_1 + c_2 \varphi_1 - c_3 P R_2 + c_4 \varphi_2.
\end{aligned}$$

Working Framework

The order parameter $\boldsymbol{\varphi} = (\varphi_1, \varphi_2)$ lives in the 2D simplex:

$$\Delta_\circ := \{\boldsymbol{\varphi} = (\varphi_1, \varphi_2) \in \mathbb{R}^2 : \min\{\varphi_1, \varphi_2\} > 0, \varphi_1 + \varphi_2 < 1\}, \quad \Delta_\bullet := \overline{\Delta_\circ},$$

and the multi-well potential Ψ is of Flory-Huggins type. Namely, $\Psi = \Psi^{(1)} + \Psi^{(2)}$, where the `entropy` part $\Psi^{(1)}$ is

$$\Psi^{(1)}(\boldsymbol{\varphi}) = \begin{cases} \sum_{i=1}^{2} \varphi_i \ln \varphi_i + (1 - \varphi_1 - \varphi_2) \ln(1 - \varphi_1 - \varphi_2) & \text{if } \varphi_1 \geq 0,\ \varphi_2 \geq 0,\ \varphi_1 + \varphi_2 \leq 1, \\ +\infty & \text{otherwise,} \end{cases}$$

whereas the `demixing` term $\Psi^{(2)}$ is such that

$$\Psi^{(2)} \in C^2(\mathbb{R}^2), \qquad \nabla \Psi^{(2)} := \Psi^{(2)}_{\boldsymbol{\varphi}} : \mathbb{R}^2 \to \mathbb{R}^2 \text{ is Lip. continuous.}$$

RNA-Protein model (P)

$$\partial_t \boldsymbol{\varphi} - \Delta \boldsymbol{\mu} = \mathrm{S}_{\boldsymbol{\varphi}} \qquad \text{in } Q,$$

$$\boldsymbol{\mu} = -\Delta \boldsymbol{\varphi} \underbrace{+\Psi^{(1)}_{\boldsymbol{\varphi}}(\boldsymbol{\varphi})}_{\text{grad. of the singular and convex part}} \underbrace{+\Psi^{(2)}_{\boldsymbol{\varphi}}(\boldsymbol{\varphi})}_{\text{grad. of the quadratic perturbation}} \qquad \text{in } Q,$$

$$\partial_t P - \Delta P = S_P \qquad \text{in } Q,$$

$$\partial_t \mathrm{R} - \Delta \mathrm{R} = \mathrm{S}_{\mathrm{R}} \qquad \text{in } Q,$$

$$\partial_{\mathrm{n}} \boldsymbol{\varphi} = \partial_{\mathrm{n}} \boldsymbol{\mu} = \partial_{\mathrm{n}} \mathrm{R} = 0, \quad \partial_{\mathrm{n}} P = 0 \qquad \text{on } \Sigma,$$

$$\boxed{\boldsymbol{\varphi}(0) = 0,} \quad \mathrm{R}(0) = \left(\tfrac{1-P_0}{2}\right)\mathbf{1}, \quad P(0) = P_0 \in (0,1) \qquad \text{in } \Omega,$$

with source terms defined by

$$\underbrace{\min\{c_1, c_3\} \gg c_2 + c_4}_{\text{Biological fact}} \qquad \begin{cases} \mathrm{S}_{\boldsymbol{\varphi}} = -\mathrm{S}_{\mathrm{R}} = (c_1 P R_1 - c_2 \varphi_1, c_3 P R_2 - c_4 \varphi_2), \\ S_P = -c_1 P R_1 + c_2 \varphi_1 - c_3 P R_2 + c_4 \varphi_2. \end{cases}$$

Existence of global weak solutions

Suppose that

$$\boxed{\varphi_0 := 0,} \qquad P_0 \in L^2, \qquad \mathrm{R}_0 = (R_0^1, R_0^2) := \Big(\frac{1-P_0}{2}\Big)\mathbf{1},$$

$$0 \le P_0(x) \le 1 \quad \text{for a.a. } x \in \Omega, \qquad \Big\| P_0 - \frac{1}{2} \Big\|_{L^\infty(\Omega)} \le \frac{1}{2}\Big(1 - \frac{c_2 + c_4}{\min\{c_1, c_3\}}\Big).$$

Then, there exists $(\varphi, \boldsymbol{\mu}, P, \mathrm{R})$ such that

$$\varphi \in H^1(0,T;(\mathrm{H}^1)^*) \cap L^\infty(0,T;\mathrm{H}^1) \cap L^2(0,T;\mathrm{H}^2_{\mathrm{n}}), \quad \varphi \in \mathrm{L}^\infty(Q): \quad \varphi \in \Delta_\circ \quad \text{a.e. in } Q,$$

$$\boxed{\boldsymbol{\mu} \in L^p(0,T;\mathrm{H}^1) \cap L^2(\sigma,T;\mathrm{H}^1) \quad \forall\, p \in (1,2) \quad \forall\, \sigma \in (0,T),} \quad \nabla\boldsymbol{\mu} \in L^2(0,T;\mathrm{L}^2),$$

$$P \in H^1(0,T;(H^1)^*) \cap L^2(0,T;H^1) \cap L^\infty(Q),$$

$$\mathrm{R} \in H^1(0,T;(\mathrm{H}^1)^*) \cap L^2(0,T;\mathrm{H}^1) \cap \mathrm{L}^\infty(Q),$$

$$\boxed{\exists\, c_* > 0: \quad c_* < P(x,t) \le 1, \quad c_* < R_i(x,t) \le 1 \quad \text{for a.a. } (x,t) \in Q, \quad i = 1,2,}$$

$$(*) \quad \varphi \in L^4(\sigma,T;\mathrm{H}^2_{\mathrm{n}}) \cap L^2(\sigma,T;\mathrm{W}^{2,6}) \quad \forall\, \sigma \in (0,T),$$

$$(*) \quad \varphi \in L^{2p}(0,T;\mathrm{H}^2_{\mathrm{n}}) \cap L^p(0,T;\mathrm{W}^{2,6}) \quad \forall\, p \in (1,2),$$

Existence of global weak solutions

which is a `weak solution` of `(P)` in the following sense:

$$\boldsymbol{\mu} = -\Delta \boldsymbol{\varphi} + \Psi_{\boldsymbol{\varphi}}(\boldsymbol{\varphi}) \qquad \text{a.e. in } Q,$$

and the variational identities

$$\langle \partial_t \boldsymbol{\varphi}, \boldsymbol{v} \rangle_{\mathrm{H}^1} + \int_\Omega \nabla \boldsymbol{\mu} : \nabla \boldsymbol{v} = \int_\Omega \mathrm{S}_{\boldsymbol{\varphi}}(\boldsymbol{\varphi}, P, \mathrm{R}) \cdot \boldsymbol{v},$$

$$\langle \partial_t P, v \rangle_{H^1} + \int_\Omega \nabla P \cdot \nabla v = \int_\Omega S_P(\boldsymbol{\varphi}, P, \mathrm{R}) v,$$

$$\langle \partial_t \mathrm{R}, \boldsymbol{v} \rangle_{\mathrm{H}^1} + \int_\Omega \nabla \mathrm{R} : \nabla \boldsymbol{v} = \int_\Omega \mathrm{S}_{\mathrm{R}}(\boldsymbol{\varphi}, P, \mathrm{R}) \cdot \boldsymbol{v},$$

are satisfied for every $\boldsymbol{v} \in \mathrm{H}^1$, $v \in H^1$, $a.e.$ in $(0, T)$, and

$$\boldsymbol{\varphi}(0) = \mathbf{0}, \quad P(0) = P_0, \quad \mathrm{R}(0) = \left(\frac{1 - P_0}{2}\right)\mathbf{1} \qquad \text{a.e. in } \Omega.$$

The Cahn–Hilliard–Oono equation

This extends the state of art concerning the Cahn-Hilliard-Oono equation!

$$\begin{aligned}
&\partial_t\varphi - \Delta\mu = S(\varphi) := m(h-\varphi) && \text{in } Q, \quad m>0, \quad h\in(-1,1),\\
&\mu = -\Delta\varphi + F'_{\log}(\varphi) && \text{in } Q,\\
&\partial_{\mathrm{n}}\varphi = \partial_{\mathrm{n}}\mu = 0 && \text{on } \Sigma,\\
&\varphi(0) = \varphi_0 = -1 && \text{in } \Omega.
\end{aligned}$$

Roughly speaking, for T_0 “small":

$$\underbrace{\mu \in L^2(0,T;H^1)}_{\text{Previously: } (\varphi_0)_\Omega \in (-1,1)} \quad \text{vs} \quad \underbrace{\mu \in \bigcap_{\sigma\in(0,T),\, p\in(1,2)} L^2(\sigma,T;H^1)\cap L^p(0,T_0;H^1)}_{\text{Our setting: } (\varphi_0)_\Omega = (-1)_\Omega = -1 \notin (-1,1)}.$$

First energy estimate: first eq. by $\mu \Rightarrow$ $\boxed{\int_\Omega S(\varphi)\mu \sim \int_\Omega |\nabla\mu| \mathrm{dx} + |\mu_\Omega|.}$

$$\boxed{(\varphi_0)_\Omega \in (-1,1) + \text{MZ inequality} \quad \Rightarrow \quad F'_{\log}(\varphi)\in L^2(0,T;L^1) \overset{\text{comparison}}{\Rightarrow} \mu_\Omega \in L^2(0,T) \overset{\text{Poincaré}}{\Rightarrow} \mu \in L^2(0,T;H^1)}$$

- A. Miranville and R. Temam: 2016.
- A. Miranville: 2011, 2013, 2017.
- A. Giorgini, M. Grasselli, and A. Miranville: 2017.
- J. He: 2021.
- P. Colli, G. Gilardi, E. Rocca, and J. Sprekels: 2022.

The Flory–Huggins potential

Property ((1), Miranville–Zelik, Kenmochi...)

For every compact subset $K \subset \Delta_\circ$, *there exist constants* $c_\Psi, C_\Psi > 0$ *such that, for every* $\phi \in \Delta_\circ$, $\boxed{\phi_\Omega \in K}$ *it holds that*

$$\boxed{c_\Psi \int_\Omega |\Psi^{(1)}_\varphi(\phi)| \leq \int_\Omega \Psi^{(1)}_\varphi(\phi) \cdot (\phi - \phi_\Omega) + C_\Psi.}$$

Property (($\star$), Grasselli-Scarpa-S. '22)

There exist constants $c_\Psi, C_\Psi > 0$, $R \in (0, 1/2)$, $q \in (2, +\infty)$, *and a decreasing positive function* $F \in L^q(0, R) \cap C^0(0, R)$ *such that, for every measurable* $\phi = (\phi^1, \phi^2) : \Omega \to \Delta_\circ$ *satisfying*

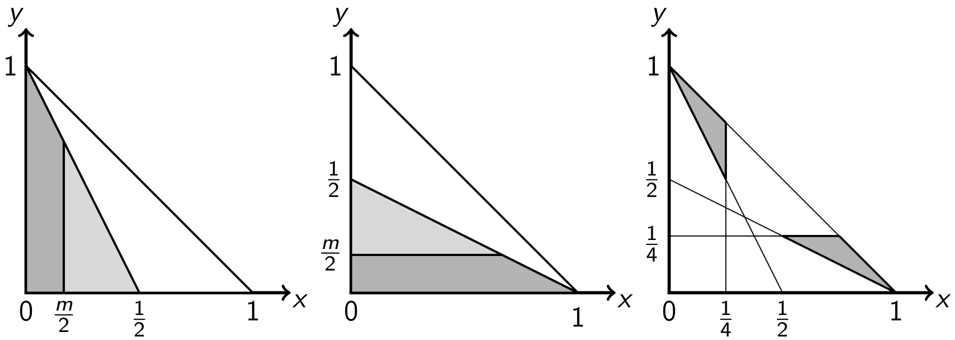
$$0 < \min\{\phi^1_\Omega, \phi^2_\Omega\} < \phi^1_\Omega + \phi^2_\Omega \leq R,$$

it holds that

$$\boxed{c_\Psi \min\{\phi^1_\Omega, \phi^2_\Omega\} \int_\Omega |\Psi^{(1)}_\varphi(\phi)| \leq \int_\Omega \Psi^{(1)}_\varphi(\phi) \cdot (\phi - \phi_\Omega) + C_\Psi(\phi^1_\Omega + \phi^2_\Omega)\Big(1 + F(\min\{\phi^1_\Omega, \phi^2_\Omega\})\Big).}$$

Rough idea of the proof of Property $(\star)$

Let $\phi = (\phi^1, \phi^2) : \Omega \to \Delta_\circ$ and set $0 < \underbrace{\min\{\phi^1_\Omega, \phi^2_\Omega\}}_{=:m} < \underbrace{\phi^1_\Omega + \phi^2_\Omega}_{=:M} \leq R$.



Idea: estimate $\int_\Omega \Psi^{(1)}_\varphi(\phi) \cdot (\phi - \phi_\Omega)$ in suitable partitions of $\Delta_\circ$.

Schematics of the Proof

1. `Approximation`: smoothing of Ψ and truncation of $\mathsf{S}_\varphi, \mathsf{S}_\mathsf{R}$, and S_P;

2. `Preliminary estimate on` φ: parabolic-type estimate for $t \sim 0$;
3. `Dual estimate`: L^1-control of $\Psi^{(1)}$ and of the convex conjugate $(\Psi^{(1)})^*$;
4. `Energy estimate`: control of $\nabla \boldsymbol{\mu} \in L^2(0, T; \mathrm{L}^2)$;

5. `Mean value property for` φ; mean value behaviour as $t \sim 0$;
6. `Estimate of` $\boldsymbol{\mu}$: understand the behaviour as $t \sim 0$;

7. `Passing to the limit`.

Step I: Approximation

Idea: $\Psi^{(1)} \rightsquigarrow \Psi^{(1)}_\lambda$ Lip., $S_\varphi \rightsquigarrow S^\lambda_\varphi \in L^\infty$, $S_R \rightsquigarrow S^\lambda_R \in L^\infty$, and $S_P \rightsquigarrow S^\lambda_P \in L^\infty$.

$$\text{For any } \lambda \in (0,1), \quad \underbrace{\Psi^{(1)}_\lambda : \mathbb{R}^2 \to \mathbb{R},}_{\text{Yosida reg.}} \quad \underbrace{\boldsymbol{J}_\lambda := (I_{\mathbb{R}^2} + \lambda \Psi^{(1)}_\varphi)^{-1}}_{\text{Resolvent operator}},$$

and suitable truncations $S^\lambda_\varphi, S^\lambda_P$, and S^λ_R for the source terms. Then, $(P)_\lambda$ can be solved and

$$\varphi_\lambda \in H^1(0,T;(H^1)^*) \cap L^\infty(0,T;H^1) \cap L^2(0,T;H^3), \quad \boldsymbol{\mu}_\lambda \in L^2(0,T;H^1),$$
$$P_\lambda \in H^1(0,T;(H^1)^*) \cap L^2(0,T;H^1), \quad R_\lambda \in H^1(0,T;(H^1)^*) \cap L^2(0,T;H^1).$$

Lemma (Approximated max-min principle)

There exists a threshold $c_* > 0$ independent of λ such that

$$c_* \le P_\lambda(t) \le 1, \quad c_* \le R_{\lambda,i}(t) \le 1 \quad \text{a.e. in } \Omega, \quad i = 1,2, \quad \forall t \in [0,T].$$

Remark: the threshold is explicit as $0 < c_* \le (c_2 + c_4)(8\min\{c_1, c_3\})^{-1}$.

Step II: Preliminary estimate on φ_λ

We test the first equation by φ_λ and the second by $-\Delta\varphi_\lambda$:

$$\frac{1}{2}\|\varphi_\lambda(t)\|^2 + \int_{Q_t} |\Delta\varphi_\lambda|^2 + \underbrace{\int_{Q_t} \Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda)\cdot(-\Delta\varphi_\lambda)}_{\geq 0 \quad \texttt{by convexity}} = \int_{Q_t} S^\lambda_\varphi \cdot \varphi_\lambda - \underbrace{\int_{Q_t} \Psi^{(2)}_\varphi(\varphi_\lambda)\cdot(-\Delta\varphi_\lambda)}_{\texttt{Young ineq.}}.$$

From the bdd of S^λ_φ and the Lip. continuity of $\Psi^{(2)}_\varphi$, we have

$$\frac{1}{2}\|\varphi_\lambda(t)\|^2 + \frac{1}{2}\int_{Q_t} |\Delta\varphi_\lambda|^2 \leq C\int_0^t (\|\varphi_\lambda(s)\| + \|\varphi_\lambda(s)\|^2)\,\mathrm{ds}.$$

So, the Gronwall lemma (+ `elliptic regularity`) yields

$$\boxed{\|\varphi_\lambda\|_{L^\infty(0,T;\mathbf{L^2})\cap L^2(0,T;\mathbf{H^2_n})} \leq C.}$$

One can plug this estimate into the above lines to deduce that

$$\boxed{\|\varphi_\lambda\|_{L^\infty(0,t;\mathbf{L^2})\cap L^2(0,t;\mathbf{H^2_n})} \leq Ct^{1/2} \qquad \forall\, t\in[0,T].}$$

Iterating the argument, we infer the refinement with $Ct^{3/4}$ and eventually

$$\boxed{\forall\,\alpha\in[0,1), \quad \exists\, C_\alpha > 0: \quad \|\varphi_\lambda\|_{L^\infty(0,t;\mathbf{L^2})\cap L^2(0,t;\mathbf{H^2_n})} \leq C_\alpha t^\alpha \qquad \forall\, t\in[0,T].}$$

Step III: Dual estimate

We integrate in time the first equation, test it by $\boldsymbol{\mu}_\lambda$, and the second one tested by $\boldsymbol{\varphi}_\lambda$:

$$\int_0^t \int_{Q_s := \Omega\times[0,s]} |\nabla \boldsymbol{\mu}_\lambda|^2 \,\mathrm{ds} + \int_{Q_t} |\nabla \boldsymbol{\varphi}_\lambda|^2 + \underbrace{\int_{Q_t} \Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda)\cdot \boldsymbol{\varphi}_\lambda}_{=\int_{Q_t}\Psi^{(1)}_\lambda(\boldsymbol{\varphi}_\lambda)+\int_{Q_t}(\Psi^{(1)}_\lambda)^*(\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda))} = \int_0^t\int_{Q_s} \mathsf{S}^\lambda_{\boldsymbol{\varphi}}\cdot \boldsymbol{\mu}_\lambda \,\mathrm{ds} - \underbrace{\int_{Q_t}\Psi^{(2)}_{\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda)\cdot\boldsymbol{\varphi}_\lambda}_{\text{prev. est.}},$$

where $(\Psi^{(1)}_\lambda)^*$ stands for the convex conjugate of $\Psi^{(1)}_\lambda$. Besides,

$$\int_0^t\int_{Q_s} \mathsf{S}^\lambda_{\boldsymbol{\varphi}}\cdot\boldsymbol{\mu}_\lambda\,\mathrm{ds} = \int_0^t\int_{Q_s}\mathsf{S}^\lambda_{\boldsymbol{\varphi}}\cdot(-\Delta\boldsymbol{\varphi}_\lambda)\,\mathrm{ds} + \int_0^t\int_{Q_s}\mathsf{S}^\lambda_{\boldsymbol{\varphi}}\cdot\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda)\,\mathrm{ds} + C$$

$$\leq C + \underbrace{\int_0^t\int_{Q_s}\begin{pmatrix} c_1 P_\lambda R_{\lambda,1}\\ c_3 P_\lambda R_{\lambda,2}\end{pmatrix}\cdot\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda)\,\mathrm{ds}}_{=:I} - \underbrace{\int_0^t\int_{Q_s}\begin{pmatrix} c_2 J^1_\lambda(\boldsymbol{\varphi}_\lambda)\\ c_4 J^2_\lambda(\boldsymbol{\varphi}_\lambda)\end{pmatrix}\cdot\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda)\,\mathrm{ds}}_{\text{somehow OK}}$$

max-min for P_λ and R_λ $\Rightarrow$ $\exists\varepsilon_0 : \quad \varepsilon_0\begin{pmatrix} c_1 P_\lambda R_{\lambda,1}\\ c_3 P_\lambda R_{\lambda,2}\end{pmatrix}\in\Delta_\bullet \quad \forall\,\lambda\in(0,1)$ $\Rightarrow$ Young's ineq.

$$I = \int_0^t\int_{Q_s}\begin{pmatrix} c_1 P_\lambda R_{\lambda,1}\\ c_3 P_\lambda R_{\lambda,2}\end{pmatrix}\cdot\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda)\,\mathrm{ds} \leq \frac{1}{\varepsilon_0}\int_0^t\int_{Q_s}\left[\Psi^{(1)}_\lambda\left(\varepsilon_0\begin{pmatrix} c_1 P_\lambda R_{\lambda,1}\\ c_3 P_\lambda R_{\lambda,2}\end{pmatrix}\right) + (\Psi^{(1)}_\lambda)^*(\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda))\right]\mathrm{ds}$$

$$\leq \frac{1}{\varepsilon_0}T|Q|\max_{\mathrm{r}\in\Delta_\bullet}\Psi^{(1)}(\mathrm{r}) + \frac{1}{\varepsilon_0}\int_0^t\int_{Q_s}(\Psi^{(1)}_\lambda)^*(\Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\boldsymbol{\varphi}_\lambda))\,\mathrm{ds}.$$

Step III: Dual estimate

Summing up, we have

$$\int_0^t \int_{Q_s} |\nabla \boldsymbol{\mu}_\lambda|^2 \,\mathrm{ds} + \int_{Q_t} |\nabla \varphi_\lambda|^2 + \int_{Q_t} \Psi^{(1)}_\lambda(\varphi_\lambda) + \int_{Q_t} \left|(\Psi^{(1)}_\lambda)^*(\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda))\right| \leq C \int_0^t \int_{Q_s} \left|(\Psi^{(1)}_\lambda)^*(\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda))\right| \mathrm{ds} + C.$$

Then Gronwall's lemma yields that

$$\left\|\Psi^{(1)}_\lambda(\varphi_\lambda)\right\|_{L^1(Q)} + \left\|(\Psi^{(1)}_\lambda)^*(\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda))\right\|_{L^1(Q)} \leq C.$$

Furthermore, Yosida + convex analysis produce

$$\lambda^{1/2} \left\|\Psi_{\lambda,\varphi}(\varphi_\lambda)\right\|_{L^2(0,T;\mathrm{L}^2)} \leq C.$$

Step IV: Energy estimate

We test the first eq. by $\boldsymbol{\mu}_\lambda$, the second by $\partial_t \varphi_\lambda$:

$$\frac{1}{2}\int_\Omega |\nabla \varphi_\lambda(t)|^2 + \int_\Omega \Psi_\lambda^{(1)}(\varphi_\lambda(t)) + \int_{Q_t} |\nabla \boldsymbol{\mu}_\lambda|^2 = \underbrace{\int_\Omega \Psi_\lambda(\varphi_0) - \int_\Omega \Psi_\lambda^{(2)}(\varphi_\lambda(t))}_{\leq C} + \int_{Q_t} \mathrm{S}_\varphi^\lambda \cdot \boldsymbol{\mu}_\lambda .$$

We have

$$\begin{aligned}\int_{Q_t} \mathrm{S}_\varphi^\lambda \cdot \boldsymbol{\mu}_\lambda &= \int_{Q_t} \begin{pmatrix} c_1 P_\lambda R_{\lambda,1} \\ c_3 P_\lambda R_{\lambda,2} \end{pmatrix} \cdot \boldsymbol{\mu}_\lambda - \int_{Q_t} \begin{pmatrix} c_2 J_\lambda^1(\varphi_\lambda) \\ c_4 J_\lambda^2(\varphi_\lambda) \end{pmatrix} \cdot \boldsymbol{\mu}_\lambda \\ &\leq \underbrace{\int_{Q_t} \begin{pmatrix} c_1 P_\lambda R_{\lambda,1} \\ c_3 P_\lambda R_{\lambda,2} \end{pmatrix} \cdot \boldsymbol{\mu}_\lambda}_{I} + C - \underbrace{\int_{Q_t} \begin{pmatrix} c_2 J_\lambda^1(\varphi_\lambda) \\ c_4 J_\lambda^2(\varphi_\lambda) \end{pmatrix} \cdot \Psi_{\lambda,\varphi}^{(1)}(\varphi_\lambda)}_{II} .\end{aligned}$$

Besides,

$$\begin{aligned} I &\leq C + \int_{Q_t} \begin{pmatrix} c_1 P_\lambda R_{\lambda,1} \\ c_3 P_\lambda R_{\lambda,2} \end{pmatrix} \cdot \Psi_{\lambda,\varphi}^{(1)}(\varphi_\lambda) \\ &\leq C + \frac{1}{\varepsilon_0}\int_{Q_t} \Psi_\lambda^{(1)}\left(\varepsilon_0 \begin{pmatrix} c_1 P_\lambda R_{\lambda,1} \\ c_3 P_\lambda R_{\lambda,2} \end{pmatrix}\right) + \frac{1}{\varepsilon_0}\int_{Q_t} (\Psi_\lambda^{(1)})^*(\Psi_{\lambda,\varphi}^{(1)}(\varphi_\lambda)) \leq \frac{1}{\varepsilon_0}|Q| \max_{\mathrm{r}\in\Delta_\bullet} \Psi^{(1)}(\mathrm{r}) + \frac{C}{\varepsilon_0} + C .\end{aligned}$$

Step IV: Energy estimate

Moreover, we have

$$II = \int_{Q_t} \begin{pmatrix} c_2 J^1_\lambda(\varphi_\lambda) \\ c_4 J^2_\lambda(\varphi_\lambda) \end{pmatrix} \cdot \Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda) \geq -|Q|(c_2 + c_4) \max_{\mathrm{r}\in\Delta_\bullet} \Psi^{(1)}(\mathrm{r}).$$

Therefore, we obtain that

$$\frac{1}{2}\int_\Omega |\nabla\varphi_\lambda(t)|^2 + \int_\Omega \Psi^{(1)}_\lambda(\varphi_\lambda(t)) + \int_{Q_t} |\nabla\boldsymbol{\mu}_\lambda|^2 \leq C \qquad \forall\, t \in [0, T],$$

whence

$$\|\varphi_\lambda\|_{L^\infty(0,T;\mathbf{H}^1)} + \left\|\Psi^{(1)}_\lambda(\varphi_\lambda)\right\|_{L^\infty(0,T;\mathbf{L}^1)} + \|\nabla\boldsymbol{\mu}_\lambda\|_{L^2(0,T;\mathbf{L}^2)} \leq C.$$

Next, comparison in the first eq. yield

$$\|\varphi_\lambda\|_{H^1(0,T;(\mathbf{H}^1)^*)} \leq C.$$

Finally, by the properties of the Yosida regularisation, we derive that

$$\lambda^{1/2}\,\|\Psi_{\lambda,\varphi}(\varphi_\lambda)\|_{L^\infty(0,T;\mathbf{L}^2)} \leq C.$$

Step V: Mean value property

Goal: passing from "$\nabla \boldsymbol{\mu} \in L^2(0,T;\mathrm{L}^2)$" to "$\boldsymbol{\mu} \in L^p(0,T;\mathrm{H}^1)$" $\forall p \in (1,2)$.

$$\texttt{(MVP)} + (\star) \Longrightarrow \quad \Psi^{(1)}_{\lambda,\boldsymbol{\varphi}}(\varphi) \in L^p(0,T;\mathrm{L}^1) \overset{comparison}{\Longrightarrow} \quad \boldsymbol{\mu}_\Omega \in L^p(0,T) \overset{\text{Poincaré}}{\Longrightarrow} \boldsymbol{\mu} \in L^p(0,T;\mathrm{H}^1)$$

Lemma (Mean value properties (MVP))

Set $\alpha_0 := (P_0)_\Omega \in (0,1)$. *Then*

$$(\varphi_{\lambda,1}(t))_\Omega + (\varphi_{\lambda,2}(t))_\Omega \leq \min\{\alpha_0 - c_*, 1-\alpha_0 - 2c_*\} < 1 \qquad \forall\, t \in [0,T],$$

$$(\varphi_{\lambda,i}(t))_\Omega \leq \frac{1-\alpha_0}{2} - c_* < 1 \quad \forall\, t \in [0,T], \qquad \text{for } i = 1,2,$$

$$\exists \lambda_0 \in (0,1), c_0 > 0 : \quad c_0(1 - e^{-c_{2i}t}) \leq (\varphi_{\lambda,i}(t))_\Omega \leq c_{2i-1}t \qquad \forall\, t \in [0,T], \forall \lambda \in (0,\lambda_0).$$

Step VI: Estimate of $\boldsymbol{\mu}$

- Case $t \in (\sigma, T)$, for every $\sigma \in (0, T)$: standard method ✓
- What happen when $t \sim 0$? By the (MVP) $\exists T_0 \in (0, T), c_0' \in (0, 1)$:

$$0 < c_0' t \leq \min\{(\varphi_{\lambda,1}(t))_\Omega, (\varphi_{\lambda,2}(t))_\Omega\} < (\varphi_{\lambda,1}(t))_\Omega + (\varphi_{\lambda,2}(t))_\Omega \leq (c_1 + c_3)t \leq \frac{R}{2}, \quad \forall t \in (0, T_0),$$

where $R \in (0, 1/2)$ is given by Property $(\star)$.
Property $(\star)$ with $\phi = \boldsymbol{J}_\lambda(\varphi_\lambda(t))$ and $t \in (T_\lambda, T_0)$ implies

$$c_\Psi(c_0' t - C\lambda^{1/2}) \int_\Omega |\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda(t))| \leq \int_\Omega \Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda(t)) \cdot (\boldsymbol{J}_\lambda(\varphi_\lambda(t)) - (\boldsymbol{J}_\lambda(\varphi_\lambda(t)))_\Omega)$$
$$+ C_\Psi((c_1 + c_3)t + 2C\lambda^{1/2}) \left(1 + F(c_0' t - C\lambda^{1/2})\right).$$

We test the second eq. by $\boldsymbol{J}_\lambda(\varphi_\lambda) - (\boldsymbol{J}_\lambda(\varphi_\lambda))_\Omega$ and $\forall \alpha \in [0, 1)$ $\|\varphi_\lambda\|_{L^\infty(0,t;\mathbf{L}^2)} \leq C_\alpha t^\alpha \Rightarrow$

Step VI: Estimate of $\boldsymbol{\mu}$

$$c_\Psi(c_0' t - C\lambda^{1/2}) \int_\Omega |\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda(t))| \leq C_\Psi\big((c_1+c_3)t + 2C\lambda^{1/2}\big)\left(1 + F(c_0' t - C\lambda^{1/2})\right) + C_\alpha\,(1 + \|\nabla\boldsymbol{\mu}_\lambda(t)\| + \|\varphi_\lambda(t)\|)\,(t^\alpha + \lambda^{1/2}) \quad \forall t \in (T_\lambda, T_0), \alpha \in (0,1).$$

Equivalently, for $t \in (T_\lambda, T_0)$, $T_\lambda := 2C(c_0')^{-1}\lambda^{1/2}$,

$$c_\Psi \int_\Omega |\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda(t))| \leq \underbrace{C_\Psi \frac{(c_1+c_3)t + 2C\lambda^{1/2}}{c_0' t - C\lambda^{1/2}}}_{\leq C}\left(1 + F(c_0' t - C\lambda^{1/2})\right) + C_\alpha \underbrace{\frac{t^\alpha + \lambda^{1/2}}{c_0' t - C\lambda^{1/2}}}_{\leq \frac{2}{c_0'}\frac{1}{t^{1-\alpha}}}(1 + \|\nabla\boldsymbol{\mu}_\lambda(t)\| + \|\varphi_\lambda(t)\|)$$

Therefore, for $a.e$ $t \in (T_\lambda, T_0)$,

$$\int_\Omega |\Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda(t))| \leq \underbrace{C\left(1 + F(c_0' t - C\lambda^{1/2})\right)}_{\text{OK: } L^{2+}(T_\lambda,\, T_0)} + C_\alpha \underbrace{\left(1 + \frac{1}{t^{1-\alpha}}\right)}_{\in L^\bullet(T_\lambda, T_0)?} \underbrace{(1 + \|\nabla\boldsymbol{\mu}_\lambda(t)\| + \|\varphi_\lambda(t)\|)}_{L^2(T_\lambda, T_0)}.$$

$$\forall \ell \in (1,+\infty)\ \exists \alpha \in (0,1),\ C_\ell > 0 : \quad \left\| t \mapsto \frac{1}{t^{1-\alpha}} \right\|_{L^\ell(T_\lambda, T_0)} \leq C_\ell$$

Step VI: Estimate of $\boldsymbol{\mu}$

Therefore, by the Hölder inequality we get

$$\forall\, p \in (1,2), \quad \exists\, C_p > 0 : \quad \left\| \Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda) \right\|_{L^p(T_\lambda, T_0; \mathrm{L}^1)} \leq C_p .$$

Setting

$$\chi_\lambda : [0, T] \to [0,1]\,, \qquad \chi_\lambda(t) := \begin{cases} 0 & \text{if } t \in [0, T_\lambda], \\ 1 & \text{if } t \in (T_\lambda, T], \end{cases}$$

the above can be rewritten as

$$\forall\, p \in (1,2), \quad \exists\, C_p > 0 : \quad \left\| \chi_\lambda \Psi^{(1)}_{\lambda,\varphi}(\varphi_\lambda) \right\|_{L^p(0, T_0; \mathrm{L}^1)} \leq C_p .$$

Comparison in the second eq. then leads us to

$$\forall\, p \in (1,2), \quad \exists\, C_p > 0 : \quad \| \chi_\lambda (\boldsymbol{\mu}_\lambda)_\Omega \|_{L^p(0,T_0)} \leq C_p \overset{\text{Poincaré}}{\Longrightarrow} \| \chi_\lambda \boldsymbol{\mu}_\lambda \|_{L^p(0,T_0; \mathrm{H}^1)} \leq C_p .$$

Step VII: Passing to the limit $\lambda \to 0$

M. Grasselli, L. Scarpa and A. S., On a phase field model for RNA-Protein dynamics. Preprint arXiv:2203.03258 [math.AP], (2022), 1-54.

Step VII: Passing to the limit $\lambda \to 0$

`Trust us, it can be done!`

Thus proof is concluded. $\square$

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