Modeling the growth of p_{62}-Ubiquitin aggregates involved in cellular autophagy

Julia Delacour[1 2 3]

under the co-supervision of
Marie Doumic [1], Christian Schmeiser [2 3]
in collaboration with Peter Szmolyan [4]

[1]LJLL (UPMC), [2]SMICH program, [3]University of Vienna [4]Technical University of Vienna

5/02/2020

1. Presentation of the model
   - model
   - system of equations

2. Study of the system of equations
   - study the stability of the zero steady-state using blow-up
   - study of the polynomially growing regime using slow-fast dynamics (Fenichel theory)

Introduction

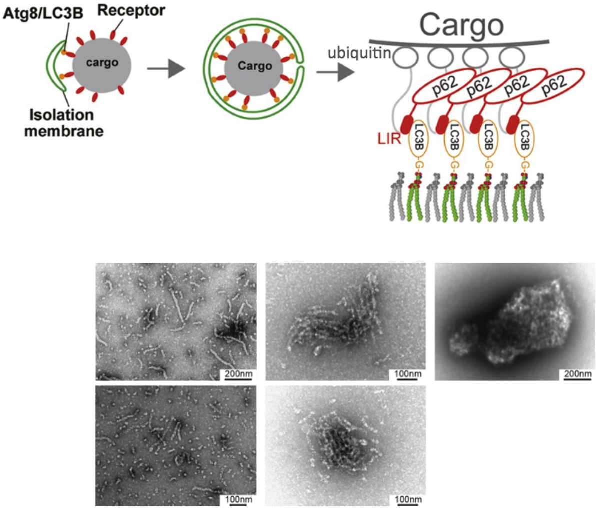


FIGURE 1 – figures from (top) [WZF+15] and (bottom) [ZSD+18]

We model the growth of p_{62}-Ubiquitin aggregates

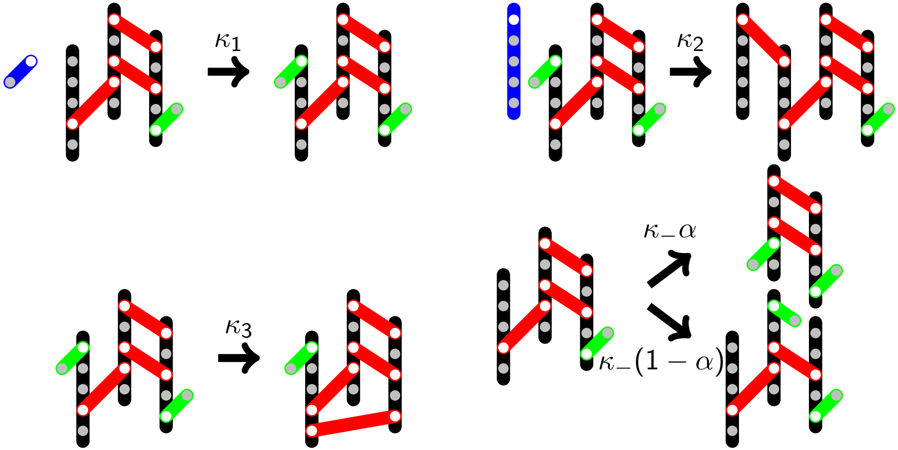
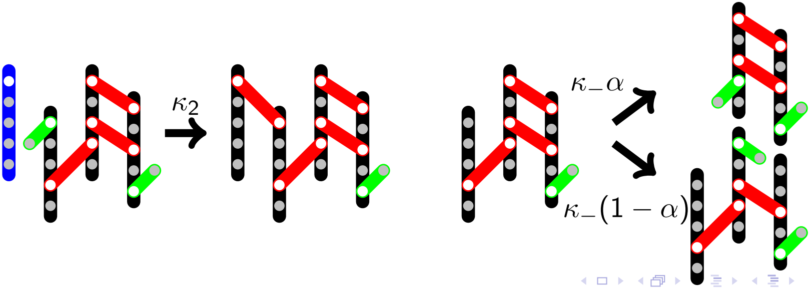


FIGURE 2 – reactions taken into account

The model leads to an ODE system

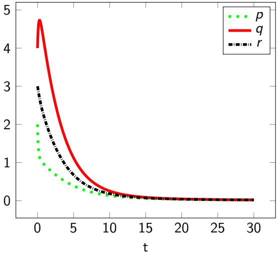
$$
\begin{cases}
\dot{p} = (\kappa_1 - \kappa_3 p)(n\mathbf{r} - p - 2q) + \kappa_- q\left(1 - (n-1)\dfrac{p}{(n-2)\mathbf{r}}\right) - (\kappa_2 + \kappa_{-1})p \\
\dot{q} = \kappa_2 p + \kappa_3 p(n\mathbf{r} - p - 2q) - \kappa_- q \\
\dot{r} = \kappa_2 p - \kappa_- q\alpha, \ \text{with } \alpha = \dfrac{n\mathbf{r} - 2q}{(n-2)\mathbf{r}} \\
n\mathbf{r} - p - 2q \geq 0 \quad 0 \leq \alpha \leq 1
\end{cases}
\tag{1}
$$

Obtention of the equation for the evolution of r

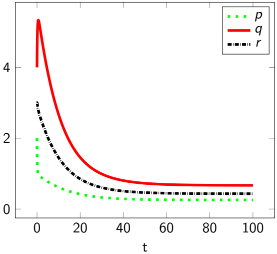


The simulations reveal three regimes

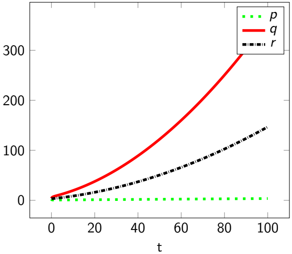
Evolution of an aggregate (p, q, r) of initial size $(2, 4, 3)$ with parameters $\kappa_1 = \kappa_2 = \kappa_3 = \kappa_{-1} = 1$



a) $\kappa_- = 0.93$
zero steady-state
$(0, 0, 0)$



b) $\kappa_- = 0.6$
non-trivial
steady-state



c) $\kappa_- = 0.2$
polynomially
growing solution

The conditions under which the three regimes happen are conjectured

(1) can undergo three regimes under the following conditions :

- if $\kappa_-^2(n-1) + \kappa_-(\kappa_{-1}+\kappa_1)(n-2) \geq \kappa_1\kappa_2(n-2)^2 > 0(\boldsymbol{a})$ holds, then $(0,0,0)$ is stable.
- if $\kappa_-^2(n-1) + \kappa_-(\kappa_{-1}+\kappa_1)(n-2) \leq \kappa_1\kappa_2(n-2)^2 \leq 0(\boldsymbol{b_1})$ and $4\kappa_1\kappa_2(n-2)^2 \leq \kappa_-^2 n^2(n-1) + 2\kappa_-(\kappa_{-1}+\kappa_1)n(n-2) \leq 0(\boldsymbol{b_2})$ holds,
  then (p,q,r) converges towards a non-trivial steady-state.
- if $4\kappa_1\kappa_2(n-2)^2 \geq \kappa_-^2 n^2(n-1) + 2\kappa_-(\kappa_{-1}+\kappa_1)n(n-2) > 0(\boldsymbol{c})$ holds,
  then (p,q,r) undergoes a polynomial growth, more precisely :

$$
\begin{aligned}
p &= p_1 t + o(t) \\
q &= q_2 t^2 + o(t^2) \\
r &= r_2 t^2 + o(t^2).
\end{aligned}
$$

The stability of the zero steady-state can be studied thanks to blow-up

Differentiation matrix associated with (1) not well-defined
$\implies$ change of variable $\tau = \int_0^t \frac{ds}{r(s)}$.

$(0,0,0)$ is not an hyperbolic point for the new system.

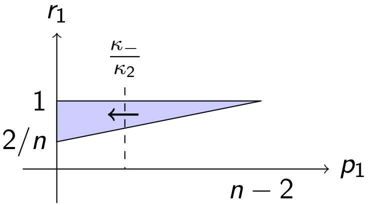
blow-up in the q-direction : $(p_1, q_1, r_1) := (\frac{p}{q}, q, \frac{r}{q})$.

$$
\begin{cases}
q_1' = q_1 r_1 \left(\kappa_2 p_1 - \kappa_-\right) , \\
p_1' = \kappa_1 (n r_1 - p_1 - 2) r_1 + \kappa_- r_1 - \dfrac{\kappa_-(n-1)}{n-2} p_1 - (\kappa_2 + \kappa_{-1}) p_1 r_1 \\
\qquad - p_1 r_1 (\kappa_2 p_1 - \kappa_-) , \\
r_1' = (1 - r_1) \left(\kappa_2 p_1 r_1 + \dfrac{\kappa_-}{n-2} (2 - (n-2) r_1) \right) .
\end{cases}
$$

$(0,0,0)$ is asymptotically locally stable when (a) holds

Theorem

If (a) holds, then $(0,0,0)$ is locally asymptotically stable.



$$nr - p - 2q \geq 0$$
$$0 \leq \alpha < 1$$

We distinguish two cases :

- $\kappa_2 p_1 - \kappa_- < 0$
  then, $\dot{q}_1 < 0$.
- $\kappa_2 p_1 - \kappa_- > 0$
  then, $\dot{p}_1 < 0$ under (a)

Hence, when $q \to 0$, then $p := p_1 q$, $\quad r := r_1 q \to 0$, because p_1, r_1 bdd.

Study of the asymptotical locally stability of the polynomially growing regime using slow-fast dynamics

Theorem

Assuming that (C) holds, if p, q, and r tend towards infinity, then they grow asymptotically locally in the following polynomial manner with t, namely

$$p = p_1 t + o(t),$$
$$q = q_2 t^2 + o(t^2),$$
$$r = r_2 t^2 + o(t^2).$$

A Poincaré-compactification-like change of variable leads to a slow-fast dynamics with three separated timescales

Change of variable (inspired by Poincaré-compactification) :

$$(p,q,r) \to (u := \frac{p}{\sqrt{p+q}}, v := \frac{2p+2q-nr}{\sqrt{p+q}}, w := \frac{1}{\sqrt{p+q}})$$

$$W := \varepsilon w \quad \varepsilon \ll 1$$

$$\begin{cases} \dot{u} = \dfrac{1}{\varepsilon W}(-\kappa_3 u(u-v) + \kappa_{-3}) + O(1) \\ \dot{v} = 2\kappa_1(u-v) - 2\kappa_{-1}u - n\kappa_2 u + \dfrac{n\kappa_{-3}}{(n-2)}\dfrac{(1-\varepsilon uW)}{(2-\varepsilon vW)}(2u-nv) + O(\varepsilon) \\ \dot{W} = -\varepsilon\dfrac{W^2}{2}(\kappa_1(u-v) - \kappa_{-1}u - n\kappa_{-3}\dfrac{(n-1)}{(n-2)}\dfrac{(1-\varepsilon uW)}{(2-\varepsilon vW)}u) \end{cases}$$

Slow-fast dynamics system with three timescales completely separated : $\frac{1}{\varepsilon}$, 1 and ε.

An equation for $W = \frac{1}{\sqrt{p+q}}$ concludes the proof

$$\frac{dW}{dt} = -\frac{W^2}{2} \underbrace{\left(4n(n-2)^2\kappa_1\kappa_2 - 2n^2(n-2)\kappa_-(\kappa_1+\kappa_{-1}) - n^3(n-1)\kappa_-^2\right)}_{>0 \quad iff\,(c)\,holds}$$

W grows like $\frac{1}{t}$ under (c).
q, r grow like t^2, p grow like t, when $p+q$ tend towards infinity.

References

- Freddy Dumortier, Jaume Llibre, and Joan Artés, *Qualitative theory of planar differential systems*, Qualitative Theory of Planar Differential Systems (2007).
- Bettina Wurzer, Gabriele Zaffagnini, Dorotea Fracchiolla, Eleonora Turco, Christine Abert, Julia Romanov, and Sascha Martens, *Oligomerization of p62 allows for selection of ubiquitinated cargo and isolation membrane during selective autophagy*, eLife **4** (2015), e08941.
- Gabriele Zaffagnini, Adriana Savova, Alberto Danieli, Julia Romanov, Shirley Tremel, Michael Ebner, Thomas Peterbauer, Martin Sztacho, Riccardo Trapannone, Abul K Tarafder, Carsten Sachse, and Sascha Martens, *p62 filaments capture and present ubiquitinated cargos for autophagy*, The EMBO Journal **37** (2018), no. 5, e98308.

Conclusion

- system of equations describing the growth of p_{62}-ubiquitin aggregates
- study of the system through dynamical systems methods (blow-up, slow-fast dynamics)
- perspective :
  description of the growth of several p_{62}-ubiquitin aggregates taking into account coagulation of aggregates observed experimentally which leads to a transport-coagulation equation,
  theoretical study and simulations of transport-coagulation equations to compare with the experimental data.

Thank you for your attention