Modeling proteasome dynamics in Parkinson's disease

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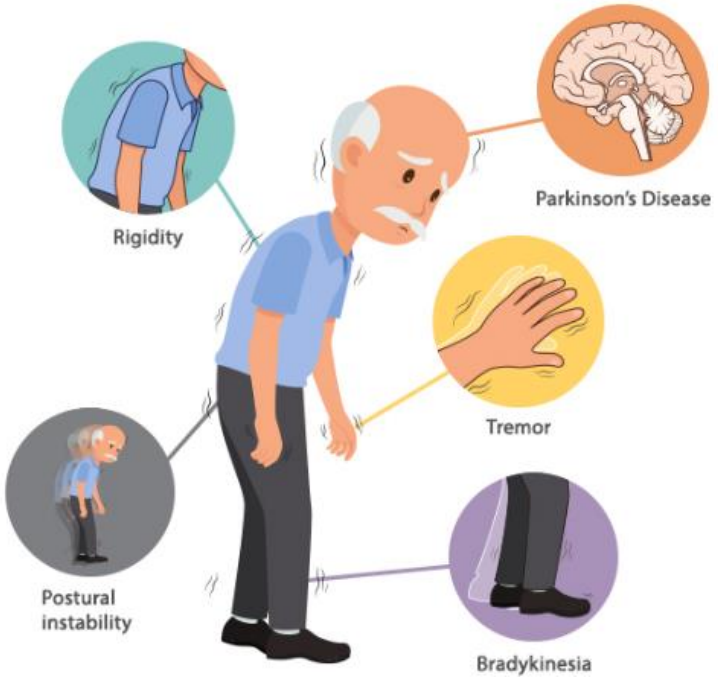
Parkinson's disease

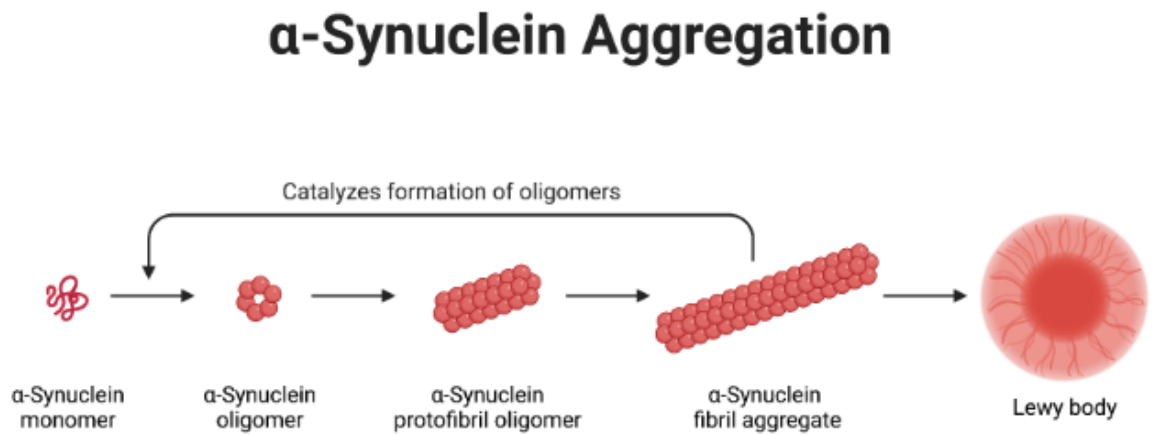
- Progressive neurodegenerative disorder.
- Primarily affects movement control,resulting in stiffness, slowness of movement, and tremors.



https://neurologysleepcentre.com/blog/what-is-parkinsons-disease/

Parkinson's disease

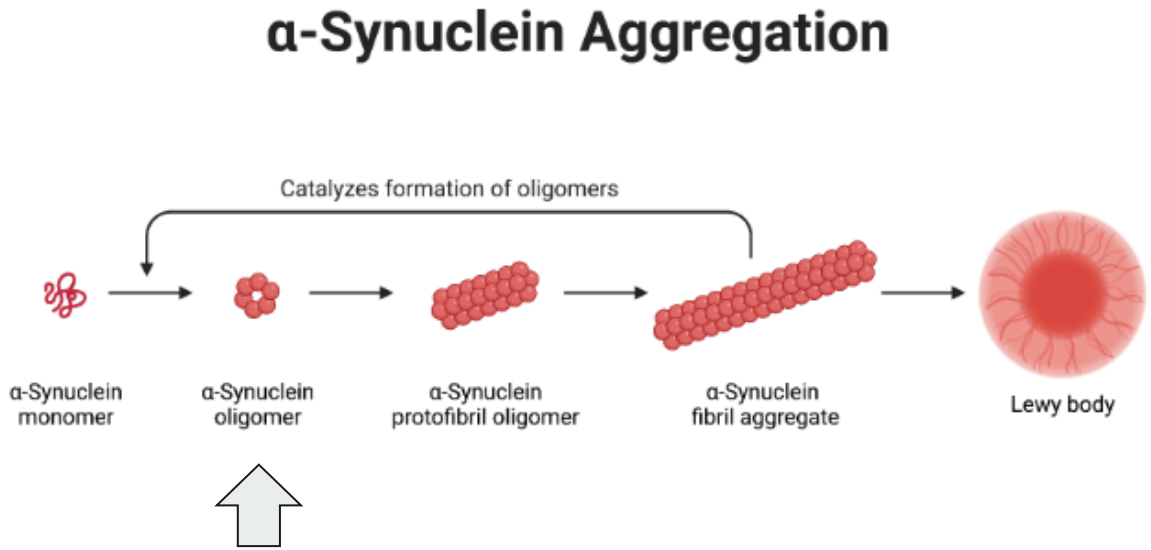
Key feature



https://www.biorender.com/template/a-synuclein-aggregation

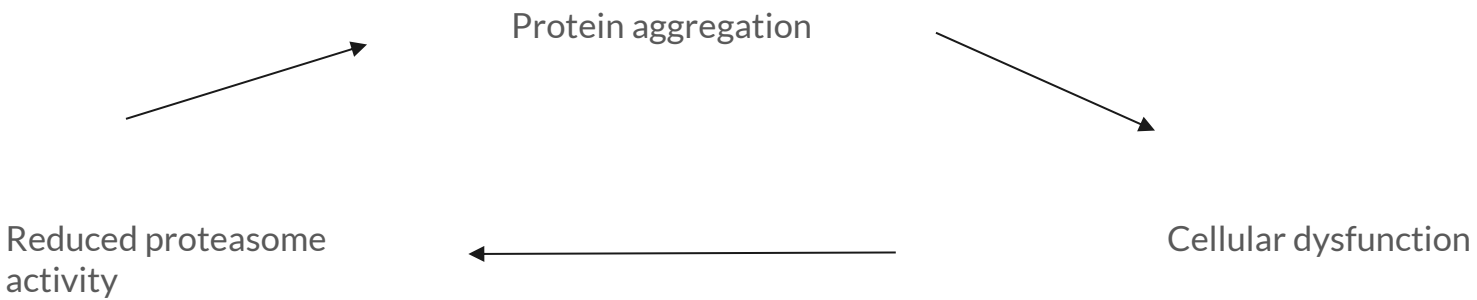
Parkinson's disease

Main cause: soluble oligomers!

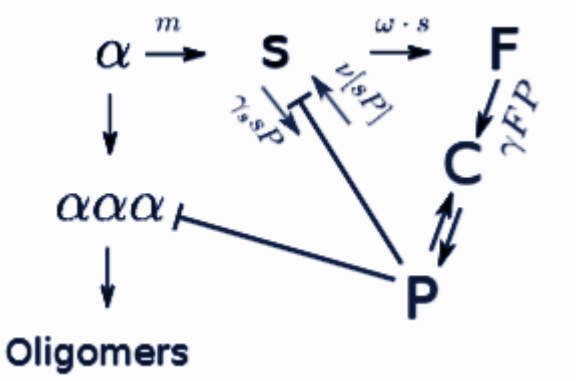


Ubiquitin-proteasome system (UPS)

- Maintaining cellular protein homeostasis by degrading over 70% of intracellular proteins.



Deterministic model of protease dynamics



$$\frac{dF}{dt} = \frac{m}{1+P} - \gamma \cdot F \cdot P,$$

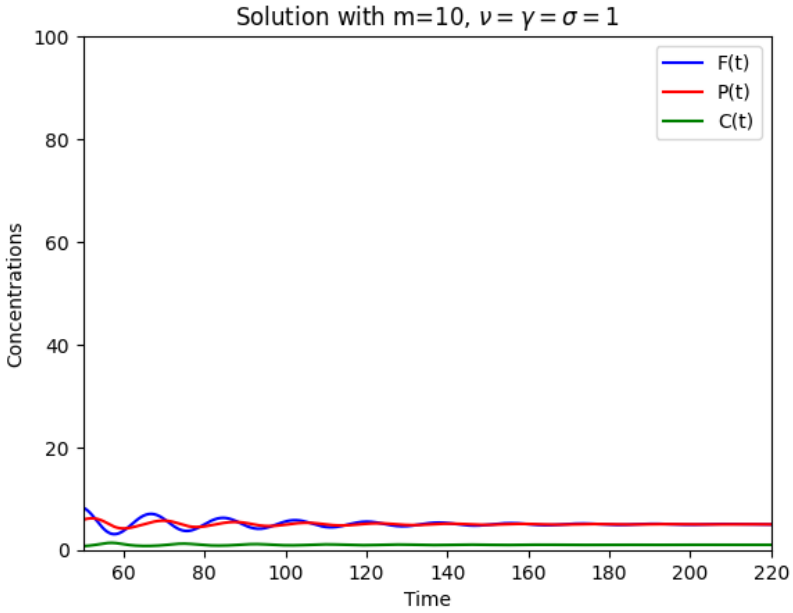
$$\frac{dC}{dt} = \gamma \cdot F \cdot P - \nu \cdot C,$$

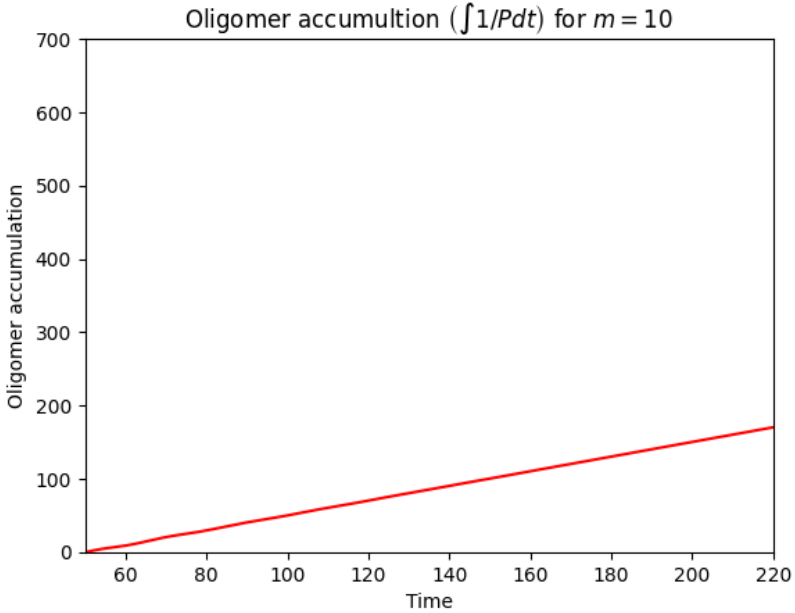
$$\frac{dP}{dt} = \sigma - P - \gamma \cdot F \cdot P + \nu \cdot C.$$

Key idea: when the production of αSN protofilaments exceeds the degradation capacity of the proteasome, it leads to oscillations in proteasome availability!

Results of original model

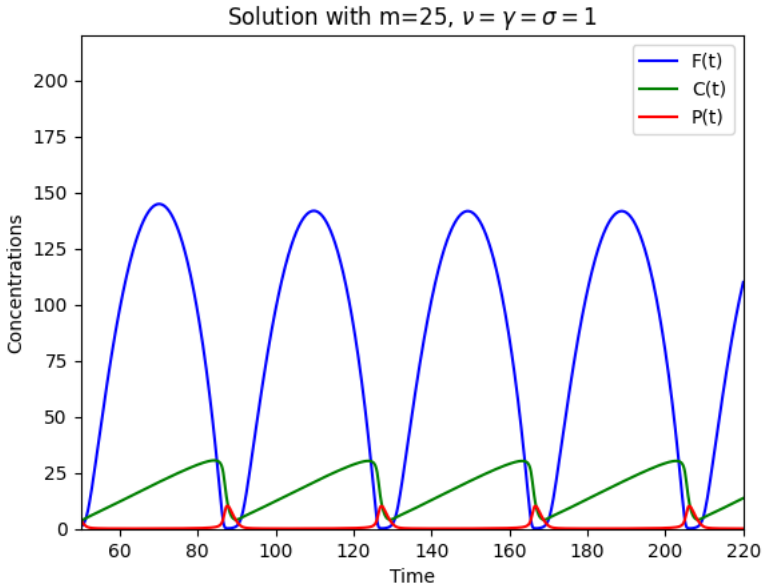
No oscillations = Healthy. Oligomers accumulate at slow constant rate.

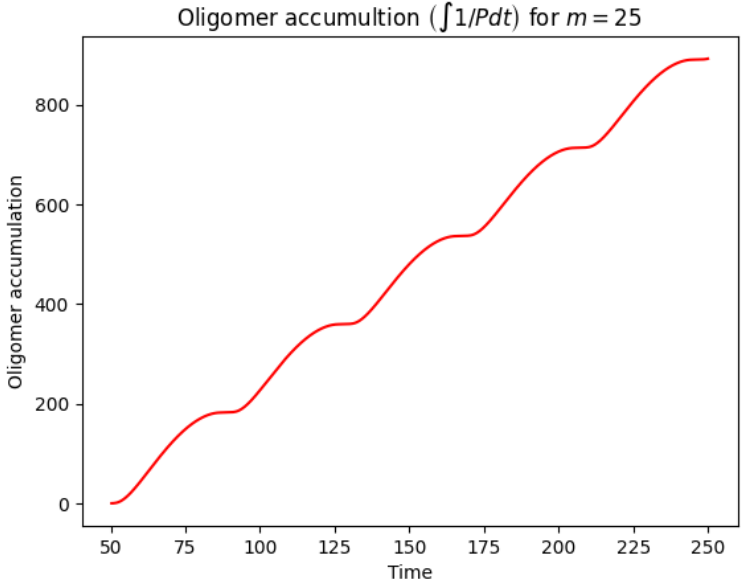




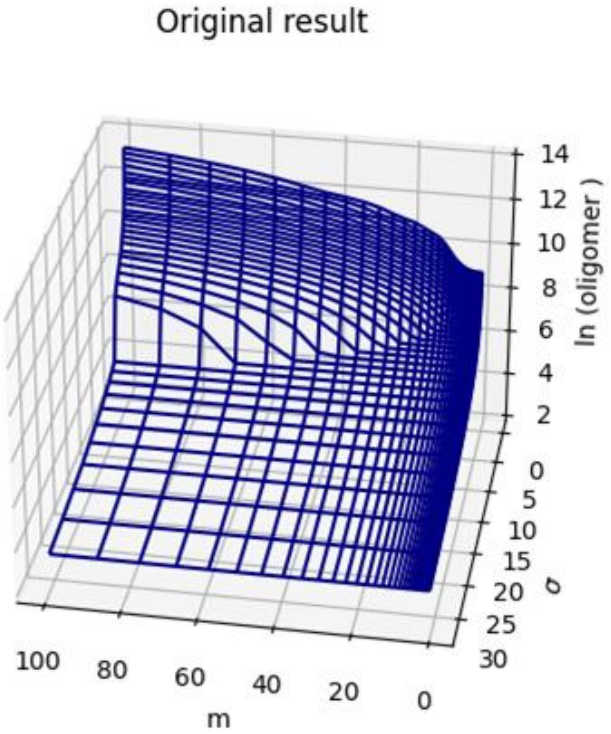
Results of original model

Oscillations = Disease. Oligomers accumulate with quick jumps and grow a lot.





Results of original model



No matter the values of γ,ν,σ, **if m is made big enough, we get oscillations (disease).**

$$m > m_T = (1+\sigma)^2\left(\frac{\nu}{\gamma\sigma} + 1 + \nu\right) \longrightarrow \text{Disease}$$

$$m < m_T \longrightarrow \text{Healthy}$$

m: Influx rate of protofilaments.

σ : Production rate of proteasome.

Question

How does this threshold behaviour change if we add other feedbacks to the model?

- Proteasome induced by protofibrils.
- Proteasome induced by oligomers.
- Proteasome induced by fibrils.

How to determine the threshold

1. Calculate the fixed points (P*, C*, F*) of the model by setting the derivatives to 0.

$$\begin{aligned} \frac{m}{1+P^*} - \gamma F^* P^* &= 0 \\ \gamma F^* P^* - \nu C^* &= 0 \\ \sigma - P^* - \gamma F^* P^* + \nu C^* &= 0 \\ \Rightarrow P^* = \sigma, \quad F^* = \frac{m}{\gamma P^*(1+P^*)}, \quad C^* &= \frac{m}{\nu(1+P^*)} \end{aligned}$$

1. Calculate the Jacobian matrix J of the system of equations:

$$J = \begin{pmatrix} -\gamma P & 0 & -\frac{m}{(P+1)^2} - \gamma F \\ \gamma P & -\nu & \gamma F \\ -\gamma P & \nu & -1 - \gamma F \end{pmatrix}$$

How to determine the threshold

3. Obtain the **characteristic equation** of the Jacobian matrix.

$$\lambda^3 + a\lambda^2 + b\lambda + c = 0$$

$$\begin{aligned} a &= 1+\nu+\gamma\left(\frac{m}{\gamma\sigma(1+\sigma)}+\sigma\right) \\ b &= \nu+\gamma\sigma(1+\nu)-\frac{\gamma\sigma m}{(1+\sigma)^2} \\ c &= \nu\gamma\sigma, \end{aligned}$$

4. The roots of this equation determine the behaviour of the system. Using that a > 0 and c > 0:

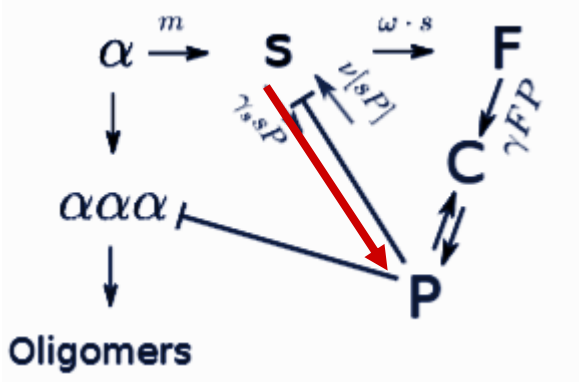
If b > 0 ⟶ Stable: System tends to fixed point. **Healthy**

If b < 0 ⟶ Oscillatory. **Disease**

Proteasome induced by proto-fibrils

Equations:

$$\frac{dF}{dt} = \frac{m}{1+P} - \gamma F \cdot P$$
$$\frac{dC}{dt} = \gamma F \cdot P - \nu C$$
$$\frac{dP}{dt} = \sigma - P - \gamma F \cdot P + \nu C + \beta \frac{m}{1+P}$$



Fixed point: $P^* = \frac{1}{2}\left(-1+\sigma+\sqrt{4\beta m + (1+\sigma)^2}\right)$, $F^* = \frac{m}{\gamma P^*(1+P^*)}$, $C^* = \frac{m}{\nu(1+P^*)}$

Characteristic polynomial:

$$\lambda^3 + a\lambda^2 + b\lambda + c = 0$$

$$a = 1 + \nu + \gamma P^* + \frac{m}{P^*(1+P^*)} + \frac{\beta m}{(1+P^*)^2}$$
$$b = \nu + \gamma P^*(1+\nu) - \frac{\gamma P^* m}{(1+P^*)^2} + \frac{\beta m(\nu + \gamma P^*)}{(1+P^*)^2}$$
$$c = \gamma \nu P^* \left(1 + \frac{\beta m}{(1+P)^2}\right)$$

Proteasome induced by proto-fibrils

Once again, a, c > 0 and as before, b>0 means **healthy** and b<0 means **disease**.

However, in this case:

$$\text{For } m \to \infty, \text{ we have } b \to \frac{\gamma}{\sqrt{\beta}} \left((2+\nu)\beta - 1\right) \sqrt{m}$$

Therefore:

$$\beta > \frac{1}{2+\nu} \quad \to \text{No threshold on } m. \text{ No matter how big } m \text{ is, the result is } \textbf{healthy}$$

$$\beta < \frac{1}{2+\nu} \quad \to \text{If } m \text{ is big enough, we have } \textbf{disease}.$$

Explanation

$$\beta > \frac{1}{2+\nu} \rightarrow \text{No threshold on } m. \text{ No matter how big } m \text{ is, the result is } \textbf{healthy}$$

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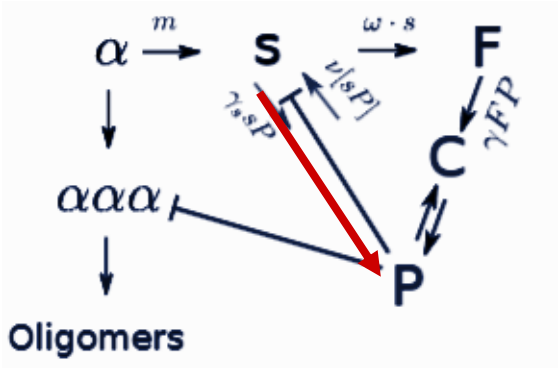
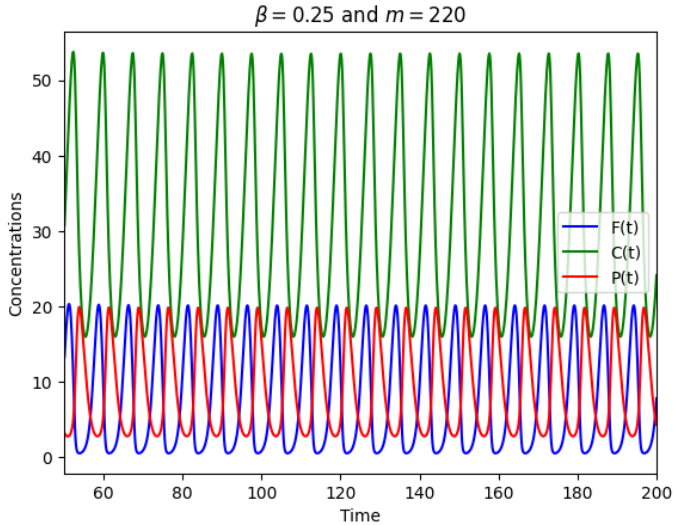
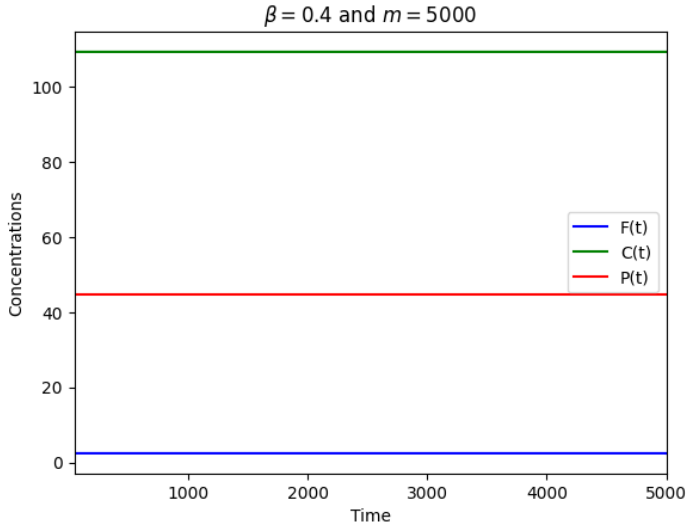


- Big m → many fibrils → P is occupied in the complexes → No regulation of oligomers.
- β is also big → great production of P → enough free P to control oligomers. Increasing m also indirectly increases the production of P through the red line.
- ν is small → C degrades slowly → P takes long to come back from complexes → β needs to be big to compensate.

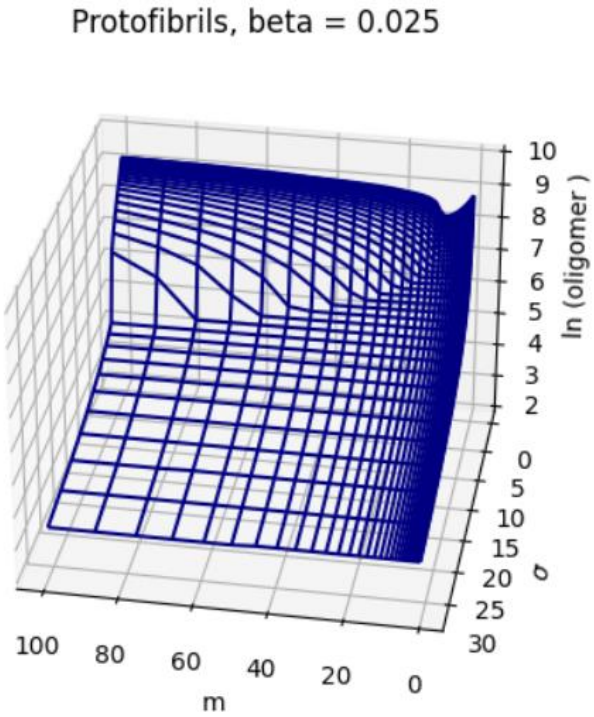
Proteasome induced by proto-fibrils

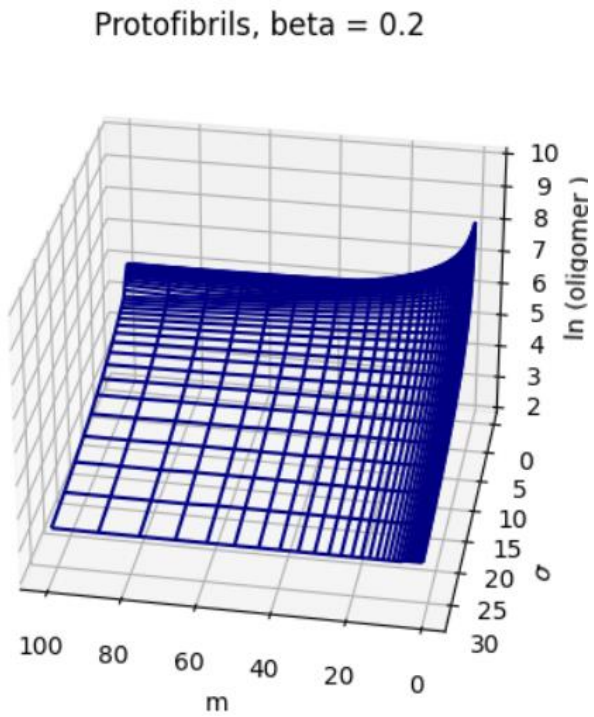
For example, for ɣ=ν=σ = 1, if β < 1/3, making m big enough leads to disease, but if β > 1/3, even very big values of m don't lead to disease.





Proteasome induced by proto-fibrils

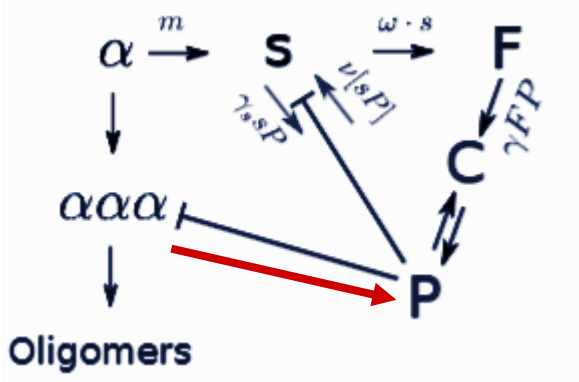




Proteasome induced by oligomers

Equations:

$$\frac{dF}{dt} = \frac{m}{1+P} - \gamma F \cdot P$$
$$\frac{dC}{dt} = \gamma F \cdot P - \nu C$$
$$\frac{dP}{dt} = \sigma - P - \gamma F \cdot P + \nu C + \beta \frac{1}{P}$$



Fixed point:

$$P^* = \frac{1}{2}\left(\sigma + \sqrt{4\beta + \sigma^2}\right), \quad F^* = \frac{m}{\gamma P^*(1+P^*)}, \quad C^* = \frac{m}{\nu(1+P^*)}$$

Characteristic polynomial:

$$\lambda^3 + a\lambda^2 + b\lambda + c = 0$$

$$a = 1 + \nu + \gamma P^* + \frac{m}{P^*(1+P^*)} + \frac{\beta}{P^{*2}}$$
$$b = \nu + \gamma P^*(1+\nu) - \frac{\gamma P^* m}{(1+P^*)^2} + \frac{\beta\gamma}{P^*} + \frac{\beta\nu}{P^{*2}}$$
$$c = \gamma\nu P^* + \frac{\beta\gamma\nu}{P^*}$$

Proteasome induced by oligomers

Once again: a, c > 0 and as before, b>0 means **healthy** and b<0 means **disease**.

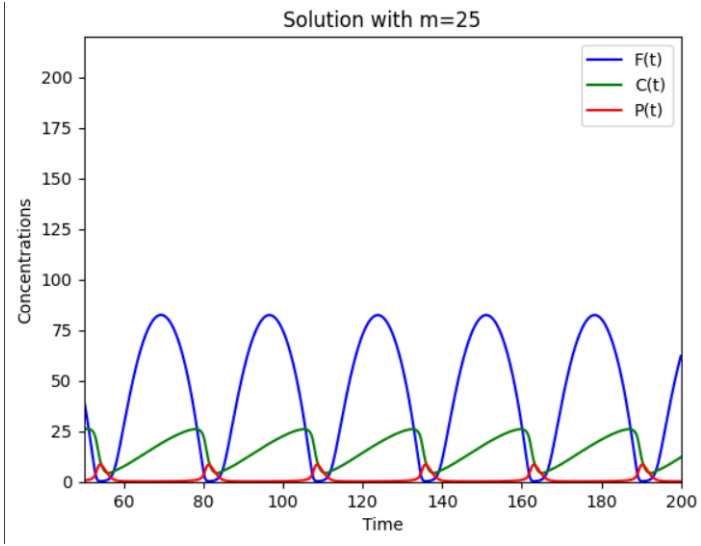
However, in this case: $$\text{If } m \to \infty, \text{ we have } b \to -\frac{\gamma P^*}{(1+P^*)^2} m$$

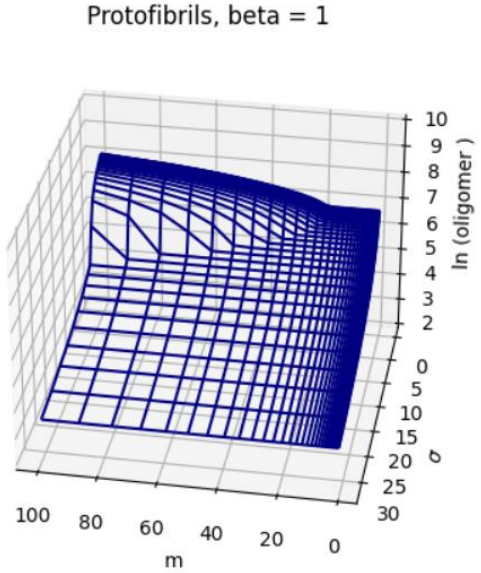
So that no matter the values of the other parameters, we can always find an m big enough to make b<0 and have **disease.**
In particular, we have disease when:

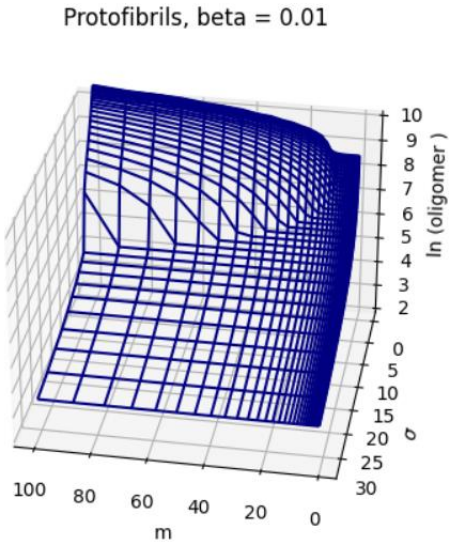
$$m > m_T = (1+P^*)^2 \left(\frac{\nu}{\gamma P^*} + 1 + \nu + \frac{\beta}{P^{*2}} \right)$$

Similar behaviour to original model.

Proteasome induced by oligomers



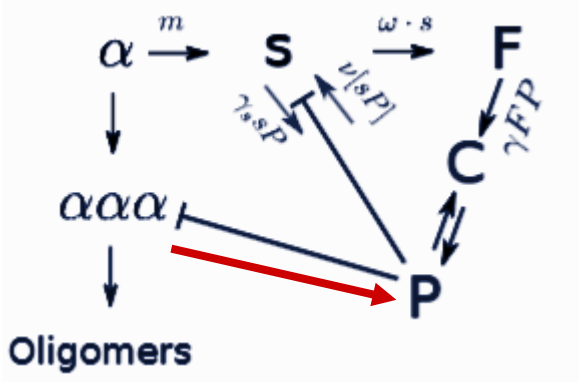




Explanation

Equations:

$$\frac{dF}{dt} = \frac{m}{1+P} - \gamma F \cdot P$$
$$\frac{dC}{dt} = \gamma F \cdot P - \nu C$$
$$\frac{dP}{dt} = \sigma - P - \gamma F \cdot P + \nu C + \beta \frac{1}{P}$$



For a given value of β, we can make m big enough to ensure that all the proteasomes are occupied trying to get rid of fibrils and they can't control oligomers.

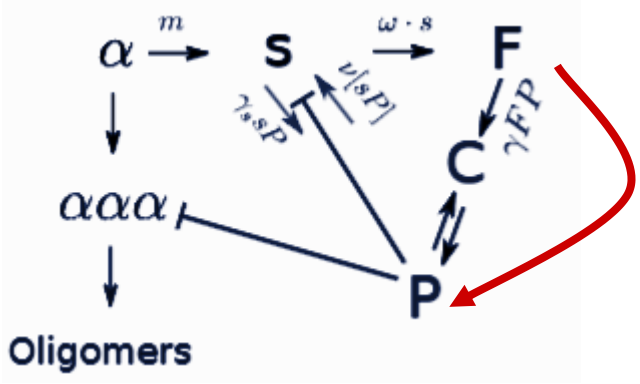
Proteasome induced by Fibrils

Equations:

$$\frac{dF}{dt} = \frac{m}{1+P} - \gamma F \cdot P$$

$$\frac{dC}{dt} = \gamma F \cdot P - \nu C$$

$$\frac{dP}{dt} = \sigma - P - \gamma F \cdot P + \nu C + \beta F$$

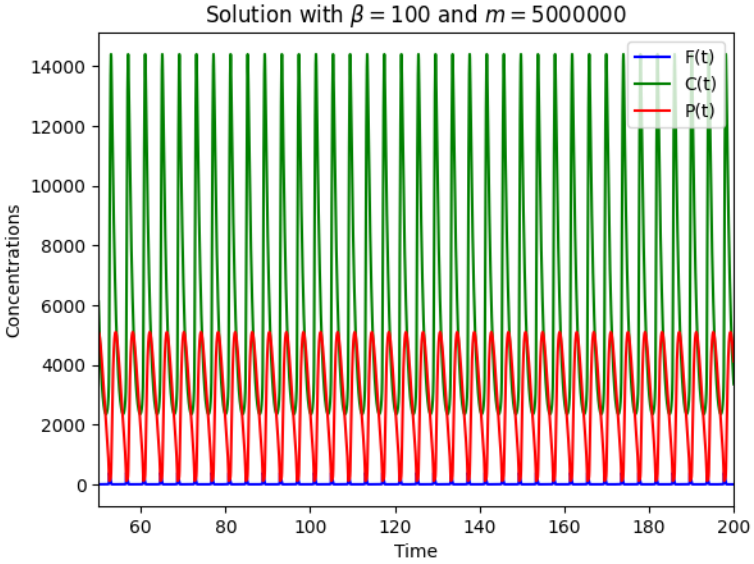


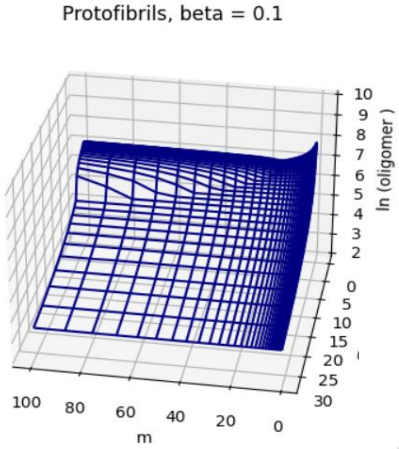
Fixed points and the analysis done before are now much more difficult to get a closed expression.

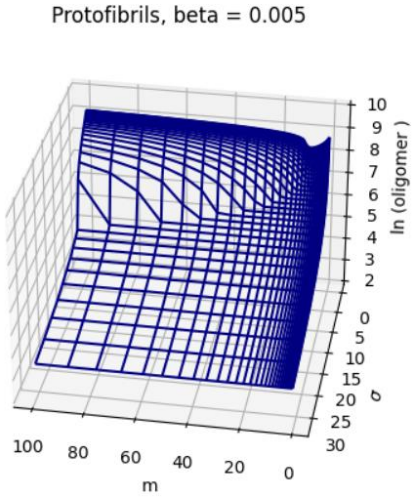
But we can still show that for $m \to \infty$, then $b \to -\infty$. Therefore, no matter the values of the constants, for big enough m, we get disease.

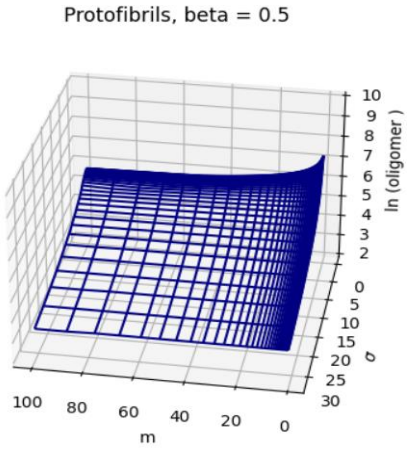
Similar behaviour to original model.

Proteasome induced by Fibrils









Conclusions

Everything is about maintaining a delicate balance .

- The original model demonstrates a critical threshold for the production rate m. When m exceeds this threshold: oscillations in proteasome availability and rapid oligomer accumulation.
- Adding proteasome feedback to protofibrils changes this behaviour.
- Despite increased proteasome production, the efficiency of complex formation and degradation remains a limiting factor. (not fast enough)
- Further research is needed to refine the model by incorporating additional factors.