An aggregated mathematical model for the progression of Alzheimer's disease with treatment implications



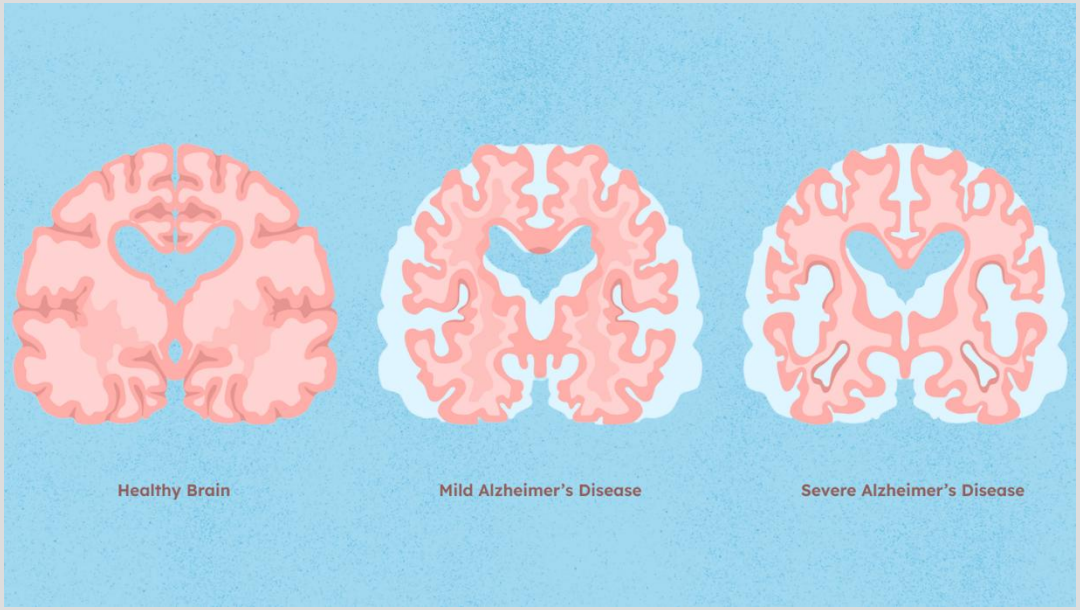


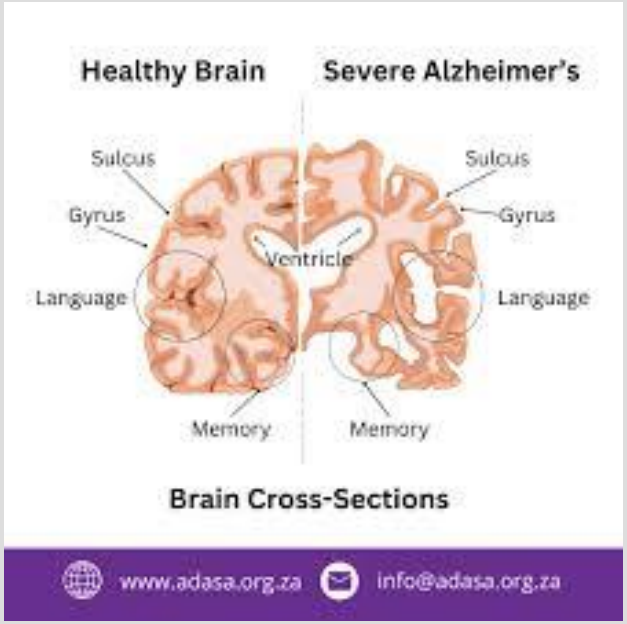
International Meetings on
Differential Equations and Applications

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Alzheimer's Disease

- a progressive, neuro-degenerative brain disorder which destroys memory and cognitive skills.
- the most debilitating form of dementia in older people
- currently no cure is available





https://www.everydayhealth.com/alzheimers-disease/progression-mild-moderate-severe-stages/



Cause? Amyloid-*β* Cascade Hypothesis

- the cause of Alzheimer's is still mostly unknown, but it is associated with the presence of abnormal proteins in the brain: **misfolded amyloid-beta (*Aβ*) proteins**

- **amyloid-*β*** (Aβ) is a peptide, typically 40–42 amino acids long, which plays a normal and healthy role in synaptic regulation

- **misfolded Aβ proteins** accumulate into toxic oligomers and form plaques which damage neurons; they also induce other Aβ molecules to become misfolded leading to a chain reaction

- the **amyloid cascade hypothesis** states that the buildup of misfolded *Aβ*-plaques in the brain is the trigger for the cognitive decline in Alzheimer's disease.

Folding of Amyloid-β Proteins

A complicated biochemical process which progresses from

- the initial combinations of **monomeres** through
- an intermediate stage of forming **proto-oligomeres** (generally small and transient, chemically unstable components) to
- the formation of structurally stable **oligomeres** (generally, units of from 30 to 50 monomeres),

- Mechanisms of this process:
  - **polymerization** (small molecules-monomers-link up)
  - **depolymerization** (breaking down bigger units releasing monomers)
  - **concatenation** (combinations of larger chains)
  - **fragmentation** (break-up of larger chains into smaller ones)

Mathematical Models

- **All models are wrong but some are useful**

George Box, statistician

- **Models should be as simple as possible but not simpler than that.**

Albert Einstein

Previous Literature

- N.Torres, E. Molina and L. Pujo-Menjouet, (2025)
  An optimal control problem for anti-inflammatory treatments of Alzheimer's disease, *J. of Math.Biology* **91**:1, https://doi.org/10.1007/s00285-025-02227-8
  simplified ODE-model

- Ciuperca I, Pujo-Menjouet L, Matar-Tine L, Torres N, Volpert V. (2024)
  A qualitative analysis of an A*β*-monomer model with inflammation processes for Alzheimer's disease.
  R. Soc. Open Sci. **11**: 231536, https://doi.org/10.1098/rsos.231536
  simplified PDE-model with ODE approximation

- I.M. Bulai, F. Ferraresso and F. Gladiali, (2025)
  Optimal control of monomers and oligomers degradation in an Alzheimer's disease model, *J. of Math.Biology* **91**:27
  https://doi.org/10.1007/s00285-025-02256-3
  ODE model for monomere →oligomere chain

- Wenrui Hao and Avner Friedman, (2016)
  Mathematical model on Alzheimer's disease,
  B*MC Systems Biology* **10**:108, doi: 10.1186/s12918-016-0348-2
  detailed PDE model

Nonlinear Dynamics 2026, joint work with

Heinz Schättler, Washington University, St. Louis, USA

and **Elżbieta Ratajczyk, Lublin University of Technology, Poland**

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RESEARCH

An aggregated mathematical model for the progression of Alzheimer's disease with treatment implications

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Our Modeling Approach

4 state variables

x - Concentration of ***Aβ*-monomers**

y - Concentration of aggregated **proto-oligomers**

z - Concentration of **oligomers**

I - Pro-inflammatory **cytokines/interleukins**
(also: net-effect between pro-inflammatory and anti-inflammatory actions of these interleukins)

Schematic Representation of the Mathematical Model

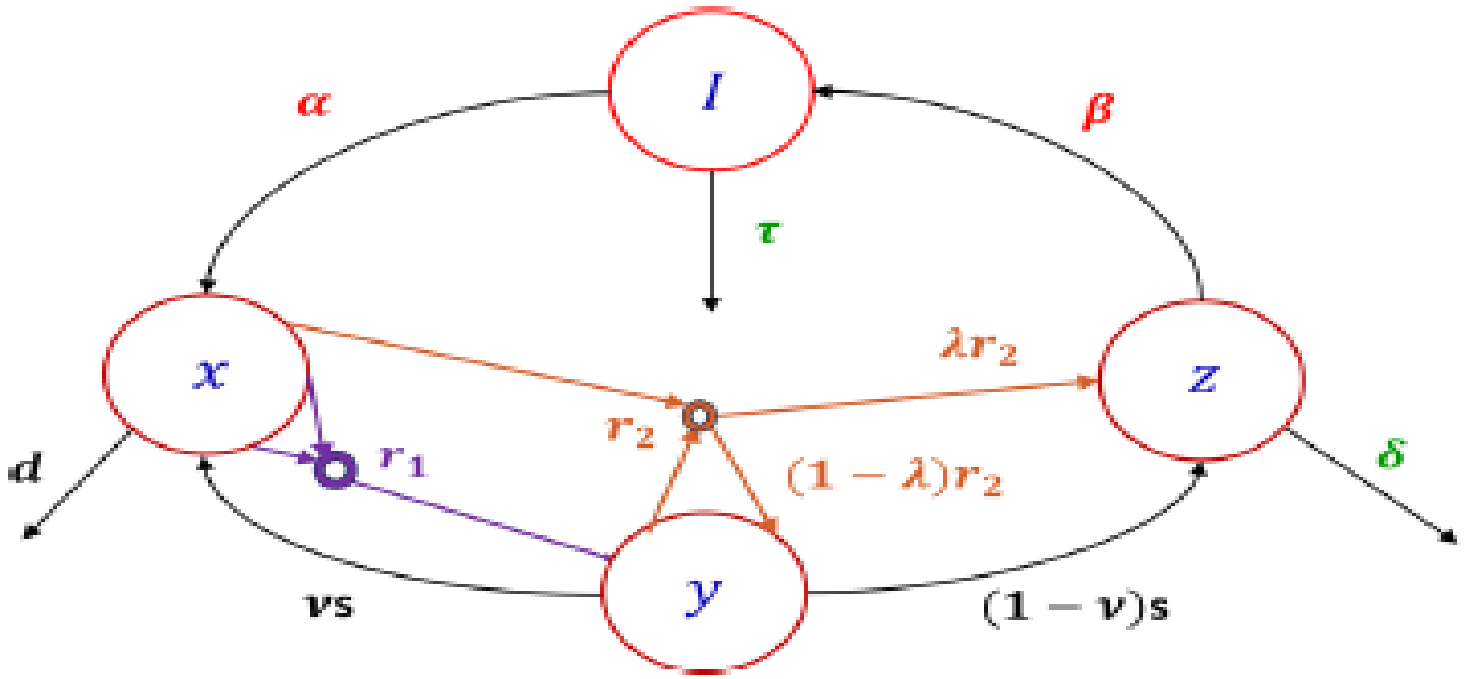
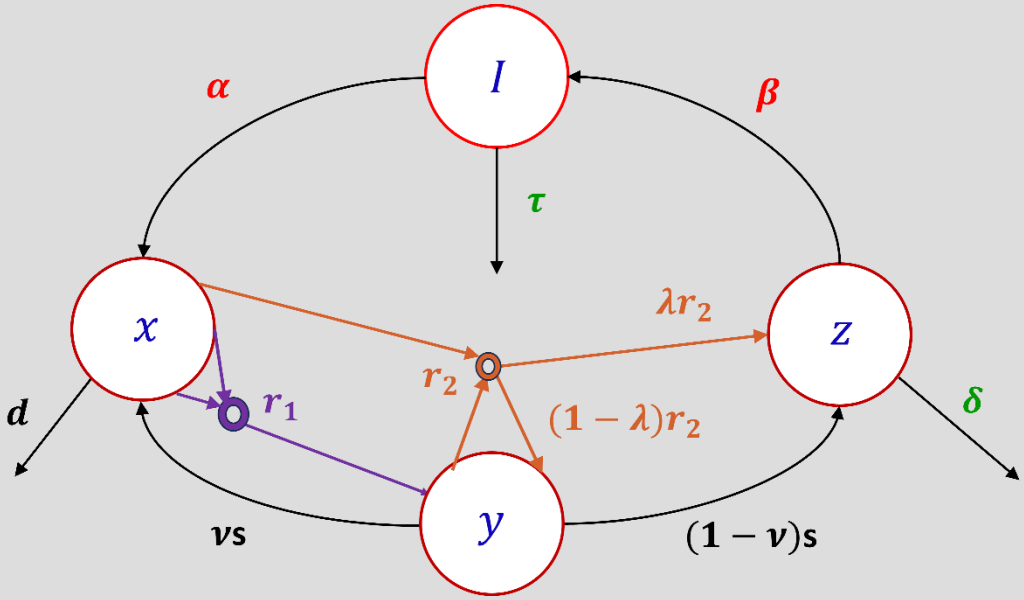


Fig. 1 Schematic illustration of the dynamics (1)-(4): arrows represent linear flows while the purple annulus represents the interaction of two monomeres x to form a proto-oligomere $y = x^2$ and the brown annulus represents the interaction of a monomere x with a proto-oligomere y to form xy. Of these, a fraction λ become stable oligomeres z and the remaining fraction remain proto-oligomeres

Our Model



$$\dot{x} = \alpha I - r_1 x^2 - r_2 xy + \nu s y - dx$$

$$\dot{y} = r_1 x^2 + (1-\lambda) r_2 xy - sy$$

$$\dot{z} = \lambda r_2 xy + (1-\nu) sy - \delta z$$

$$\dot{I} = \beta z - \tau I$$

x - Concentration of *Aβ*-monomers

x - dynamics

$$\dot{x} = \alpha I - r_1 x^2 - r_2 xy + \nu sy - dx$$

- αI : **stimulation of free monomers** by (all kind of) proinflammatory cytokines; may also be considered the net effect between pro-inflammatory and anti-inflammatory actions of these interleukins (and other agents)

- x^2 and xy are standard interaction terms with x^2 representing the **polymerization of two monomeres** to initiate a new chain of proto-oligomers and xy representing the **polymerization** of a **monomer** with an existing **proto-oligomer**

- νsy : the **inflow of monomers by depolymerization**, ν small

- dx : standard **degradation** term

y - dynamics

$\boldsymbol{y}$ - Concentration of aggregated proto-oligomeres

$$\dot{y} = r_1 x^2 + (1-\lambda) r_2 xy - sy$$

- $r_1 x^2$: inflow through **polymerization of free monomers**
- $(1-\lambda) r_2 xy$: the combination of a **free monomer with a proto-oligomer**,
  the factor $(1-\lambda)$ represents the fraction of these polymerizations which **remain proto-oligomers**, λ small
- sy : **loss** in the concentration of proto-oligomers through **depolymerization** of monomers or formation of **oligomers**

z - dynamics

$\boldsymbol{z}$ - Concentration of oligomeres

$$\dot{z} = \lambda r_2 xy + (1 - \nu)sy - \delta z$$

- $\lambda r_2 xy$: the proportion **of** **combinations of a free monomer** with a **proto-oligomer** which form a now structurally stable oligomer
- $(1 - \nu)sy$: the proportion of **outflow of proto-oligomers** which turn into stable oligomers
- δz : standard **degradation** term;

I - dynamics

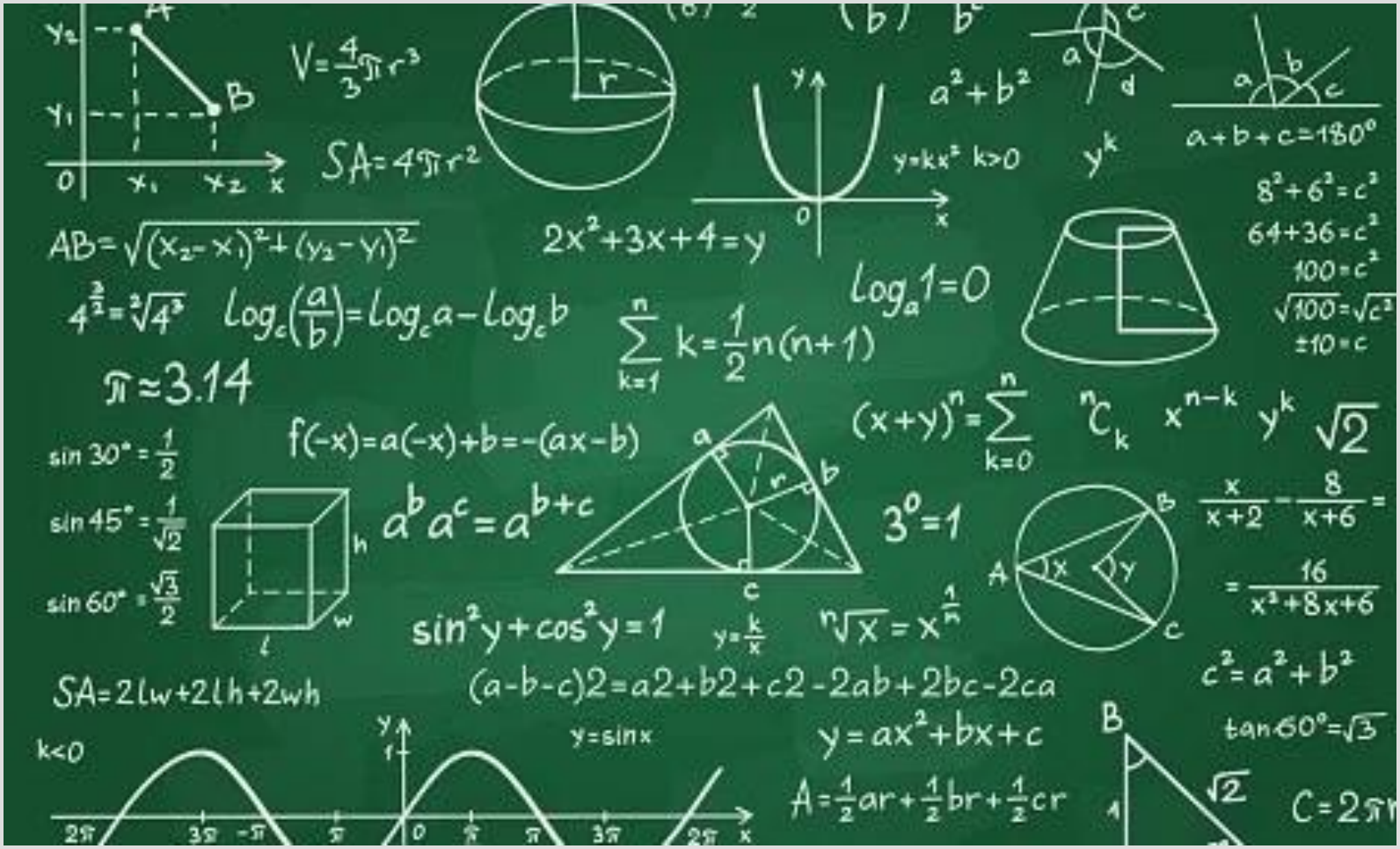
I - **Pro-inflammatory cytokines**/interleukins (net-effect net effect between pro-inflammatory and anti-inflammatory actions of these interleukins)

$$\dot{I} = \beta z - \tau I$$

βz : **stimulation of proinflammatory cytokines by oligomers**
more precisely: oligomers interact with **microglial cells** and in their combination they cause an inflammatory reaction which leads to the release of these cytokines; as in the other papers we have assumed that the microglia are close to equilibrium or capacity and their role has been subsumed in the parameter β

- τI : standard **degradation** term;

Now some mathematics!



Positive Invariance

Proposition 3.1 *The first octant* $\mathcal{O} = \{(x, y, z, I) \in \mathbb{R}^4 : x \geq 0, y \geq 0, z \geq 0, I \geq 0\}$ *is positively invariant under the dynamics, i.e., given any point* $(x_0, y_0, z_0, I_0) \in \mathcal{O}$, *the corresponding solution to equations (1)-(4) with initial condition* (x_0, y_0, z_0, I_0) *exists for all times* $t \geq 0$ *and remains in* $\mathcal{O}$. *Away from the origin, all trajectories lie in the interior of* $\mathcal{O}$ *for* $t > 0$.

- the origin is an equilibrium point
- the dynamics points inward at all other boundary strata
- for example, for some **2-dimensional boundary strata** we have that

$$x = 0,\ I = 0: \qquad \dot{x}(0) = \nu s y > 0, \qquad \dot{I}(0) = \beta z > 0$$

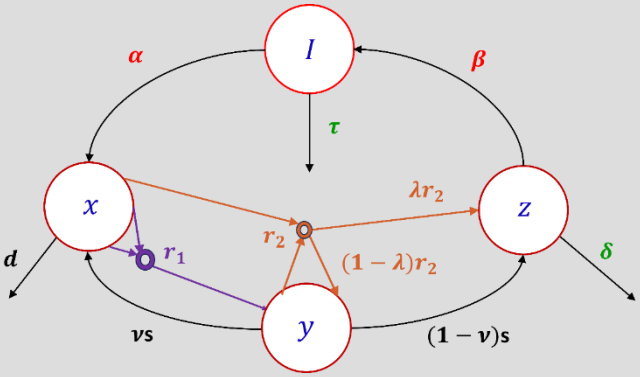
$$z = 0,\ I = 0: \quad \dot{z}(0) = \lambda r_2 x y + (1 - \nu) s y > 0, \qquad \ddot{I}(0) = \beta \dot{z}(0) > 0.$$

or at a **1-dimensional stratum**

$$y = z = I = 0: \quad \dot{y}(0) = r_1 x^2 > 0, \qquad \ddot{z}(0) = (\lambda r_2 x + (1 - \nu) s)\dot{y}(0) > 0$$
$$I^{(3)}(0) = \beta \ddot{z}(0) > 0.$$

- solutions exist for all times $t \geq 0$

- this quantity plays a central role for the dynamics



$$\eta = \alpha\beta - \delta\tau$$

η is the difference between the products of

- the stimulating parameters α and β
- and the inhibiting parameters τ and δ

Equilibrium Points

trivial equilibrium point: $(0,0,0,0)$

has eigenvalues $-d$, $-s$, $-\delta$, and $-\tau$ and is always **locally asymptotically stable**

for $\eta = \alpha\beta - \delta\tau > 0$ there exists a second equilibrium point which has all positive coordinates:

positive equilibrium point: $(x_*(\eta), y_*(\eta), z_*(\eta), I_*(\eta))$

Global Stability of the Trivial Equilibrium for $\eta \leq 0$

PROPOSITION: for $\eta \leq 0$ every trajectory starting in $\mathcal{O}$ converges to the trivial equilibrium point as $t \to \infty$

Proof. **LaSalle's invariance principle**

For $V = x + y + z + \frac{\alpha}{\tau} I$ we have that

$$\dot{V} = -dx + \frac{\eta}{\tau} I \leq 0 \quad \text{for all} \quad (x, y, z, I) \in \mathcal{O}$$

The lower level sets $\Omega_c = \{(x, y, z, I) \in \mathcal{O} : V \leq c\}$ are **compact** and **positively invariant**

⇒ For any solution $\chi(t)$ of the dynamics, it follows that

$$\lim_{t \to \infty} dist(\chi(t), M) = 0$$

where M is the largest invariant subset of $\{(x, y, z, I) \in \mathcal{O} : \dot{V} = 0\}$

the set M consists of only the **trivial equilibrium point**

$\eta > 0$: Positive Equilibrium $(x_*(\eta), y_*(\eta), z_*(\eta), I_*(\eta))$

The value $x_* = x_*(\eta)$ is the positive solution to the quadratic equation

$$\lambda r_1 r_2 \eta x^2 + \{(1-\lambda) r_2 \delta \tau d + (1-\nu) s r_1 \eta\} x - s \delta \tau d = 0.$$

which we rewrite in the form $a\eta x^2 + (b_0 + b_1\eta)x - c = 0$

$$x_* = \frac{b_0 + b_1\eta}{2a\eta}\left[\sqrt{1 + \frac{4ac\eta}{(b_0 + b_1\eta)^2}} - 1\right]$$

the second branch has negative x_*-values and is irrelevant for our problem

The remaining coordinates of the positive equilibrium point are determined by the following equations:

$$x_* = \frac{\alpha\beta - \delta\tau}{\beta d} I_* \qquad \Longleftrightarrow \qquad \beta d x_* = \eta I_*.$$

$$y_* = \frac{\delta\tau d I_*}{(1-\nu)s\beta d + \lambda r_2 \eta I_*}.$$

$$0 = \alpha I_* - d x_* - \delta z_*.$$

Asymptotic Behavior for $\eta \to 0+$

$$\lim_{\eta \to 0+} x_* = \frac{c}{b_0} = \frac{s}{(1-\lambda)r_2}.$$

finite limit

$$\lim_{\eta \to 0+} \eta I_* = \frac{s\beta d}{(1-\lambda)r_2},$$

$$\lim_{\eta \to 0+} \eta y_* = \frac{\delta \tau d}{(1-\nu(1-\lambda))r_2},$$

$$\lim_{\eta \to 0+} \eta z_* = \frac{s\tau d}{(1-\lambda)r_2}.$$

pole of order 1

bifurcation at infinity

For $\eta > 0$ Stability of the Positive Equilibrium Point

THEOREM Regardless of the values of the parameters, for $\eta > 0$ the positive equilibrium point $(x_*(\eta), y_*(\eta), z_*(\eta), I_*(\eta))$ is **hyperbolic** with **one unstable** (i.e., positive real) eigenvalue and **three stable** (i.e., with negative real parts) eigenvalues

Outline of the proof: all states are evaluated at equilibrium point

$$A = \begin{pmatrix} -(2r_1x + r_2y + d) & -r_2x + \nu s & 0 & \alpha \\ 2r_1x + (1-\lambda)r_2y & (1-\lambda)r_2x - s & 0 & 0 \\ \lambda r_2 y & \lambda r_2 x + (1-\nu)s & -\delta & 0 \\ 0 & 0 & \beta & -\tau \end{pmatrix}$$

Characteristic polynomial:

$$\chi_A(t) = \det(t \cdot \mathrm{Id} - A) = t^4 + a_3t^3 + a_2t^2 + a_1t + a_0,$$

Proof: Step 1

- a lengthy calculation shows that the determinant is always negative

$$a_0 = -\eta\{ \text{ sum of positive terms } \} < 0$$

(!)

- it follows that there is always **at least one positive** and **one negative** real eigenvalue

- it is not difficult to see that a_2 and a_3 are always positive

- By **Descartes's sign rule** there exists **exactly one positive** real eigenvalue, but we do not know anything about the complex eigenvalues

Proof: Step 2

for $\eta > 0$ **small** the remaining two eigenvalues are complex conjugate with negative real part

$$A = \begin{pmatrix} -(2r_1x + r_2y + d) & -r_2x + \nu s & 0 & \alpha \\ 2r_1x + (1-\lambda)r_2y & (1-\lambda)r_2x - s & 0 & 0 \\ \lambda r_2 y & \lambda r_2 x + (1-\nu)s & -\delta & 0 \\ 0 & 0 & \beta & -\tau \end{pmatrix}$$

$$y = \frac{\rho}{r_2\eta} + y_0 + o(\eta)$$

$$\rho = \frac{\delta\tau d}{1 - \nu(1-\lambda)}$$

$$\Rightarrow \quad A = A(\eta) = A_{-1} \cdot \frac{1}{\eta} + A_0 + o(\eta)$$

$$A_{-1} = \lim_{\eta \to 0+} \eta A = \begin{pmatrix} -\rho & 0 & 0 & 0 \\ (1-\lambda)\rho & 0 & 0 & 0 \\ \lambda\rho & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

the matrix A_{-1} has one negative eigenvalue, $-\rho$, and a triple eigenvalue at 0

$$A_0 = \begin{pmatrix} -2\frac{r_1}{r_2}\frac{s}{1-\lambda} - r_2 y_0 - d & -\frac{1-\nu(1-\lambda)}{1-\lambda}s & 0 & \alpha \\ 2\frac{r_1}{r_2}\frac{s}{1-\lambda} + (1-\lambda) r_2 y_0 & 0 & 0 & 0 \\ \lambda r_2 y_0 & \frac{1-\nu(1-\lambda)}{1-\lambda}s & -\delta & 0 \\ 0 & 0 & \beta & -\tau \end{pmatrix}.$$

We have $a_3 = -tr(A) = -\mu_1(\eta) - \mu_2(\eta) - \mu_3(\eta) - \mu_4(\eta)$

⇧ negative ⇧ positive eigenvalue

$$a_3 = a_3(\eta) = \rho \cdot \frac{1}{\eta} + \left(\tau + \delta + 2\frac{r_1}{r_2}\frac{s}{1-\lambda} + r_2 y_0 + d\right) + o(\eta).$$

Now we need to evaluate the negative eigenvalue od A

Let $\hat{A} = \eta A$ and $\widehat{\mu_1} = \eta \mu_1$

The negative eigenvalue $\widehat{\mu_1}(\eta)$ is simple and thus depends analytically on η. Computing its derivative at $\eta = 0$ we get that

$$\hat{\mu}_1'(0) = -2\frac{r_1}{r_2}\frac{s}{1-\lambda} - r_2 y_0 - d + \big(1 - \nu(1-\lambda)\big)s$$

Reverting to the original matrix and eigenvalues, using $\mu_2(\eta) > 0$, and the formula for a_3 we get for the case of complex conjugate eigenvalues that

$$2\,\Re\mathrm{e}\big(\mu_3(\eta)\big) < -(\tau + \delta) - \big(1 - \nu(1-\lambda)\big)s + o(\eta) < 0$$

There are no Hopf-bifurcations

Proof: Step 3

- If there is a Hopf-bifurcation (a pair of purely imaginary eigenvalues) , then the characteristic polynomial has the following form:

$$\chi_A(t) = (t+a)(t-b)(t^2+\gamma^2)$$
$$= t^4 + (a-b)t^3 + (\gamma^2 - ab)t^2 + \gamma^2(a-b)t - ab\gamma^2.$$

- for the coefficients of the characteristic polynomial this implies that

$$a_1(a_2a_3 - a_1) = a_0a_3^2 < 0. \quad \Longrightarrow \quad a_1 > a_2a_3.$$

- a short calculation verifies that $a_2a_3 > a_1$



Manifolds Of Hyperbolic Equilibrium

Based on **Hartman-Grobman theorem** there exists a **homeomorphism** between the phaseportait of the nonlinear system near the **hyperbolic** equilibirum point and its linearization

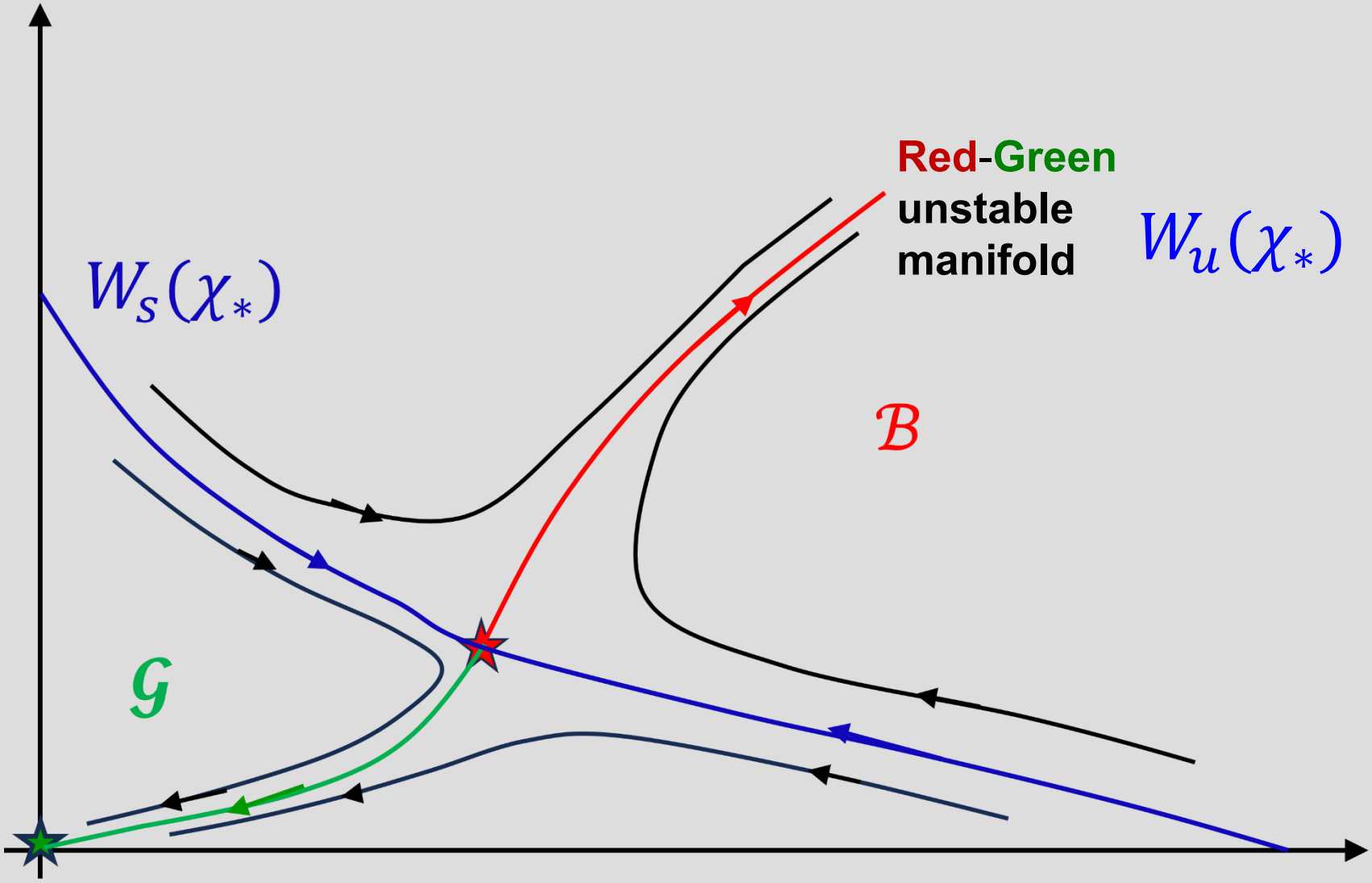
- **Stable manifold** of the positive equilibrium point

$$W_s(\chi_*)(U) = \left\{\chi_0 \in U : \chi(t;\chi_0) \in U \quad \text{for all} \quad t \geq 0 \quad \text{and} \quad \lim_{t\to\infty} \chi(t;\chi_0) = \chi_* \right\}$$

- **Unstable manifold** of the positive equilibrium point

$$W_u(\chi_*)(U) = \left\{\chi_0 \in U : \chi(t;\chi_0) \in U \quad \text{for all} \quad t \leq 0 \quad \text{and} \quad \lim_{t\to-\infty} \chi(t;\chi_0) = \chi_* \right\}$$

Qualitative Representation



Good and Bad Regions

- **GOOD**: Region of attraction of the trivial equilibrium point

$$\mathcal{G} = \left\{ \chi_0 \in \mathcal{O} : \lim_{t \to \infty} \chi(t; \chi_0) = 0 \right\}$$

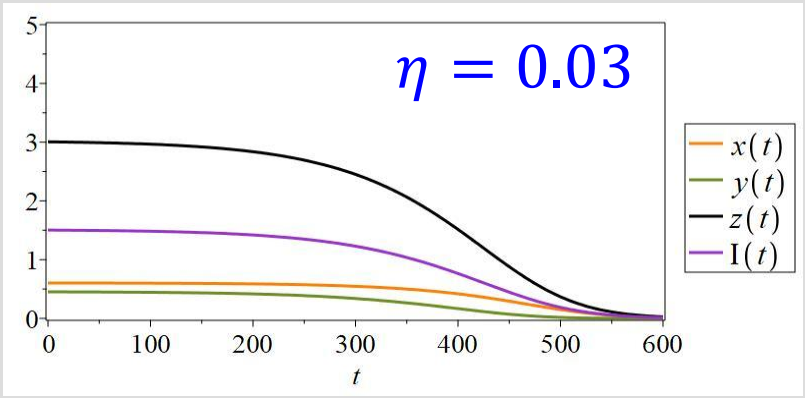
- **BAD**: Region of divergence

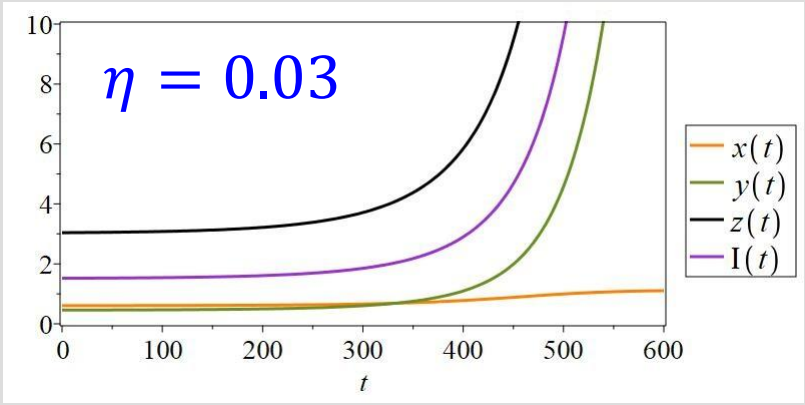
$$\mathcal{B} = \left\{ \chi_0 \in \mathcal{O} : \text{ as } t \to +\infty, \text{ at least one component of } \chi(t; \chi_0) \text{ diverges to } +\infty \right\}.$$

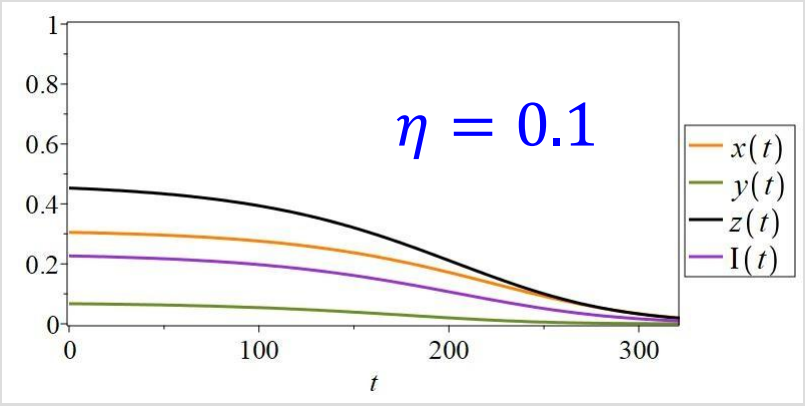
Numerical Examples

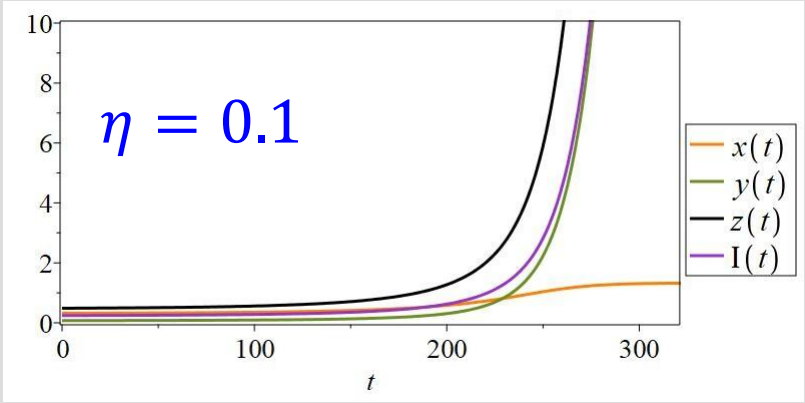
parameter	interpretation	value used
α	stimulation of monomeres by I	$\alpha = \frac{\eta+\delta\tau}{\beta}$
β	stimulation of I through oligomeres	0.5
δ	degradation rate of oligomeres	0.03
τ	degradation rate of I	1
η	$\eta = \alpha\beta - \delta\tau$	0.01; 0.1; 0.5; 1
d	degradation rate of monomers	0.15
r_1	bi-monomeric polymerization rate: $x \cdot x \looparrowright xx \in Y$	0.1
r_2	polymerization rate of monomeres x attaching to proto-oligomeres y: $x \cdot y \looparrowright xy \in Y \cup Z$	0.2
λ	fraction of the polymerization $x \cdot y \looparrowright xy \in Z$ which form oligomeres z	0.01
s	loss rate in the concentration of proto-oligomeres	0.2 and 0.3
ν	fraction of the loss in y due to depolymerization: $x \cdot y \looparrowleft y \in Y$	0.01

Numerical Examples









Initial condition in Good region

Initial condition in Bad region

Behavior of the States: Case 1

THEOREM Given an initial condition $\chi_0 = (x_0, y_0, z_0, I_0)$ suppose that

$$\lim_{t\to\infty} x(t) = \xi < \frac{s}{(1-\lambda)r_2}$$

Then also the states (y, z, I) have a limit as $t \to \infty$ and the limit is an equilibrium point. In particular

$$\mathcal{G} = \{\chi_0 : \lim_{t\to\infty} x(t) = 0\}$$

Proof. for example, the existence of the limit for y follows from

$$\dot{y} = a(t)y + b(t) \qquad b(t) = r_1 x^2(t) \to r_1 \xi^2$$

$$a(t) = (1-\lambda)r_2 x(t) - s \to (1-\lambda)r_2 \xi - s < 0$$

Behavior of the States: Case 2

THEOREM Given an initial condition $\chi_0 = (x_0, y_0, z_0, I_0)$ suppose that

$$\lim_{t\to\infty} x(t) = \xi > \frac{s}{(1-\lambda)r_2} \quad \text{and} \quad \int_0^\infty (x(t) - \xi)dt < \infty$$

Let $\zeta = (1-\lambda)r_2\xi > 0$. Then there exist positive constants c_1, c_2, c_3, so that the states (y, z, I) are asymptotic to $c_i e^{\zeta t}$ as $t \to \infty$:

$$y \sim c_1 e^{\zeta t} \qquad z \sim c_2 e^{\zeta t} \qquad I \sim c_3 e^{\zeta t}$$

Furthermore, ζ is the unique positive root of the polynomial

$$P(\zeta) = \alpha\beta(\lambda\zeta + (1 - \nu + \lambda\nu)s)$$

$$- (\zeta + (1 - \nu + \lambda\nu)s)(\zeta + \tau)(\zeta + \delta)$$

Outline of Proof

$$y(t) \sim c_1 e^{\zeta t} \Leftrightarrow \lim_{t\to\infty} y(t) e^{-\zeta t} = c_1$$

Defining $\psi(t) = y(t)e^{-\zeta t}$ and $\theta(t) = (1-\lambda) r_2 (x(t) - \xi)$ it holds that

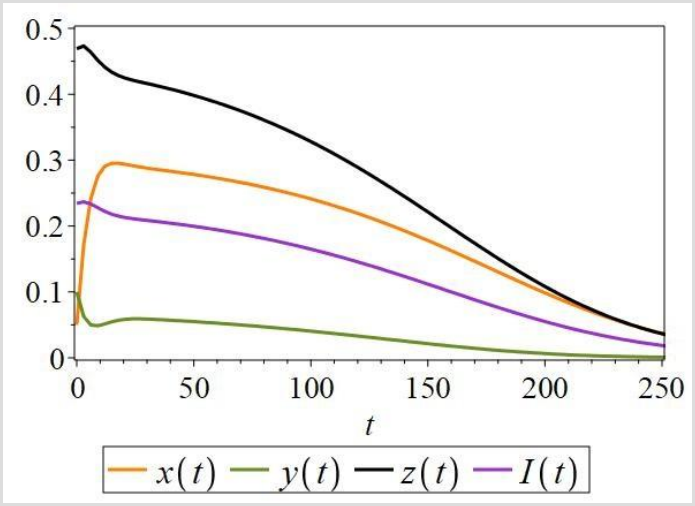
$$\dot{\psi}(t) = r_1 x(t)^2 \, e^{-\zeta t} + \theta(t)\psi(t)$$

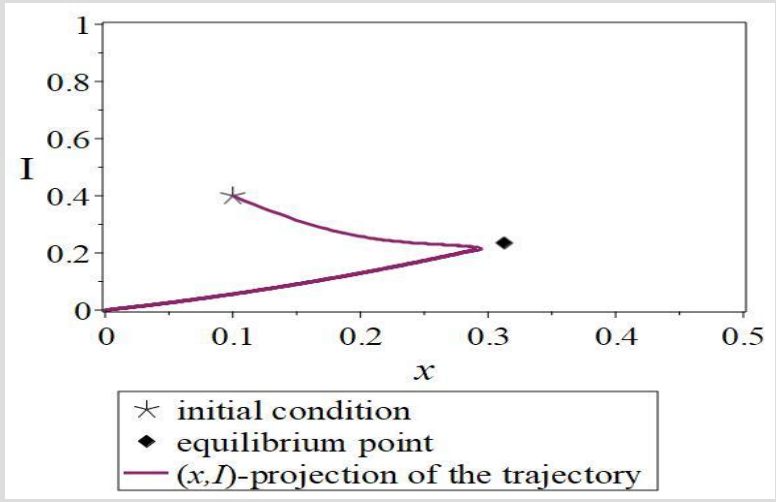
The result for y then follows from the representation

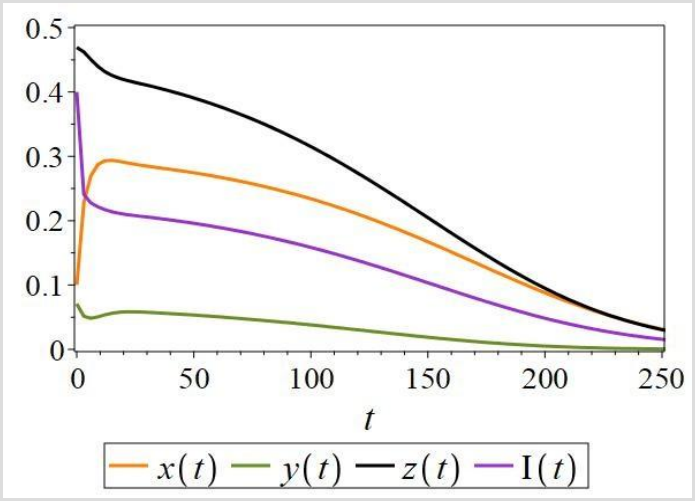
$$\begin{aligned}
\psi(t) &= \exp\left(\int_0^t \theta(u)du\right)\left\{\psi(0) + \int_0^t \exp\left(-\int_0^u \theta(v)dv\right) r_1 x(u)^2 e^{-\zeta u} du\right\} \\
&= \exp\left(\int_0^t \theta(u)du\right)\psi(0) + \int_0^t \exp\left(\int_u^t \theta(v)dv\right) r_1 x(u)^2 e^{-\zeta u} du.
\end{aligned}$$

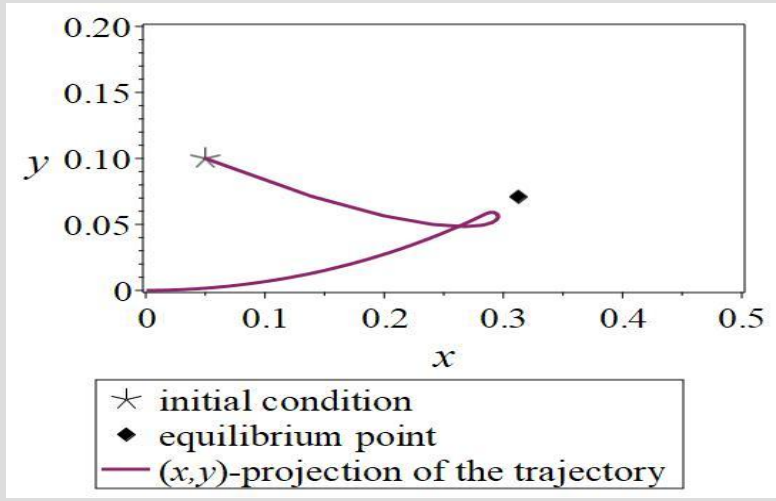
and analogously for z and I

Solutions from Initial Conditions in $\mathcal{G}$ near Stability Boundary



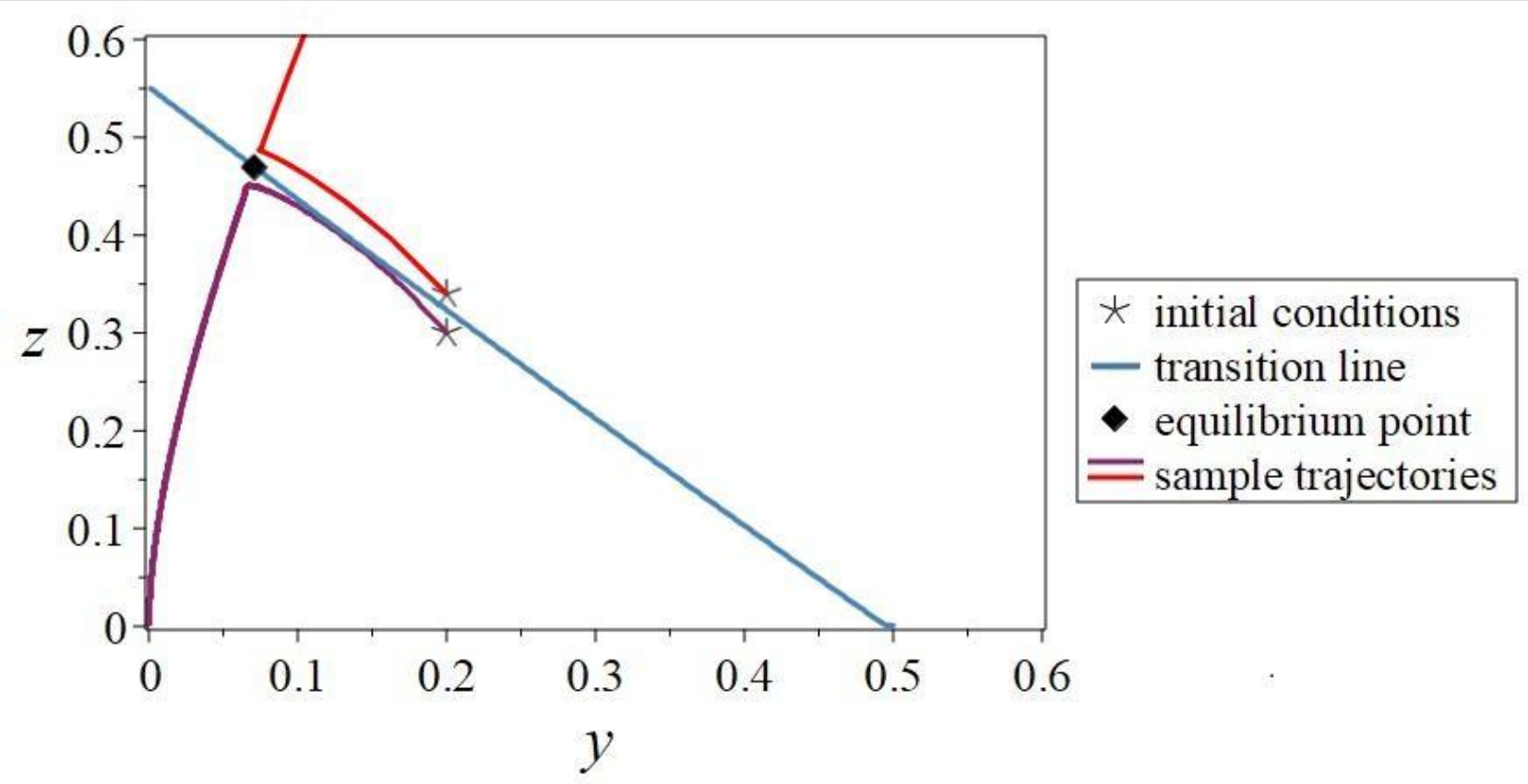




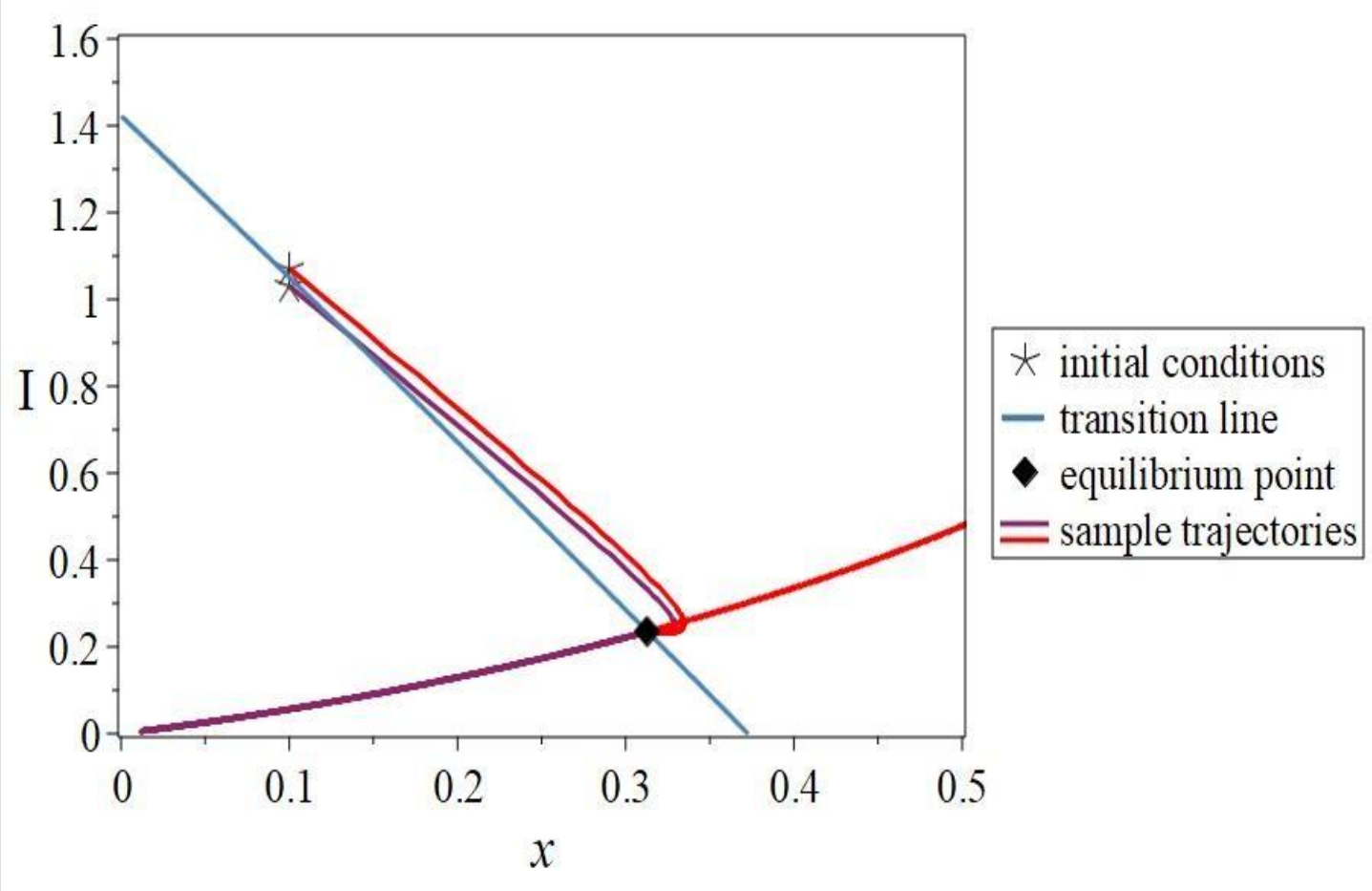


Computation of the Stability Boundary

- basic procedure: compute solutions of the dynamics while fixing two of the variables at their equilibrium value and then determine the initial conditions for the remaining two variables when the limits flip from 0 to ∞. This gives us 1-dimensional slices through the stable manifold $W_s(x_*)$



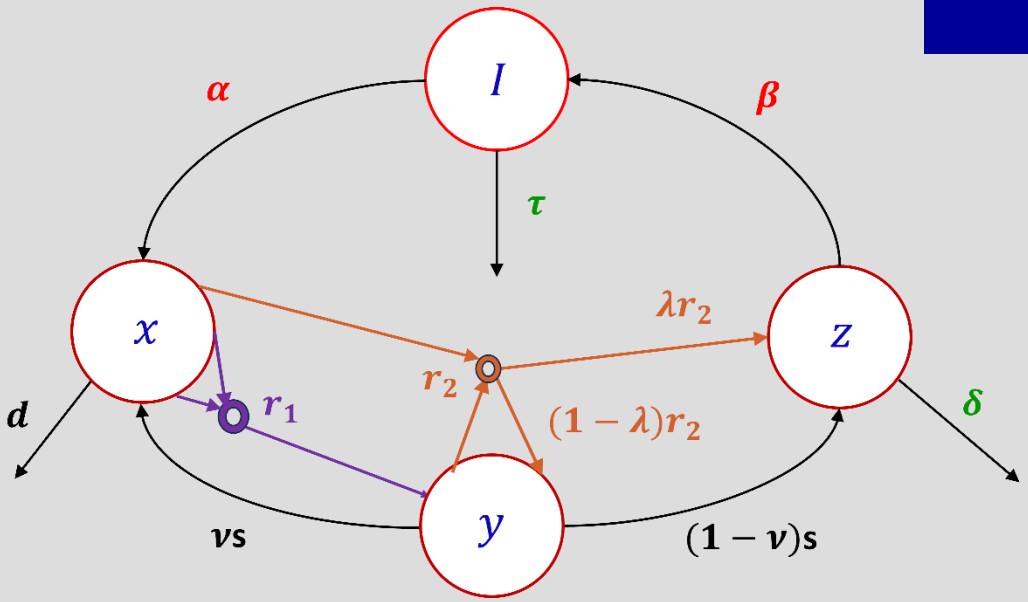
Solutions from Initial Conditions near Stability Boundary



Purple: initial condition in Good region

Red: initial condition in Bad region

Towards Optimal Control



What are possible **controls** (therapeutic interventions in the model?

$$\eta = \alpha\beta - \delta\tau$$

$$\dot{x} = \alpha I - r_1 x^2 - r_2 xy + \nu s y - dx$$

$$\dot{y} = r_1 x^2 + (1-\lambda) r_2 xy - sy$$

$$\dot{z} = \lambda r_2 xy + (1-\nu) sy - \delta z$$

$$\dot{I} = \beta z - \tau I$$



Interpretations and Medical Connections

- Treatments which **up-regulate anti inflammatory cytokines** such as TGF-β1 (**e.g., through anti-depressants, lithium, statins or even just aspirin**).
  Mathematically to an **increase in the effective degradation rate τ of I**

- Treatment which **target and clear amyloid plaques** by removing oligomers bound in it (early-onset Alzheimer's). **Donanemab** and **lecanemab** are two recently approved drugs for it.
  Mathematically correspond to **an increase in δ**

- Treatments **reducing pro-inflammatory cytokines** (**TNF-α inhibitors**) mathematically correspond to a **reduction of either α or β**

Towards Optimal Control: Objective

Let $\chi = (x, y, z, I)^T$ and define the objective as

$$J(u) = \langle c, \chi(T) \rangle + \int_0^T \langle a, \chi(t) \rangle + \sum_i b_i \boldsymbol{u_i(t)}\, dt$$

weighted average of the states at the terminal time T

weighted average of the states during the therapy horizon

total weighted dosages given as penalty terms measuring side-effects

- The controls u enter linearly (as an L_1-term), not quadratic (as an L_2-term), since only such a term has pharmacological meaning and represents side effects

- Various control options: single-input and multi-input problems

Conclusions, open questions, further work

- **Theoretical analysis** gave a structure of the phase portrait **independent of the parameter values**
- Still open questions: **Existence of periodic orbits? When does the limit of the *x*-coordinates exist?**
- The relevance of the quantity $\eta = \alpha\beta - \delta\tau$

  biological interpretation and connection with existing treatments
- Further study of the model **parameters as treatment modalities**
- **Optimal control** point of view: search for most effective combination therapies



Thank you for your attention

