

Mathematical Problems in Gels and Applications

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Drug delivery systems research is focused on supplying drug in the right place in the body at the right time.

Certain hormonal systems fluctuate over time. Hormone therapies are known to be more effective if timed according to the natural body frequency.

We present a model of a chemomechanical oscillator, made of a **polyelectrolyte gel membrane**, that releases hormones in rhythmic pulses. The rhythmic delivery is fueled by exposure to a constant level of glucose.

Mixed oscillatory, singularly perturbed 3-dimensional system, two **slow** and one **fast time scales** and **monotonically competitive**.

Polyelectrolyte gels

Polyelectrolyte gels consist of crosslinked elastic network holding fluid.

- ▶ The fluid holds **ions** of different types
- ▶ Negative charge is attached to the network.
- ▶ Competing **elastic**, **mixing**, **Van-der-Waals** and **electrostatic** forces cause the gel to undergo volume phase transitions. This, in turn, causes sharp changes in the membrane permeability.

Constant supply of glucose keeps the membrane oscillating between **collapsed** and **swollen** states, closing and opening.

- ▶ Experimental device
- ▶ Chemo-mechanical model
- ▶ Hysteresis and Hopf bifurcation
- ▶ Monotone dynamical systems (Smale and Hirsh)
- ▶ Oscillations and limit cycles
- ▶ Conclusions

This is joint work with R. Siegel, Y. Mori, L. Yao, MCC.
NSF DMS-1211896

- ▶ A Dynamic Model of Polyelectrolyte Gels, SIAM J. Appl. Math., 2013, Vol 73, no. 7, pp. 104–123, H.Chen, Y. Mori, MCC.
- ▶ Analysis and simulation of a model of polyelectrolyte gel in one spatial dimension, *Nonlinearity*, MCC, H. Chen and Y. Mori, vol 27, 2014, 1-45, 2014.
- ▶ Long-Time Existence of Classical Solutions to a one-dimensional Swelling Gel, *Math. Models and Meth. in Appl. Sciences*, M.R. Chen and MCC, vol 25, 165-194, 2015.
- ▶ Effects of permeability and viscosity in polymeric gels, *Math. Meth. Appl.Sci.*, B.Chabaud and MCC, in press, 2015.
- ▶ Rhythmomimetic drug delivery, MCC, L. Yao, Y. Mori and R.E. Siegel, SIAM Reviews, in revision, (2015)

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- ▶ Mechanics of gels (elatic polymer network +fluid) system in an external fluid environment
- ▶ Chemical reactions in environment that produce ions
- ▶ Transport and diffusion of these ions across the gel membrane
- ▶ Chemical reaction of one ion spices with the polymer.

Balance Laws: biphasic mixtures

Gel is an **incompressible** mixture of **solid** (*polymer network*) and **fluid**, interacting with its environment (e.g. air, **fluid** or another gel)

- In Ω_t (current configuration of the gel):

$$\frac{\partial \rho_i}{\partial t} + \operatorname{div}(\rho_i \mathbf{v}_i) = 0, \quad \rho_i = \phi_i \gamma_i, \quad \gamma_i = \text{constant},$$

$$\rho_i \dot{\mathbf{v}}_i = \nabla \cdot \mathcal{T}_i - \phi_i \nabla p + \mathbf{f}_i, \quad i=1, \text{ polymer}; \quad i=2, \text{ fluid}$$

$$\phi_1 + \phi_2 = 1$$

- In \mathcal{R}_t (domain of surrounding fluid)

$$\rho_f \left(\frac{\partial \mathbf{v}_f}{\partial t} + \mathbf{v}_f \cdot \nabla \mathbf{v}_f \right) = \nabla \cdot \mathcal{T}_f - \nabla p + \mathbf{f}_f,$$

$$\nabla \cdot \mathbf{v}_f = 0$$

$$\phi = \phi(\mathbf{x}, t), \quad \mathbf{v} = \mathbf{v}(\mathbf{x}, t), \quad \mathcal{T} = \mathcal{T}(\mathbf{x}, t), \quad p = p(\mathbf{x}, t) \dots$$

Alternate derivation in the viscosity dominating regime by Onsager's principle of maximum dissipation.

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Alternate derivation in the viscosity dominating regime by Onsager's principle of maximum dissipation.

Deformation and Stress

- ▶ polymer deformation map: $\mathbf{y} = \mathbf{y}(\mathbf{x}, t)$, $\mathbf{x} \in \Omega$.
- ▶ $\Omega_t = \mathbf{y}(\Omega)$: current configuration of gel.
- ▶ $\Gamma_t := \partial\Omega_t$: interface gel-surrounding fluid.
- ▶ $F = \nabla_{\mathbf{x}}\mathbf{y}$: Deformation gradient tensor.
- ▶ polymer volume fraction $\phi_1 \equiv \phi$; fluid $\phi_2 = 1 - \phi_1$.
- ▶ $\Psi(F, \phi)$: free energy density.
- ▶ Cauchy stress tensors:
 \mathcal{T}_1 : polymer; \mathcal{T}_2 : solvent; \mathcal{T}_f : environmental fluid.
- ▶ p : hydrostatic pressure associated with constraint:

$$\nabla \cdot (\phi_1 \mathbf{v}_1 + \phi_2 \mathbf{v}_2) = 0.$$

Boundary conditions at the gel-fluid interface, Γ_t

- Interface Γ_t moves with polymer: $\mathbf{v}_1 \cdot \mathbf{n} \equiv v_\Gamma$ on Γ_t .

- Balance of mass of fluid phase across Γ_t :

$$(\mathbf{v}_f - \mathbf{v}_1) \cdot \mathbf{n} = \phi_2(\mathbf{v}_2 - \mathbf{v}_1) \cdot \mathbf{n} \equiv w$$

- Continuity of tangential velocity across Γ_t :

$$(\mathbf{v}_f - \mathbf{v}_1)_\parallel = (\mathbf{v}_2 - \mathbf{v}_1)_\parallel \equiv \mathbf{q}$$

- Balance of linear momentum of fluid across Γ_t :

$$\mathcal{T}_f \mathbf{n} - \mathcal{T}_1 \mathbf{n} - \mathcal{T}_2 \mathbf{n} + [p] \mathbf{n} = 0$$

- Fluid that crosses the interface experiences viscous forces.

Mechanical model: energy

$$\mathcal{E} = \int_{\Omega_t} \Psi(F, \phi) := \int_{\Omega_t} \phi_1 \mathcal{W}(F) + \mathcal{W}_{\text{FH}}(\phi_1, 1 - \phi_1).$$

- ▶ $\mathcal{W}(F)$: elastic energy density.
- ▶ \mathcal{W}_{FH} : Flory-Huggins energy of mixing

$$\mathcal{W}_{\text{FH}} = \frac{k_B T}{v_s} \left(\frac{v_s}{v_p} \phi_1 \ln \phi_1 + \phi_2 \ln \phi_2 + \chi \phi_1 \phi_2 \right),$$

v_s : volume occupied by a single molecule of solvent.

$$\mathcal{T}_1 = \phi_1 \frac{\partial \mathcal{W}}{\partial F} F^T + (\mathcal{W}_{\text{FH}}(\phi_1) - \phi_1 \frac{d}{d\phi_1} \mathcal{W}_{\text{FH}}(\phi_1)) I + \mathcal{T}_1^d(\nabla \mathbf{v}_1, \phi)$$

$$\mathcal{T}_2 = \mathcal{T}_2^d(\nabla \mathbf{v}_2, \phi)$$

$$\frac{d}{dt} \mathcal{E}_{total} = -I_{\text{visc}} - J_{\text{visc}},$$

$$J_{\text{visc}} = \int_{\Gamma_t} \left(\eta_{\perp} w^2 + \eta_{\parallel} |\mathbf{q}|^2 \right)$$

$$I_{\text{visc}} = \int_{\Omega_t} \left(\sum_{i=1}^2 2\eta_i \|\nabla \mathbf{v}_i\|^2 + \kappa |\mathbf{v}_1 - \mathbf{v}_2|^2 \right) d\mathbf{x} + \int_{\mathcal{R}_t} 2\eta_f \|\nabla \mathbf{v}_f\|^2$$

w : normal component of fluid velocity at interface

\mathbf{q} : tangential fluid velocity at interface

Ions and network charge

In-fluid electric charge:

- ▶ $0 \leq c_k = c_k(x, t)$, $k = 1, \dots, N$: in-fluid ion concentration variables
- ▶ z_1, \dots, z_N valence

Network charge:

c_p : concentration of network charge; $z_p < 0$.

Ions and network charge

In-fluid electric charge:

- ▶ $0 \leq c_k = c_k(x, t)$, $k = 1, \dots, N$: in-fluid ion concentration variables
- ▶ z_1, \dots, z_N valence

Network charge:

c_p : concentration of network charge; $z_p < 0$.

- ▶ Φ : electrostatic potential
- ▶ ε : dielectric coefficient

$$\begin{aligned}\mathcal{E} = & \int_{\Omega_t} \phi_1 \mathcal{W}(F, c_0) + \mathcal{W}_{\text{FH}}(\phi) + \mathcal{W}_{\text{C}}(\Phi, \mathbf{c}, \phi) + \mathcal{W}_{\text{ion}}(\mathbf{c}, \phi) \\ & + \int_{\mathcal{R}_t} \mathcal{W}_{\text{C}}^{\text{f}}(\Phi, \mathbf{c}) + \mathcal{W}_{\text{ion}}^{\text{f}}(\mathbf{c}).\end{aligned}$$

Ionic and Coulombic energies

$$\mathcal{E} = \int_{\Omega_t} \phi_1 \mathcal{W}(F, c_0) + \mathcal{W}_{\text{FH}}(\phi) + \mathcal{W}_{\text{C}}(\Phi, \mathbf{c}, \phi) + \mathcal{W}_{\text{ion}}(\mathbf{c}, \phi) \\ + \int_{\mathcal{R}_t} \mathcal{W}_{\text{C}}^{\text{f}}(\Phi, \mathbf{c}) + \mathcal{W}_{\text{ion}}^{\text{f}}(\mathbf{c}).$$

$$\mathcal{W}_{\text{FH}} = \frac{k_B T}{v_s} \left(\frac{v_s}{v_p} \phi_1 \ln \phi_1 + \phi_2 \ln \phi_2 + \chi \phi_1 \phi_2 \right).$$

$$\mathcal{W}_{\text{C}} = \frac{1}{2} \varepsilon |\nabla \Phi|^2, \quad \mathcal{W}_{\text{C}}^{\text{f}} = \frac{1}{2} \varepsilon^{\text{f}} |\nabla \Phi|^2.$$

$$\mathcal{W}_{\text{ion}} = k_B T \sum_k c_k \log c_k.$$

Chemical potential:

$$\mu_k := \frac{\partial \mathcal{W}_{\text{ion}}}{\partial c_k} + q z_k \Phi = k_B T \ln c_k + q z_k \Phi + k_B T$$

Electrodiffusion of ions

Poisson-Nernst-Planck system with advection: ¹.

$$\begin{aligned}\frac{\partial(\phi_2 c_k)}{\partial t} + \nabla \cdot (\phi_2 \mathbf{v}_2 c_k) &= \text{Pe}^{-1} \nabla \cdot (D_k (\nabla c_k + c_k z_k \nabla \Phi)) \quad \text{in } \Omega_t, \\ \frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{v}_f c_k) &= \text{Pe}^{-1} \nabla \cdot (D_k (\nabla c_k + c_k z_k \nabla \Phi)) \quad \text{in } \mathcal{R}_t, \\ -\beta^2 \nabla \cdot (\epsilon \nabla \Phi) &= \begin{cases} \phi_1 \rho_p + \sum_{k=1}^N z_k \phi_2 c_k & \text{in } \Omega_t \\ \sum_{k=1}^N z_k c_k & \text{in } \mathcal{R}_t \end{cases},\end{aligned}$$

$RHS := \nabla \cdot (c_k \nabla \mu_k)$: dimensionless form.

The dimensionless parameters are given by:

- ▶ $\text{Pe} = \frac{V_0}{D_0/L}$: Péclet number
- ▶ $\beta = \frac{r_d}{L}$, $r_d = \sqrt{\frac{\epsilon k_B T/q}{q c_0}}$: Debye length.

$r_d \approx 1$ nm motivates electroneutral limit: $\beta \rightarrow 0$.

Φ Lagrange multiplier to maintain electroneutrality.

¹Well posedness of P-N-P system coupled with Navier-Stokes equations, studied by Ralph Ryham, PhD thesis, Penn State, 2007

Lorentz and Helmholtz forces

The ions and the electrostatic potential they generate exert a Lorentz force on the fluid. There are **friction**, **electrostatic** and **Helmholtz** forces:

$$\begin{aligned}\mathbf{f}_1 &= \mathbf{f}_{\text{fric}} + \mathbf{f}_1^{\text{elec}} + \mathbf{f}^{\text{hel}}, \\ \mathbf{f}_1^{\text{elec}} &= -\rho_p \phi_1 \nabla \Phi \\ \mathbf{f}^{\text{hel}} &= \frac{1}{2} \phi_1 \nabla \left(\frac{\partial \epsilon}{\partial \phi_1} |\nabla \Phi|^2 \right)\end{aligned}$$

$$\begin{aligned}\mathbf{f}_2 &= -\mathbf{f}_{\text{fric}} + \mathbf{f}_2^{\text{elec}}, \\ \mathbf{f}_2^{\text{elec}} &= -q \phi_2 (\mathbf{z} \cdot \mathbf{c}) \nabla \Phi \\ \mathbf{f}_f &= \mathbf{f}_f^{\text{elec}} = -q (\mathbf{z} \cdot \mathbf{c}) \nabla \Phi\end{aligned}$$

$$\begin{aligned}\mathcal{E}_{total} &= \int_{\Omega_t} \mathcal{W}(F, c_0) + \mathcal{W}_{FH}(\phi) + \mathcal{W}_C(\Phi, \mathbf{c}, \phi) + \mathcal{W}_{ion}(\mathbf{c}, \phi) \\ &+ \int_{\mathcal{R}_t} \mathcal{W}_C^f(\Phi, \mathbf{c}) + \mathcal{W}_{ion}^f(\mathbf{c})\end{aligned}$$

Assume constitutive equations and boundary conditions hold. Then:

$$\frac{d}{dt} \mathcal{E}_{total} = -I_{visc} - I_{diff} - J_{visc},$$

$$I_{diff} = \int_{\Omega_t \cup \mathcal{R}_t} \frac{D_a c_a}{k_B T} |\nabla \mu_a|^2,$$

$$I_{visc} = \int_{\Omega_t} \left(\sum_{i=1}^2 2\eta_i \|\nabla \mathbf{v}_i\|^2 + \kappa |\mathbf{v}_1 - \mathbf{v}_2|^2 \right) d\mathbf{x} + \int_{\mathcal{R}_t} 2\eta_f \|\nabla \mathbf{v}_f\|^2,$$

$$J_{visc} = \int_{\Gamma_t} \left(\eta_{\perp} w^2 + \eta_{\parallel} |\mathbf{q}|^2 \right).$$

Alternate derivation of governing system by Onsager's principle of

First order volume phase transition

Gels experience phase transitions between collapsed and swollen phases driven by changes of temperature and pH

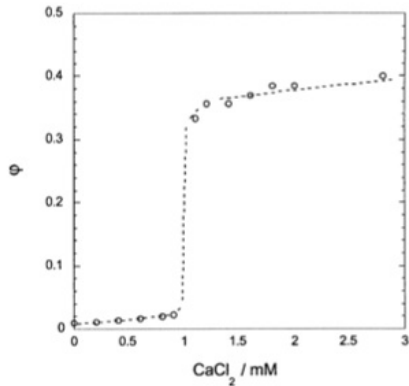
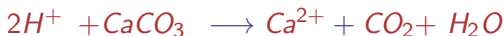
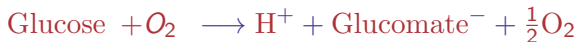
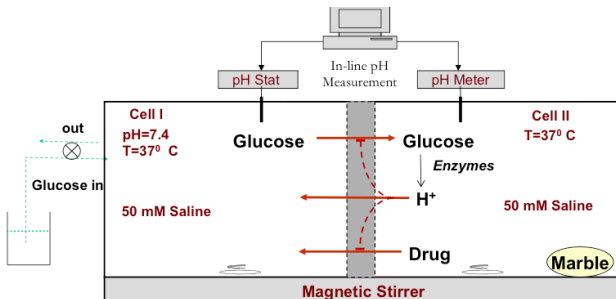


Figure 1. Variation of the polymer volume fraction in a sodium polyacrylate hydrogel swollen in 40 mM NaCl solution as a function of the CaCl_2 concentration in the surrounding liquid.

Siegel's cyclic hormone delivery experiment



Ref.: Dhanarajan, Siegel, Firestone, Epstein, Pojman, Misra 1995-2010

Swelling forces

Swelling tendency of the hydrogel due to three thermodynamic driving forces:

- ▶ **Mixing** force results from the following competing effects:
 - ▶ Water to mix with hydrogel to increase **entropy**
 - ▶ **Hydrophobic** or **hydrophilic** polymer-water interactions
 - ▶ **Polymer-polymer** Van der Waals, short range, interaction
- ▶ **Elastic** force opposes swelling or shrinking of the hydrogel away from an equilibrium state.
- ▶ **Ionic** force of acidic pendant groups, leading to an excess of mobile counterions and salt inside the hydrogel compared to the external medium, promoting osmotic water flow into the hydrogel and hence swelling.

R.A. Siegel & X. Zou, J. Chem Phys 110(1999), 2267; R.A. Siegel & G.P. Misra, J. Controlled Release 81(2002), 1; R.A. Siegel & J-C. Leroux, Chaos(1999), 9, 267. ,

Model

Membrane Cross-sectional area A

- ▶ Reference configuration $[0, L_0]$, ϕ_0 (polymer volume fraction); σ_0 concentration of negative groups bound to network
- ▶ $[0, L_0] \rightarrow [0, L(t)]$; $L(t)\phi(t) = L_0\phi_0$
- ▶ $C_H^M(t)$: hydrogen ion concentration
- ▶ $C_{AH}(t)$: concentration of network-bound protons

Reaction Chamber (Region II) Volume V

- ▶ C_H^{II} : Concentration of hydrogen ions
- ▶ C_G : Glucose concentration
- ▶ C_{Na}, C_{Cl}

Environment (Region I)

- ▶ C_H^I : Concentration of hydrogen ions
- ▶ C_G, C_{Na}, C_{Cl}

λ : Donnan ratio, $\alpha = \frac{\phi_0}{\phi}$: swelling ratio

Governing system

Membrane motion:

$$\frac{dL}{dt} = -(H(\phi) - R(\lambda, \phi))$$

Balance of H^+ in membrane:

$$\frac{d}{dt}(L(C_{AH} + C_H^M)) = 2K_h(1 - \phi)(\lambda \frac{(C_H^{II} + C_H^I)}{2} - C_H^M)$$

Balance of H^+ -ions in chamber (II):

$$\frac{d}{dt}C_H^{II} = \frac{AK_G^0}{V}e^{-\beta\phi}C_G - \frac{AK_h}{V}(1 - \phi)(\lambda C_H^{II} - C_H^M) - K_{Mar}C_H^{II}$$

Langmuir relation:

$$C_{AH} = \frac{\phi}{\phi_0} \left(\frac{\sigma_0 C_H^M}{K_A + C_H^M} \right)$$

Electroneutrality condition:

$$(1 - \phi)(\lambda - \frac{1}{\lambda})C_{NaCl} - (\frac{\phi}{\phi_0})f\sigma_0 = 0, \quad f = (1 + \frac{C_H}{K_A})^{-1}.$$

Time scales and parameter groups

$$\begin{aligned}\epsilon \frac{d\phi}{dt} &= \mathcal{R}_1(\phi, x, z) \\ \frac{dx}{dt} &= \mathcal{R}_2(\phi, x, z) \\ \frac{dz}{dt} &= \mathcal{R}_3(\phi, x, z)\end{aligned}$$

- ▶ polymer volume fraction, ϕ
- ▶ hydrogen ion concentration in membrane, x
- ▶ hydrogen ion concentration in chamber, z

$$\mathcal{D} = \{(\phi, x, z) : 0 < \phi < 1, x > 0, z > 0\}.$$

$$\epsilon \approx 1 * 10^{-5}$$

Volume phase transitions

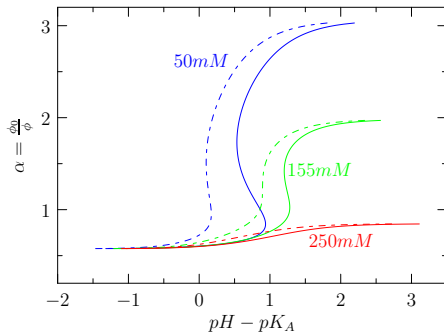
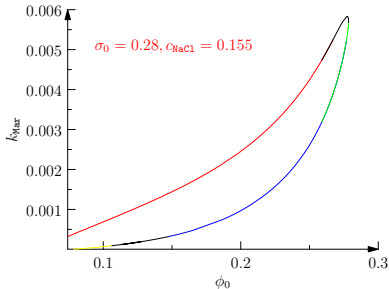
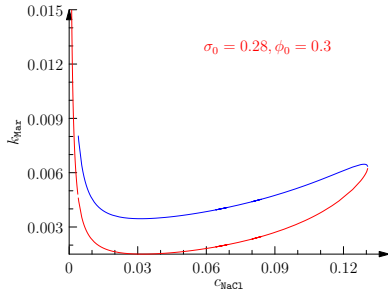


Figure: Swelling Ratio α versus $pH - pK_A$ at different salt concentrations.

K_A dissociation constant of the network-bound acidic groups CAAH

$$pK_A = -\log K_A$$

Hopf bifurcation diagrams



- ▶ Unique **hyperbolic** equilibrium point
- ▶ Eigenvalues: $\lambda_1 < 0$, $\lambda_2 = a + bi$, $\lambda_3 = a - bi$, $a > 0$.
Unstable between the two curves
- ▶ Periodic orbits for parameter values within the two curves
- ▶ Stable equilibrium solution outside the parameter region
- ▶ $\phi_0 \in [0.1, 0.3)$, $C_G = 50\text{mM}$, $\sigma_0 = 280\text{mM}$,
 $50 < C_{\text{NaCl}} < 155\text{mM}$.

Theorem: properties of solutions of the 3-dim system

1. Solutions corresponding to initial data in \mathcal{D} are bounded:

$$0 < a < \phi(t) < b < 1, \quad 0 < A < x, z < B, \quad \text{for all } t > 0.$$

2. Existence of a **two-dimensional, slow, inertial manifold**, \mathcal{M} , of the system.
3. Solutions of the 3-dim system restricted to \mathcal{M} form non-smooth, closed trajectories
 - ▶ volume fraction, ϕ , is discontinuous in two locations of the trajectory: **volume phase transitions**
 - ▶ concentration variables, x and z , are continuous with discontinuous time derivative at the transition points
4. Existence of a **stable limit cycle**, \mathcal{C} , of the two-dimensional system.
5. \mathcal{C} is the **ω -limit set** of positive semi-orbits of the 3-dim system.
6. \mathcal{C} is also limit cycle of orbits of 3-dim system.

Limit cycles

Parameters: $\sigma_0=0.28$ $cs=0.115$ $v=0.018$

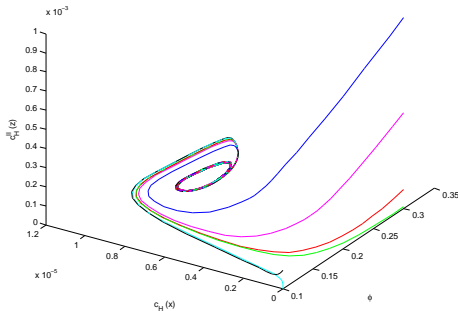


Figure: Plots of orbits of 3-dim system approaching a plane closed curve.

Poincaré-Bendixon theorem extends to 3-dim monotone syst.
Refs. M.W. Hirsh (1982, 1985) & H. Smith (1995).

Monotone dynamical systems

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}),$$

$$\mathcal{D} = \{\mathbf{x} = (\phi, x, z) \in \mathbf{R}^3 : 0 < \phi < 1; x, z > 0\}$$

1. A dynamical system φ_t is *monotone* in \mathbb{R}^n provided $\varphi_t(\mathbf{y}) \leq \varphi_t(\mathbf{x})$ whenever $\mathbf{y} \leq \mathbf{x}$.
2. The system is **competitive** in the non-negative cone \mathbb{R}_+^n provided

$$\frac{\partial f_i}{\partial x_j}(\mathbf{x}) \leq 0, \quad i \neq j, \quad \mathbf{x} \in \mathbb{R}_+^n$$

It is related to a certain monotonicity property on \mathbf{f} (Kamke condition)

Alternate cones are defined by intersections of general hyperplanes, and are equipped with the analogous order relations.

Monotonicity and Limit Cycle of 3-dim system

Proposition

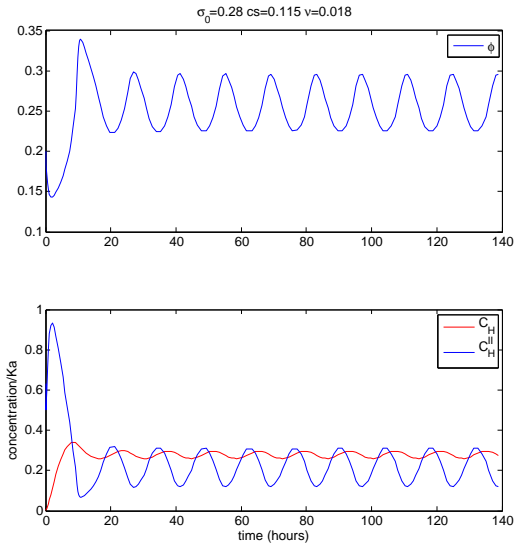
There exists an alternate cone \mathcal{K} uniquely determined by the phase space \mathcal{D} and such that the 3-dim system is competitive in \mathcal{K} .

The proof follows from the **sign symmetry** and **sign stability** of the **Jacobian** of \mathbf{f} in \mathcal{D} :

$$\begin{bmatrix} * & + & 0 \\ + & * & + \\ - & + & * \end{bmatrix}$$

This, together with the existence of a unique hyperbolic equilibrium point away from the ω -limit set, implies the existence of a **limit cycle** of the 3-dim system.

Oscillations



- ▶ Systems is qualitatively analogous to that of the evolution of HIV in the **virus persistence regime**.
- ▶ We have found that **sustainable oscillations** may vary from hour to months, according to parameters.
- ▶ Examine other parameter regimes
- ▶ Negative **glucomate groups** should also be taken into account.
- ▶ Recent work extends results to 5-dim system, to include relevant chemistry.
- ▶ **Will the device work in-vivo ?**

THANK YOU VERY MUCH !