A

Mid-Term Presentation

Of ELD 431: B.Tech. Project-1

on

Computation of steady states for Polynomial Dynamical Systems using Algebraic Geometry Methods

Presented By

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Biological networks can be analyzed through mathematical models

- Biological network is a method to represent various systems as interaction between different biological entities.
- Biomolecular circuits are component of these biological networks.
- Wherein it has been identified that circuits having two discrete and stable steady states are essential in studying different mechanisms.
- These can be analyzed in form of differential equations.

Sturm's Theorem is the tool used to find steady states of the systems

- Sturm's Theorem is an analytical tool to find steady states of a given system , which can be helpful in computing steady states for Biological systems.
- For example: "An analytical approach to bistable biological circuit discrimination using real algebraic geometry"[1].
- In the above paper use of Sturm's Theorem to obtain steady states has been discussed.

$f(x)$ is a univariate polynomial then Sturm's Theorem gives number of real roots of $f(x)$ in a particular interval

- For this we first construct *Sturm sequence* , set of polynomials $F = \{f_0, f_1, \dots\dots, f_m\}$ *defined as*

$$f_0 = f(x),$$
$$f_1 = f'(x),$$
$$f_2 = \text{-rem}(f_0, f_1)$$
$$f_3 = \text{-rem}(f_1, f_2),$$
$$:$$
$$f_m = \text{-rem}(f_{m-2}, f_{m-1}),$$
$$0 \text{ or a constant} = \text{-rem}(f_{m-1}, f_m),$$

where rem(f_i , f_{i+1}) is remainder of the polynomial long division of f_i by f_{i+1} .

- Number of real roots = Var(F,a) –Var(F,b)

where Var(F,a) is number of times consecutive non zero elements of Sturm sequence change signs.

Example of an application of Sturm's Theorem

- Let P(x) be a polynomial defined as : $P(x) = x^4 + x^3 - x - 1$.

  As we know P(x) has -1 and 1 as its real roots.

  →So, let's consider the interval in which we find real roots as [-3,2] .

- First, we construct Sturm sequence as:

$$
\begin{aligned}
p_0 &= x^4 + x^3 - x - 1, \\
p_1 &= 4x^3 + x^2 - 1, \\
p_2 &= \frac{3}{16}x^2 + \frac{3}{4}x - \frac{15}{16}, \\
p_3 &= 32x - 64, \\
p_4 &= -\frac{3}{16}
\end{aligned}
$$

- We get Var(P,-3) =3 as sign are $(+, -, -, +, -)$ and Var(P,2) =1 as sign are $(+, +, +, -, -)$
- Hence, we get Number of real roots for P(x) in [-3,2] =Var(P,-3) − Var(P,2) =3-1= 2

Motivation

- Steady states of Biological systems are essential to maintain constant internal concentration of molecules and ions in cells and organs of living systems.
- We have used Sturm's Theorem to compute the steady states for various benchmark Biological systems.
- Steady states computed using the theorem also matched with the previous results for corresponding systems.

Problem Statement

- To compute steady states of different Polynomial Dynamical Systems such as Biomolecular circuits using Sturm's Theorem as a useful Algebraic Geometry Method.
- Here in this project, we try to analyze manually and to symbolically compute such steady states
- Tools used are MATLAB, SageMath, Python.

Computations of steady states of these biological circuits can be done by Sturm's theorem

- Goodwin – Oscillator Model
- Negative autoregulation
- Toggle switch
    - ➢ MD Toggle switch
    - ➢ DD Toggle switch
- Repressilator

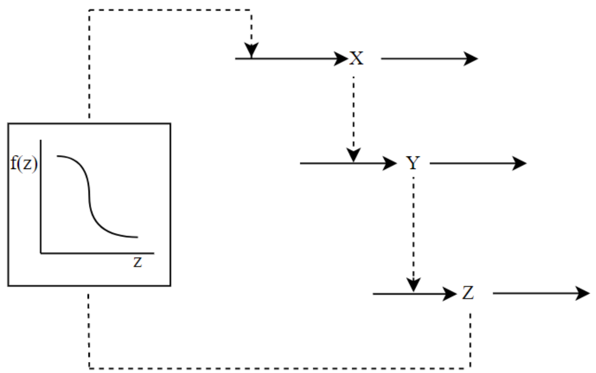
Goodwin- Oscillator is a delayed negative feedback loop model governed by 3 equations

- Three equations governing the model are:

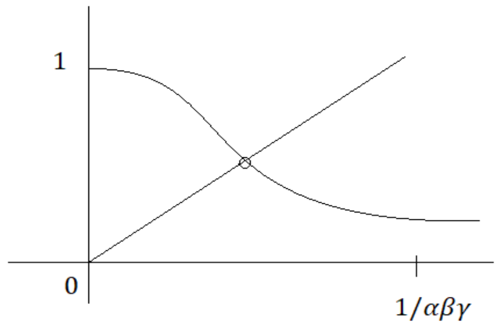
$$\dot{x} = \frac{1}{1+z^m} - \alpha x$$

$$\dot{y} = x - \beta y$$

$$\dot{z} = y - \gamma z \qquad \forall\, \alpha, \beta, \gamma\ > 0\ , m \in N$$



Goodwin model scheme



Geometric representation of single fixed point in $[0, \frac{1}{\alpha\beta\gamma}]$.

Goodwin Oscillator equations have one fixed point in $[0, \frac{1}{\alpha\beta\gamma}]$

- **Theorem-** The equations $\dot{x} = \frac{1}{1+z^m} - \alpha x$

$$\dot{y} = x - \beta y$$

$$\dot{z} = y - \gamma z \qquad \forall\, \alpha, \beta, \gamma\ > 0\ , m \in N$$

have only one fixed point in $[0, \frac{1}{\alpha\beta\gamma}]$.

- Proof: Simplifying the equations for steady state condition , $\dot{x} = \dot{y} = \dot{z} = 0$

gives $z = \frac{y}{\gamma}$, $\mathrm{y} = \frac{\mathrm{x}}{\beta}, \mathrm{z} = \frac{\mathrm{x}}{\beta\gamma}$

=> $z^{m+1} + z - \frac{1}{\alpha\beta\gamma} = 0$

Let $\frac{1}{\alpha\beta\gamma} = k$ gives $\Rightarrow p(z) = z^{m+1} + z - \mathrm{k}$

Normalized Goodwin- Oscillator equation generates Sturm sequence of max four elements

Solving using Sturm's Theorem ,we first construct the Sturm sequence.

- **Case -1 (m=1)**

Sturm sequence we get is :

$$[\ z^2 + z - \mathrm{k}\ ,\ 2z + 1\ ,\ \mathrm{k} + \frac{1}{4}\ ]$$

for which V(0) =1 $\{-, +, +\}$, V(k) =0 $\{+, +, +\}$

⇒No. of real roots in $[0, \frac{1}{\alpha\beta\gamma}]$= V(0)-V(k)= 1

- **Case -2 (m>1)**

Sturm sequence we get is :

$$[\ z^{m+1} + z - \mathrm{k}\ ,\ (\mathrm{m}+1)z^{m} + 1\ ,\ -\frac{(\mathrm{m})\mathrm{z}}{\mathrm{m}+1} + \mathrm{k}\ ,\ -(\frac{\mathrm{k}^{\mathrm{m}}(\mathrm{m}+1)^{\mathrm{m}+1}}{\mathrm{m}^{m}} + 1)\ ]$$

for which V(0) =2 $\{-, +, +, -\}$, V(k) =1 $\{+, +, +, -\}$

⇒No. of real roots in $[0, \frac{1}{\alpha\beta\gamma}]$= V(0)-V(k)= 2-1 =1

General Goodwin-Oscillator model also has single fixed point in $[\mathbf{0}, \infty)$

- The equations $\dot{x} = \frac{\alpha_1 k^n}{k^n + z^n} - \gamma_1 x$

$$\dot{y} = \alpha_2 x - \gamma_2 y$$

$$\dot{z} = \alpha_3 y - \gamma_3 z$$

- Normalizing the equations for steady states :

$$\dot{x} = \dot{y} = \dot{z} = 0$$

Gives => $z^{n+1} + k^n z - k^n = 0$

Generating Sturm sequence for normalized equation

- **Case -1 (n=1)**

Sturm sequence we get is :

$$[\ z^2 + kz - \mathrm{k}\ ,\ 2z + k\ ,\ \frac{\mathrm{k}^2}{4} + \mathrm{k}\ \ ]$$

for which V(0) =1 $\{-,+,+\}$, V(k) =0 $\{+,+,+\}$

⇒No. of real roots in $[0,\infty)$= V(0)-V(∞)= 1

- **Case -2 (n>1)**

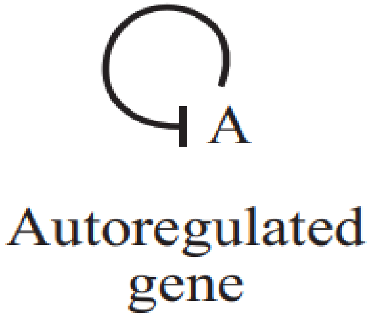
Sturm sequence we get is :

$$[\ z^{n+1} + k^n z - \mathrm{k}^\mathrm{n}\ ,\ (n+1)z^n + k^n\ ,\ -\frac{k^2(\mathrm{n})}{\mathrm{n+1}} z + \mathrm{k}^\mathrm{n}\ ,\ -(\frac{\mathrm{k}^\mathrm{n}(\mathrm{n+1})^{\mathrm{n+1}}}{\mathrm{n}^\mathrm{n}} + \mathrm{k}^\mathrm{n})\ \ ]$$

for which V(0) =2 $\{-,+,+,-\}$, V(∞) =1 $\{+,+,-,-\}$

⇒No. of real roots in $[0,\infty)$= V(0)-V(∞)= 2-1 =1.

In Negative Autoregulation the gene inhibits its own growth



- $\frac{dA}{dt} = \frac{\beta}{1+\left(\frac{A}{K}\right)^n} - \gamma A$ is the ordinary differential equation form of the circuit.

Negative Autoregulation circuit in steady state has one solution

- Circuit equation for Negative autoregulation

$$\frac{dA}{dt} = \frac{\beta}{1+\left(\frac{A}{K}\right)^n} - \gamma A$$

for steady state , $\frac{dA}{dt} = 0$

$$\frac{\beta}{1+\left(\frac{A}{K}\right)^n} = \gamma A$$

$$=> \quad A^{n+1} + K^n \mathrm{A} - \frac{K^n \beta}{\gamma} = 0,$$

Further normalization of the equation gives us equation in terms of A´ and K ´

- Let $t' = \gamma t$, $A' = \frac{A}{\frac{\beta}{\gamma}}$, $K' = \frac{K}{\frac{\beta}{\gamma}}$

$\rightarrow$ gives $(A')^{n+1} + (K')^{n}(A') - (K')^{n} = 0$

=> For n=2 , K´ > 0 ;

$$P(A') = (A')^3 + (K')^2(A') - (K')^2$$

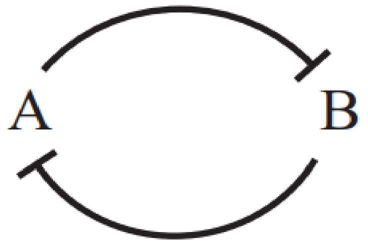
Generating Sturm sequence as:

$$[(A')^3 + (K')^2(A') - (K')^2, 3(A')^2 + (K')^2 ,\ -\frac{2(K')^2}{3}(A') + (K')^2, -(K')^2 - \frac{27}{4}\ ]$$

For which Var(0) = 2 $\{-,+,+,-\}$,Var(∞) = 1 $\{+,+,-,-\}$

Hence Number of real roots in [0 , ∞) =Var(0)− Var(∞) =2 −1 = 1.

Toggle switch is composed of two genes which inhibit each others growth



Toggle switch

- $\frac{dA}{dt} = \frac{\beta}{1+\left(\frac{B}{K}\right)^n} - \gamma A$, $\frac{dB}{dt} = \frac{\beta}{1+\left(\frac{A}{K}\right)^n} - \gamma B$ represent ordinary differential equation form of circuit.

- Analysing these gives three fixed points which are points of steady states.

Toggle Switch circuit in steady state has three solutions

- Ordinary differential equation form of circuit:

$$\frac{dA}{dt} = \frac{\beta}{1+\left(\frac{B}{K}\right)^n} - \gamma A \quad , \frac{dB}{dt} = \frac{\beta}{1+\left(\frac{A}{K}\right)^n} - \gamma B$$

=> For steady state $\;, \frac{dA}{dt} = 0 \;\; , \;\; \frac{dB}{dt} = 0$ gives

$$\frac{A^5}{K^5} - \frac{\beta}{\gamma}\frac{A^4}{K^4} + 2\frac{A^3}{K^2} - 2\frac{A^2}{K^2}\frac{\beta}{\gamma} + A\left(1 + \left(\frac{\beta}{\gamma}K\right)^2\right) - \frac{\beta}{\gamma} = 0 \,,$$

Further we let $\mathrm{t}' = \gamma \mathrm{t}$, $\mathrm{A}' = \frac{A}{\frac{\beta}{\gamma}}$, $\mathrm{B}' = \frac{B}{\frac{\beta}{\gamma}}$, $K' = \frac{K}{\frac{\beta}{\gamma}}$

$$=> \left(\frac{1}{1+\left(\frac{\mathrm{A}'}{K'}\right)^n}\right)^n A' + K'^n A' = (K')^n$$

Further normalization of the equation gives us equation in terms of A´ and K ´

- For n=2 , K´>0;

  We get $\mathrm{P}(\mathrm{A}') = (A')^5 - (A')^4 + 2(K')^2(\mathrm{A}')^3 - 2(K')^2(A')^2 + (A')(K'^2 + K'^4) - K'^4$

- Generating Sturm sequences in terms of K´ as:

```
Poly(B**5 - B**4 + 2*k**2*B**3 - 2*k**2*B**2 + (k**4 + k**2)*B - k**4, B, domain='ZZ(k)')
Poly(5*B**4 - 4*B**3 + 6*k**2*B**2 - 4*k**2*B + k**4 + k**2, B, domain='ZZ(k)')
Poly((4/25 - 4*k**2/5)*B**3 + 24*k**2/25*B**2 + (-4*k**4/5 - 16*k**2/25)*B + 24*k**4/25 - k**2/25, B, domain='ZZ(k)')
Poly((-25*k**6 + 75*k**4 - 50*k**2)/(25*k**4 - 10*k**2 + 1)*B**2 + (225*k**4 + 75*k**2)/(100*k**4 - 40*k**2 + 4)*B + (-50*k*
*8 - 150*k**6 - 25*k**4)/(50*k**4 - 20*k**2 + 2), B, domain='ZZ(k)')
Poly((-400*k**10 + 960*k**8 + 389*k**6 - 483*k**4 + 119*k**2 - 9)/(100*k**8 - 600*k**6 + 1300*k**4 - 1200*k**2 + 400)*B + (2
00*k**10 - 1230*k**8 + 743*k**6 - 156*k**4 + 11*k**2)/(50*k**8 - 300*k**6 + 650*k**4 - 600*k**2 + 200), B, domain='ZZ(k)')
Poly((400*k**16 + 200*k**14 - 11075*k**12 + 33050*k**10 - 38375*k**8 + 18500*k**6 - 2700*k**4)/(400*k**12 - 1560*k**10 + k**
8 + 3324*k**6 + 742*k**4 - 684*k**2 + 81), B, domain='ZZ(k)')
```

When we make cases for V(0) –V(∞) =3 ,generates values of K′

- Possible cases for V(0) –V(∞) =3 ,
  1. V(0) =5 ,V(∞)=2
  2. V(0) =4 ,V(∞)=1
  3. V(0) =3 ,V(∞)=0

- Solving for these we get inequalities for values for K′
- Reducing them by eliminating unwanted values we get :

$$K' \in \left(\frac{1}{2}, 1\right) \cup (1, \sqrt{2})$$

Values of K´ as set of inequalities

$$\left(\left(1<k\wedge k<\sqrt{2}\right)\vee\left(-\sqrt{2}<k\wedge k<-1\right)\right)\wedge\left(\left(\left(0<k\wedge k<\frac{\sqrt{5}}{5}\right)\vee\left(-\frac{\sqrt{5}}{5}<k\wedge k<0\right)\vee\frac{\sqrt{5}}{5}<k\vee k<-\frac{\sqrt{5}}{5}\right)\right.$$

$$\wedge\left(\left(\left(-1<k\wedge k<-\frac{1}{2}\right)\vee\left(\frac{1}{2}<k\wedge k<1\right)\vee\left(1<k\wedge k<\sqrt{2}\right)\vee\left(\sqrt{2}<k\wedge k<\mathrm{CRootOf}\left(4x^4-7x^2-9,1\right)\right)\right.\right.$$

$$\left.\vee\left(-\sqrt{2}<k\wedge k<-1\right)\vee\left(k<-\sqrt{2}\wedge\mathrm{CRootOf}\left(4x^4-7x^2-9,0\right)<k\right)\right)$$

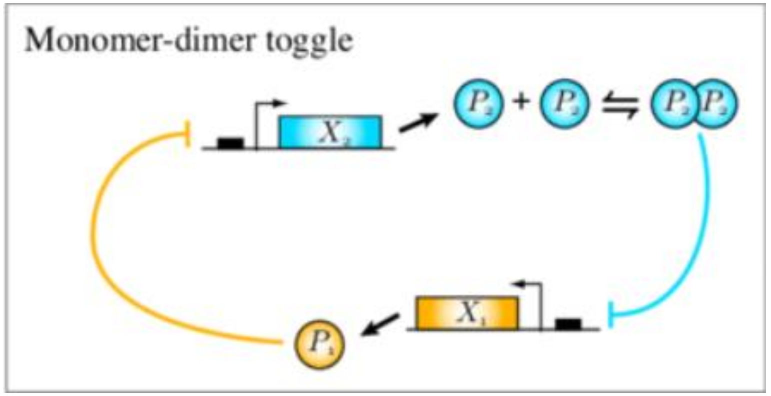
$$\wedge\left(\left(\left(-\frac{1}{2}<k\wedge k<-\frac{\sqrt{5}}{5}\right)\vee\left(0<k\wedge k<\frac{\sqrt{5}}{5}\right)\vee\left(-\frac{\sqrt{5}}{5}<k\wedge k<0\right)\vee\left(\frac{\sqrt{5}}{5}<k\wedge k<\frac{1}{2}\right)\vee\frac{\sqrt{22}}{2}<k\vee k<-\frac{\sqrt{22}}{2}\right)\right.$$

$$\wedge\left(\left(\left(-1<k\wedge k<-\frac{1}{2}\right)\vee\left(\frac{1}{2}<k\wedge k<1\right)\vee\left(1<k\wedge k<\sqrt{2}\right)\vee\left(\sqrt{2}<k\wedge k<\mathrm{CRootOf}\left(4x^4-7x^2-9,1\right)\right)\right.\right.$$

$$\vee\left(-\sqrt{2}<k\wedge k<-1\right)\vee\left(k<-\sqrt{2}\wedge\mathrm{CRootOf}\left(4x^4-7x^2-9,0\right)<k\right)\vee k<\mathrm{CRootOf}\left(4x^4-7x^2-9,0\right)\vee\mathrm{CRootOf}$$

$$\left.\left(4x^4-7x^2-9,1\right)<k\right)\wedge 0.204124145231931<k\wedge k<0.447213595499958$$

Monomer- Dimer toggle is a double-negative switch variant with one of repressor unit as Monomer



Gaskins et. al

- At equilibrium concentration of P1 and P2 in MD system are:

$P_{1eq} = \frac{\beta_1 X_{1tot}}{1+\left(\frac{P_{2eq}}{K_2}\right)^2}$, $P_{2eq} = \frac{\beta_2 X_{2tot}}{1+(\frac{P_{1eq}}{K_{md}})}$ where X_{itot} is total concentration of gene *i*.

and β_i , K_{md} , K_{dd} are constants.

Applying Sturm's theorem to MD toggle circuit equation gives inequalities satisfying Sturm sequence

- $P_{1eq} = \frac{\beta_1 X_{1tot}}{1+\left(\frac{P_{2eq}}{K_2}\right)^2}$, $P_{2eq} = \frac{\beta_2 X_{2tot}}{1+(\frac{P_{1eq}}{K_{md}})}$ on solving these for steady state gives a polynomial in $\hat{P}_{1eq}$.

- $\hat{P}^3{}_{1eq} - \left(\hat{X}_{1tot} - 2\right)\hat{P}^2{}_{1eq} - \hat{P}_{1eq}(\widehat{2X}_{1tot} - \hat{X}^2{}_{2tot} - 1) - \hat{X}_{1tot} = 0$

- When evaluated using Sturm’s Theorem generates set of inequalities.

Following are the Sturm sequence and corresponding inequalities

Sturm sequence :

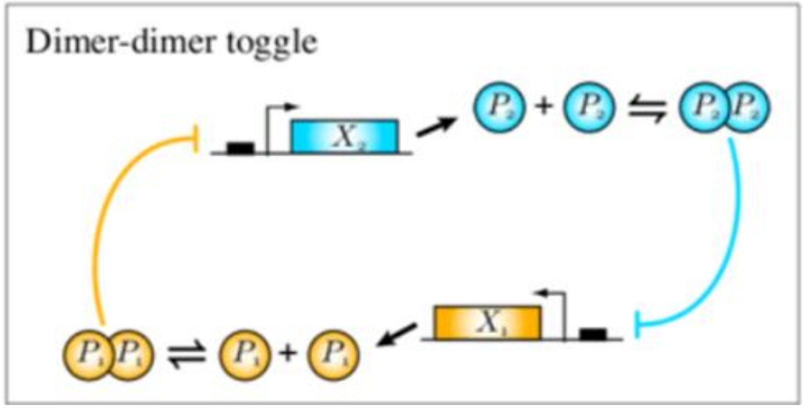
$$f_0(x) = \left(x - \hat{X}_{1tot}\right)(x+1)^2 + x\hat{X}^2{}_{2tot}$$
$$f_1(x) = \hat{X}^2{}_{2tot} + (x+1)(3x - 2\hat{X}_{1tot}+1)$$
$$f_2(x) = \frac{1}{9}(2(x+1)\left(\hat{X}_{1tot}+1\right)^2 - \left(6x + \hat{X}_{1tot} - 2\right)\hat{X}^2{}_{2tot})$$
$$f_3(x) = \frac{9\hat{X}^2{}_{2tot}(-4\hat{X}^4{}_{2tot} + (\hat{X}_{1tot}(\hat{X}_{1tot}+20)-8)\hat{X}^2{}_{2tot} - 4(\hat{X}_{1tot}+1)^3)}{4\left((\hat{X}_{1tot}+1)^2 - 3\hat{X}^2{}_{2tot}\right)^2}$$

Corresponding set of $\hat{X}_{1tot}$ and $\hat{X}_{2tot}$ for three real roots:

$$\hat{X}_{1tot} > 8$$
$$\frac{1}{8}(20\hat{X}_{1tot} + \hat{X}^2_{1tot} - 8 - \mathrm{f}(\hat{X}_{1tot})) < \hat{X}^2_{2tot} < \frac{1}{8}(20\hat{X}_{1tot} + \hat{X}^2_{1tot} - 8 + \mathrm{f}(\hat{X}_{1tot}))$$

D. Siegal-Gaskins et al , “An analytical approach to bistable biological circuit discrimination using real algebraic geometry,” Journal of The Royal Society Interface, vol. 12, no. 108, p. 20150288, Jul. 2015.

Dimer- Dimer toggle is a double-negative switch variant consisting of two dimeric repressors



Gaskins et. al

- At equilibrium concentration of P1 and P2 in DD system are:

$$P_{1eq} = \frac{\beta_1 X_{1tot}}{1+\left(\frac{P_{2eq}}{K_2}\right)^2} \quad , \quad P_{2eq} = \frac{\beta_2 X_{2tot}}{1+\left(\frac{P_{1eq}}{K_{dd}}\right)^2}$$

, where X_{itot} is total concentration of gene *i*.

and β_i , K_{md} , K_{dd} are constants.

Applying Sturm's theorem to DD toggle circuit equation gives inequalities satisfying Sturm sequence

- $P_{1eq} = \frac{\beta_1 X_{1tot}}{1+\left(\frac{P_{2eq}}{K_2}\right)^2}$, $P_{2eq} = \frac{\beta_2 X_{2tot}}{1+\left(\frac{P_{1eq}}{K_{dd}}\right)^2}$ on solving these for steady state gives a

  polynomial in $\hat{P}_{1eq}$.

- $\hat{P}^5{}_{1eq} - \hat{X}_{1tot}\, \hat{P}^4{}_{1eq} + 2\hat{P}^3{}_{1eq} - 2\hat{X}_{1tot}\, \hat{P}^2{}_{1eq} + \hat{P}_{1eq}\left(\hat{X}^2{}_{2tot} + 1\right) - \hat{X}_{1tot} = 0$

➢ As Sturm sequence contains a term $(\hat{X}^2{}_{1tot} - 5)^2$ which would make the sequence term Zero at $\hat{X}_{1tot} = \sqrt{5}$.

➢ So getting the polynomial for $\hat{X}_{1tot} = \sqrt{5}$ by substituting the value in equation

- $\hat{P}^5{}_{1eq} - \sqrt{5}\, \hat{P}^4{}_{1eq} + 2\hat{P}^3{}_{1eq} - 2\sqrt{5}\, \hat{P}^2{}_{1eq} + \hat{P}_{1eq}\hat{X}^2{}_{2tot} + \hat{P}_{1eq} - \sqrt{5} = 0$

Following is the Sturm sequence

$$f_0(x) = \left(x - \hat{X}_{1tot}\right)(x^2+1)^2 + x\hat{X}^2{}_{2tot}$$

$$f_1(x) = \hat{X}^2{}_{2tot} + (x^2+1)(5x^2 - 4x\hat{X}_{1tot} + 1)$$

$$f_2(x) = \frac{1}{25}(4(x^2+1)\,(x\left(\hat{X}^2{}_{1tot} - 5\right) + 6\hat{X}_{1tot}) - \left(20x + \hat{X}_{1tot}\right)\hat{X}^2{}_{2tot})$$

$$f_3(x) = \frac{1}{q_3}\left(\hat{X}^2{}_{2tot}\left(2\hat{X}^2{}_{1tot} - 4 + 4x^2\left(\hat{X}^2{}_{1tot} - 5\right) - 3x\hat{X}_{1tot}\left(3 + \hat{X}^2{}_{1tot}\right)\right) - 4(x^2+1)\left(\hat{X}^2{}_{1tot} + 1\right)^2\right)$$

$$f_4(x) = \frac{1}{q_4}4\left(\hat{X}^2{}_{1tot} - 5\right)^2\hat{X}^6{}_{2tot}\left(20x + \hat{X}_{1tot}\right) - \left(\hat{X}^2{}_{1tot} - 5\right)^2\hat{X}^4{}_{2tot}(x\left(9\hat{X}^4{}_{1tot} + 35\hat{X}^2{}_{1tot} - 64\right)$$
$$-2\hat{X}_{1tot}(\hat{X}^2{}_{1tot} - 62)) + 16\left(\hat{X}^4{}_{1tot} - 4\hat{X}^2{}_{1tot} - 5\right)^2\hat{X}^2{}_{2tot}(\hat{X}_{1tot} - x)$$

$$f_5(x) = \frac{1}{q_5}(256\,\hat{X}^6{}_{1tot} - 3\hat{X}^4{}_{1tot}\left(9\hat{X}^4{}_{2tot} + 32\hat{X}^2{}_{2tot} - 256\right) - 96\hat{X}^2{}_{1tot}\left(\hat{X}^4{}_{2tot} + 29\hat{X}^2{}_{2tot} - 8\right) +$$
$$256\left(\hat{X}^2{}_{2tot} + 1\right)^3)\text{ x } 25((\hat{X}^2{}_{1tot} + 1)^2 + ((\hat{X}^2{}_{1tot} + 1)^2 + (\hat{X}^2{}_{1tot} - 5)\hat{X}^2{}_{2tot})^2$$

Where,

$$q_3 = \frac{4}{25}\left(\hat{X}_{1tot} - 5\right)^2$$
$$q_4 = 100\left((\hat{X}^2{}_{1tot} - 5)\hat{X}^2{}_{2tot} + \left(\hat{X}^2{}_{1tot} + 1\right)^2\right)^2$$
$$q_5 = \left(\left(\hat{X}^2{}_{1tot} - 5\right)^2\left(16\left(\hat{X}^2{}_{1tot} + 1\right)^2 + \hat{X}^2{}_{2tot}\left(9\hat{X}^4{}_{1tot} + 35\hat{X}^2{}_{1tot} - 64\right) - 80\hat{X}^4{}_{2tot}\right)^2\right)$$

D. Siegal-Gaskins et al , “An analytical approach to bistable biological circuit discrimination using real algebraic geometry,” Journal of The Royal Society Interface, vol. 12, no. 108, p. 20150288, Jul. 2015.

Sturm sequence for special case of $\hat{X}_{1tot}=\sqrt{5}$

$$f_0(x) = x^5 - \sqrt{5}x^4 + 2x^3 - 2\sqrt{5}x^2 + x\,\hat{X}^2{}_{2tot} + x - \sqrt{5}$$

$$f_1(x) = 5x^4 - 4\sqrt{5}x^3 + 6x^2 - 4\sqrt{5}x + \hat{X}^2{}_{2tot} + 1$$

$$f_2(x) = \frac{1}{25}(24\sqrt{5}x^2 - 20x\,\hat{X}^2{}_{2tot} - \sqrt{5}\hat{X}^2{}_{2tot} + 24\sqrt{5})$$

$$f_3(x) = -\frac{5}{1728}\left(40\sqrt{5}x\hat{X}^6{}_{2tot} - 168\sqrt{5}x\hat{X}^4{}_{2tot} - 288\sqrt{5}x\hat{X}^2{}_{2tot} + 10\hat{X}^6{}_{2tot} - 285\hat{X}^4{}_{2tot} + 1440\hat{X}^2{}_{2tot}\right)$$

$$f_4(x) = -\frac{(256\hat{X}^6{}_{2tot} - 387\hat{X}^4{}_{2tot} - 15552\hat{X}^2{}_{2tot} + 55296)}{40\sqrt{5}\left(5\hat{X}^4{}_{2tot} - 21\hat{X}^2{}_{2tot} - 36\right)^2}$$

D. Siegal-Gaskins et al , "An analytical approach to bistable biological circuit discrimination using real algebraic geometry," Journal of The Royal Society Interface, vol. 12, no. 108, p. 20150288, Jul. 2015.

Following are the corresponding set of inequalities

- Corresponding set of $\hat{X}_{1tot}$ and $\hat{X}_{2tot}$ for three real roots:

$$\hat{X}_{1tot} > 4$$

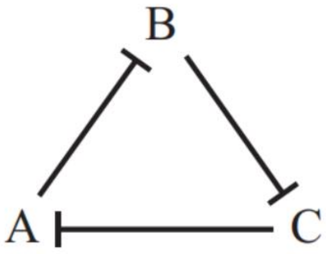
$$0 < \hat{X}^{2}{}_{2tot} \leq \frac{1}{160}(9\hat{X}_{1tot}^{4} + 35\hat{X}_{1tot}^{2} - 64 + 3\left(9\hat{X}^{8}{}_{1tot} + 70\hat{X}^{6}{}_{1tot} + 577\hat{X}^{4}{}_{1tot} + 640\hat{X}^{2}{}_{1tot} + 1024\right)^{\frac{1}{2}}$$

$$\cap$$

$$256\left(\hat{X}_{1tot}^{6} + (\hat{X}_{2tot}^{2}+1\right)^{3}) < 3\hat{X}^{4}{}_{1tot}\left(9\hat{X}^{4}{}_{2tot} + 32\hat{X}^{2}{}_{2tot} - 256\right) + 96\hat{X}^{2}{}_{1tot}(\hat{X}^{4}{}_{2tot} + 29\hat{X}^{2}{}_{2tot} - 8\big)$$

D. Siegal-Gaskins et al , “An analytical approach to bistable biological circuit discrimination using real algebraic geometry,” Journal of The Royal Society Interface, vol. 12, no. 108, p. 20150288, Jul. 2015.

Repressilator is an oscillatory genetic circuit consisting of three repressors arranged in a ring fashion



Repressilator

- $\frac{dA}{dt} = \frac{\beta}{1+\left(\frac{C}{K}\right)^n} - \gamma A$
- $\frac{dB}{dt} = \frac{\beta}{1+\left(\frac{A}{K}\right)^n} - \gamma B$
- $\frac{dC}{dt} = \frac{\beta}{1+\left(\frac{B}{K}\right)^n} - \gamma C$, equations are the ODE form of the circuit.

Repressilator circuit when solved for steady states has one fixed point

- $\frac{dM_A}{dE} = f_1(c) - \delta\, M_A$

$$= \frac{\alpha}{1+\left(\frac{c}{K}\right)^n} - \delta\, M_A = 0$$

$$=> \frac{\alpha}{1+\left(\frac{c}{K}\right)^n} = \delta\, M_A$$

- $0 = KM_A - \gamma A \Rightarrow KM_A = \gamma A$
- $\frac{K}{\alpha}\,\frac{\alpha}{\delta}\frac{1}{1+\left(\frac{c}{k}\right)^n} = A \quad , \frac{K}{\alpha}\,\frac{\alpha}{\delta}\frac{1}{1+\left(\frac{A}{k}\right)^n} = B \;, \frac{K}{\alpha}\,\frac{\alpha}{\delta}\frac{1}{1+\left(\frac{B}{k}\right)^n} = C$
- Let $t' = \gamma t$, $A' = \frac{A}{\frac{\beta}{\gamma}}$, $B' = \frac{B}{\frac{\beta}{\gamma}}$, $C' = \frac{C}{\frac{\beta}{\gamma}}$, $K' = \frac{K}{\frac{\beta}{\gamma}}$

Further normalization of the equation gives us equation in terms of A′ and K ′

- We have , for n=2

$$A' + \frac{A'}{K'^2}\left(\frac{1}{1+\left(\frac{1}{K'\left(1+\left(\frac{A'}{K'}\right)^2\right)}\right)^2}\right)^2 = 1$$

Sturm sequence for V(0):

```
k=var('k')
z0=-k**6 - k**5 ;
z1=(k**6 + 3*k**5 + k**4)/(k + 1);
z2=(81*k**8 + 242*k**7 + 240*k**6 + 80*k**5)/(81*k**2 + 162*k + 81);
z3=(-1053*k**9 - 5103*k**8 - 8910*k**7 - 7128*k**6 - 2592*k**5 - 324*k**4)/(324*k**4 + 1224*k**3 + 1804*k**2 + 1224*k + 324);
z4=(-5103*k**16 - 37827*k**15 - 121977*k**14 - 219073*k**13 - 226433*k**12 - 107853*k**11 + 33608*k**10 + 86188*k**9 + 57614*
z5=(52488000*k**21 + 595843776*k**20 + 3138829056*k**19 + 10186516584*k**18 + 22779305109*k**17 + 37149110676*k**16 + 455362
z6=(-373669453125*k**33 - 6718742842500*k**32 - 57884521243050*k**31 - 317949176422512*k**30 - 1249708512052719*k**29 - 37392
z7=(-376572715308000*k**38 - 1066639891586976OO*k**37 - 1427288480098671168*k**36 - 12062987283714794712*k**35 - 7260250781
z8=(-376572715308000*k**38 - 1066639891586976OO*k**37 - 1427288480098671168*k**36 - 12062987283714794712*k**35 - 7260250781
z9=(11859329208651782400000*k**48 + 35158079525086047052800*k**47 + 495892300888919927637504*k**46 + 4453595372214575580369024
```

Sturm sequence for V(∞):

```
i0=1;
i1=9;
i2=(-72*k**3 - 136*k**2 - 72*k)/(81*k**2 + 162*k + 81); # -ve
i3=(648*k**5 + 1620*k**4 + 1215*k**3 + 243*k**2 - 81*k)/(81*k**4 + 306*k**3 + 451*k**2 + 306*k + 81);
i4=(18225*k**13 + 139563*k**12 + 478854*k**11 + 965871*k**10 + 1259606*k**9 + 1095643*k**8 + 627169*k**7 + 218768*k**6 + 3497
i5=(10497600*k**18 + 139081536*k**17 + 801456768*k**16 + 2711476296*k**15 + 6078891969*k**14 + 9602826210*k**13 + 1102967433
i6=(-149467781250*k**31 - 2288517806250*k**30 - 16407304948350*k**29 - 72646027501212*k**28 - 219524966733690*k**27 - 466989
i7=(-1673656512480000*k**37 - 43790292839865600*k**36 - 537298446345369408*k**35 - 4138384133399074272*k**34 - 2259416377131
i8=(992916339191015625*k**47 + 19942173052463109375*k**46 + 190274896948773307500*k**45 + 1141907422305440780325*k**44 + 4798
i9=(11859329208651782400000*k**48 + 35158079525086047052800*k**47 + 495892300888919927637504*k**46 + 4453595372214575580369024
```

Considering the case V(0) - V(∞)=1 will give inequalities for K′

=> Code could not execute completely for such large values and kept running for long time.

Summary

- Sturm's Theorem was analysed and using it steady states points were found out for these systems:

➢ **Goodwin- Oscillator model** was solved using Sturm's Theorem which confirmed geometrical result of single fixed point in $\left[0, \frac{1}{\alpha\beta\gamma}\right]$ and in a generalised form it has single fixed point in $[0, \infty]$**.**

➢ **Negative Autoregulation** circuit in steady state gets reduced to a polynomial with single fixed point.

➢ **Toggle Switch circuits** when solved for three steady states with K′ as variable gives $K' \in \left(\frac{1}{2}, 1\right) \cup (1, \sqrt{2}\,)$

- **MD and DD toggle circuits** when solved for steady states using Sturm's Theorem gives varied range of possibilities for sign change in Sturm sequence for a possible solution which when checked for consistency gives a set of inequalities.

➢ **Repressilator circuits** when solved for cases of single steady state gives set of inequalities.

Routh-Hurwitz Criterion does not give the location of roots

- Routh-Hurwitz Criterion gives a test to determine if roots of a given polynomial lie in left half plane.
- Thus, providing us with the information if the system is stable.
- Whereas **Sturm's Theorem** provides us with number of roots in a particular interval.

Future work

- Multivariate Sturm's Theorem could be helpful in further studying more complex Biological systems.
- Further debugging of the computation would lead to finding better and faster methods for computation.

References

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[2] D. Gonze and W. Abou-Jaoudé, “The Goodwin Model: Behind the Hill Function,” PLoS ONE, vol. 8, no. 8, p. e69573, Aug. 2013.

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