Importing packages

In [1]:
```
using Plots
using DifferentialEquations
using LaTeXStrings
using LinearAlgebra
using ModelingToolkit
using OrdinaryDiffEq
using DiffEqBiological
using Latexify
using Sundials

gr();
```

Defining model as a reaction network with parameters

In [22]:
```
κS = 1
κF = 1
Γ = 1
n = 3
v = ( 5*10^(-3) * ( κF^(-2/3) * Γ^(-1/3) ) ) * 3600
δC = ( 1.6*10^(-3) * κF^(-2/3) ) * 3600
ρS = ( 1.6 * ( κF^(1/3) * Γ^(-1/3) ) ) * 3600
ρP = ( 6*10^(-4) * ( κF^(1/3) * Γ^(-1/3) ) ) * 3600
ρF = ( 3.5*10^(-3)*κS ) * 3600
δS = ( 0.2*10^(-3) ) * 3600
δP = ( 1*10^(-3) ) * 3600
δF = ( 5*10^(-3) ) * 3600

rnParam = [δS, δP, δF, δC, Γ, n, v, ρS, ρP, ρF, κS, κF]

rn = @reaction_network begin
    hillr(κ₁,ρ₁,F,n), ∅ --> S
    ρ₂, ∅ --> P
    hillr(S*Γ*P^2,ρ₃,κ₃,n), ∅ --> F
    2*δ₄*Γ, 2P + S --> ∅
    δ₁, S --> ∅
    δ₂, P --> ∅
    δ₃, F --> ∅
    v*P^2*S*Γ, ∅ --> P
end δ₁ δ₂ δ₃ δ₄ Γ n v ρ₁ ρ₂ ρ₃ κ₁ κ₃;
```

```
[ Warning: The RegularJump interface has changed to be matrix-free. See the documentation for more details.
@ DiffEqJump C:\Users\hmngu\.julia\packages\DiffEqJump\TfjIU\src\jumps.jl:48
```

Here, due to the limitations of Julia's inline mathematical expression in code, I have defined that:

- δ_1 is the decay rate of SHH, or $\bar{\delta_S}$
- δ_2 is the decay rate of patched receptors Ptc, or $\bar{\delta_P}$
- δ_3 is the decay rate of FGF10, or $\bar{\delta_F}$
- δ_4 is the decay rate of complex SHH-Ptc, or $\bar{\delta_C}$
- ρ_1 is the production rate of SHH, or $\bar{\rho_S}$
- ρ_2 is the production rate of patched receptors Ptc, or $\bar{\rho_P}$
- ρ_3 is the production rate of FGF10, or $\bar{\rho_F}$
- κ_1 is the Hill's constant of SHH, or $\bar{\kappa_S}$
- κ_3 is the Hill's constant of FGF10, or $\bar{\kappa_F}$

DiffEq Mathematical Model

In [23]:
```
latexify(rn,  starred=true, cdot = false, clean= true, symbolic = true,field=:symfuncs)
```

Out[23]:

$$\begin{aligned}
\frac{dS(t)}{dt} =& \frac{\rho_1 F^n}{F^n + \kappa_1^n} - \frac{2\delta_4\Gamma}{2} P^2 S - \delta_1 S \\
\frac{dP(t)}{dt} =& \rho_2 - 2\frac{2\delta_4\Gamma}{2} P^2 S - \delta_2 P + vP^2 S\Gamma \\
\frac{dF(t)}{dt} =& \frac{\rho_3 \kappa_3^n}{\kappa_3^n + \left(S\Gamma P^2\right)^n} - \delta_3 F
\end{aligned}$$

The Symbolic Jacobian Expression

In [24]:
```
latexify(jacobianexprs(rn), cdot=false)
```

Out[24]:

$$\begin{bmatrix} -\frac{2\delta_4\Gamma}{2}P^2 - \delta_1 & -2\delta_4\Gamma PS & \frac{n\rho_1 F^{-1+n}}{F^n+\kappa_1^n} - \frac{n\rho_1 F^{-1+2n}}{\left(F^n+\kappa_1^n\right)^2} \\ -2\frac{2\delta_4\Gamma}{2}P^2 + v\Gamma P^2 & -22\delta_4\Gamma PS - \delta_2 + 2v\Gamma PS & 0 \\ \frac{(-n)\kappa_3^n\rho_3\left(\Gamma P^2 S\right)^n}{S\left(\kappa_3^n+(\Gamma P^2 S)^n\right)^2} & \frac{-2n\kappa_3^n\rho_3\left(\Gamma P^2 S\right)^n}{P\left(\kappa_3^n+(\Gamma P^2 S)^n\right)^2} & -\delta_3 \end{bmatrix} \quad (1)$$

Solving the reaction network as an ODE problem

A random initial point

Consider picking (0.1, 0.1, 0.1), we will solve for the steady state given the parameters we currently have.

In [68]:
```
u0 = [0.1, 0.1, 0.1]
tspan = [0.0, 5.0]
odeProb = ODEProblem(rn, u0, tspan, rnParam)
ssProb = SteadyStateProblem(rn, u0, rnParam)

odeSol = solve(odeProb, AutoTsit5(Rosenbrock23()))
ssSol = solve(ssProb, DynamicSS(CVODE_BDF()),dt=1.0);
```

The steady state we found is:

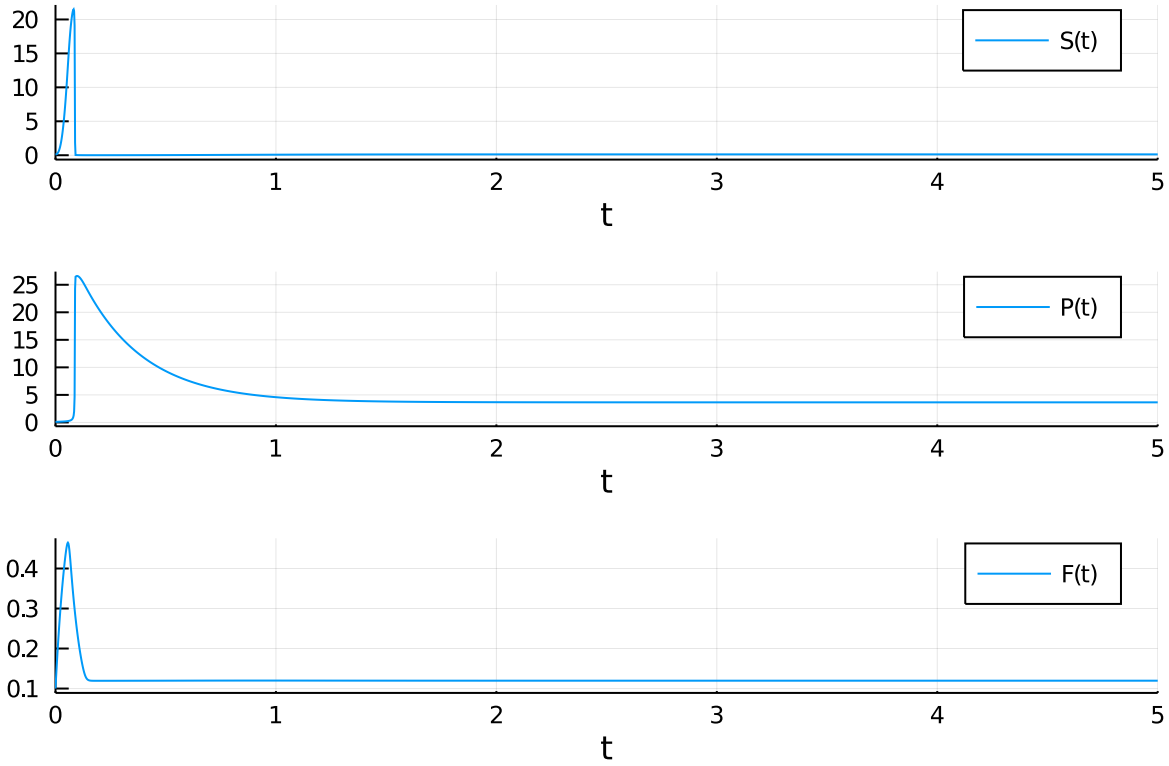
In [69]:
```
ssSol
```

Out[69]:
```
u: 3-element Array{Float64,1}:
 0.12726349892373956
 3.647262497966724
 0.11962280194505014
```

Ploting the concentrations over time

In [70]:
```
plot(odeSol, layout = (3,1))
```

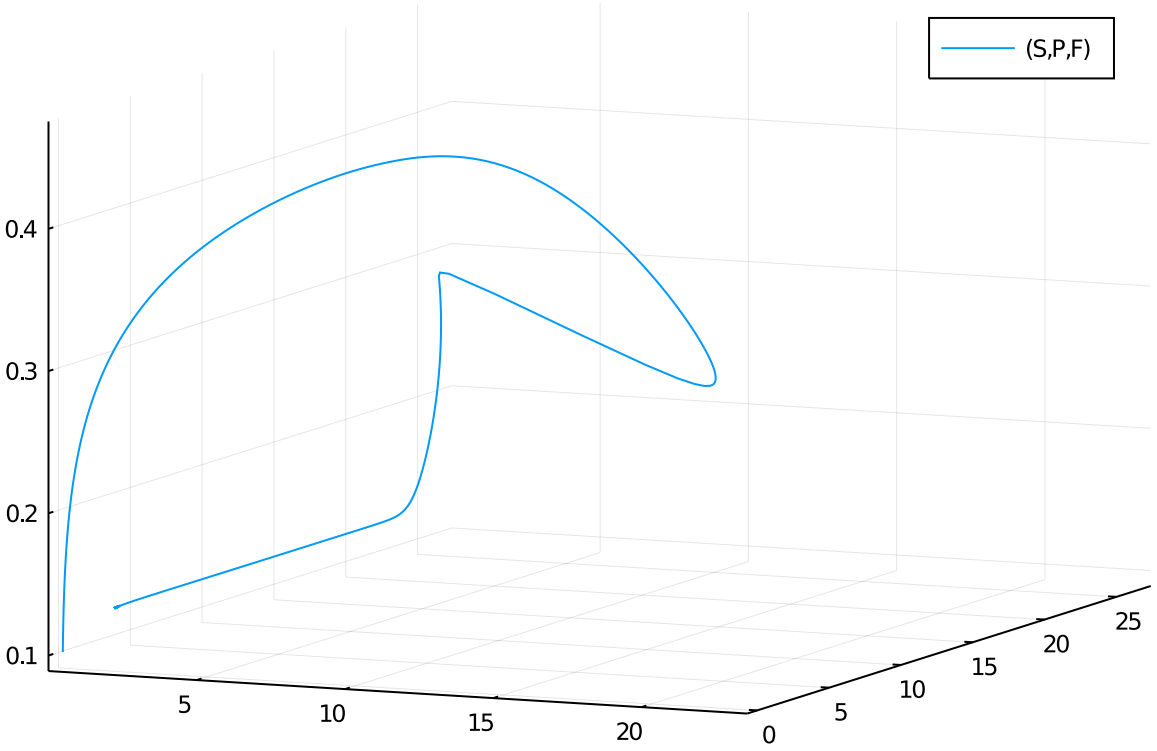
Out[70]:



Ploting the steady state space in 3D:

In [71]:
```
plot(odeSol,vars=(1,2,3),plotdensity=10000)
```

Out[71]:



Behavior of the model near the steady state

To examine the behavior of the steady state, we consider picking the initial point near the steady state we found

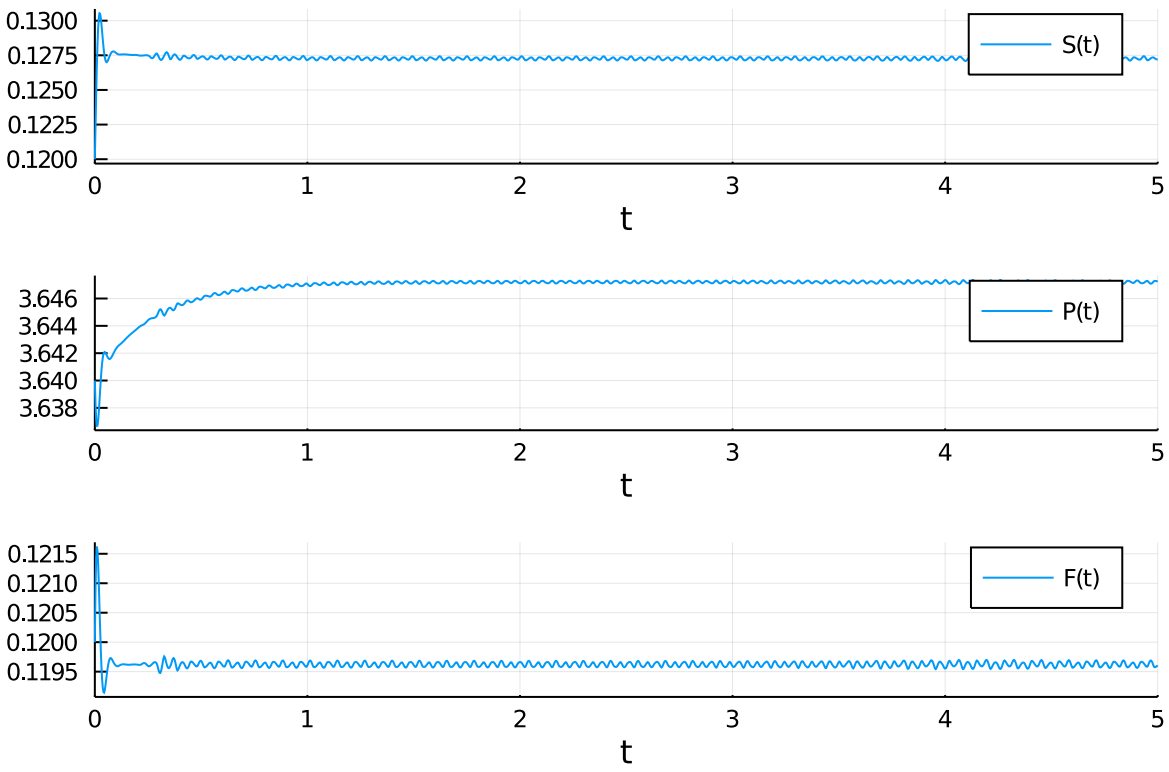
In [45]:
```
#u0 = [0.1272642106579746, 3.6472310383795565, 0.11962240351435512]
u0 = [0.12, 3.64, 0.12]
tspan = [0.0, 5.0]
odeProb = ODEProblem(rn, u0, tspan, rnParam)
ssProb = SteadyStateProblem(rn, u0, rnParam)

odeSol = solve(odeProb, AutoTsit5(Rosenbrock23()))
ssSol = solve(ssProb, DynamicSS(CVODE_BDF()),dt=1.0);
```

In [46]:
```
ssSol
```

Out[46]:
```
u: 3-element Array{Float64,1}:
 0.12726414816928983
 3.6472288141414926
 0.11962237683462228
```

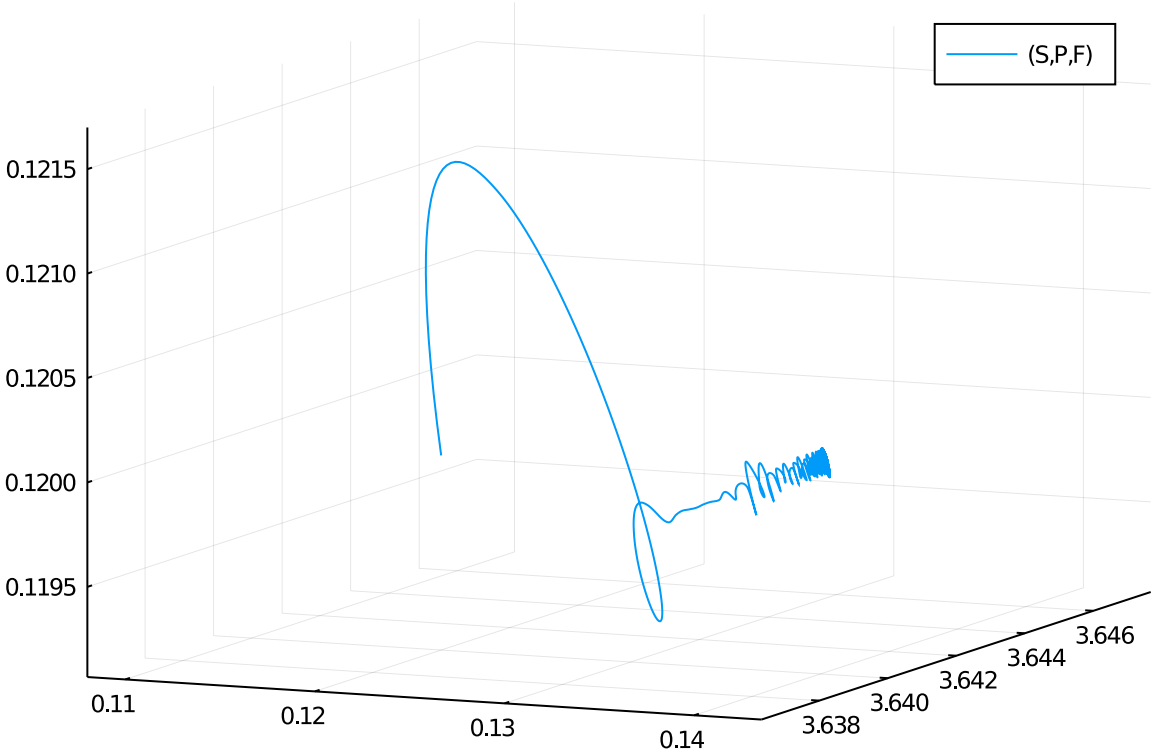
In [47]:
```
plot(odeSol, layout = (3,1))
```

Out[47]:



In [48]:
```
plot(odeSol,vars=(1,2,3),plotdensity=10000)
```

Out[48]:



As we can see there are some oscillations near the end so we increase the number of decimals near the steady state to tol of 10^{-8}

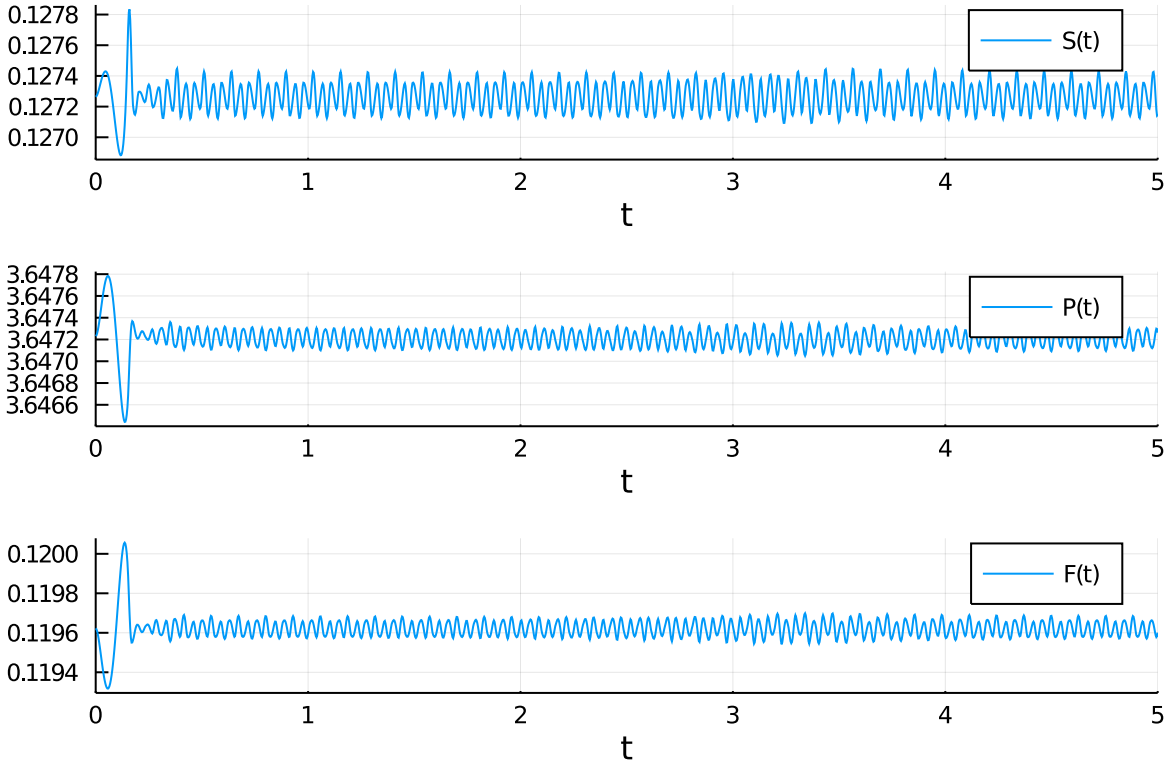
In [53]:
```
u0 = [0.12726421, 3.64723103, 0.11962240]
tspan = [0.0, 5.0]
odeProb = ODEProblem(rn, u0, tspan, rnParam)
ssProb = SteadyStateProblem(rn, u0, rnParam)

odeSol = solve(odeProb, AutoTsit5(Rosenbrock23()))
ssSol = solve(ssProb, DynamicSS(CVODE_BDF()),dt=1.0);
```

In [54]:
```
ssSol
```

Out[54]:
```
u: 3-element Array{Float64,1}:
 0.12726423645201343
 3.647230183629223
 0.1196223918114193
```

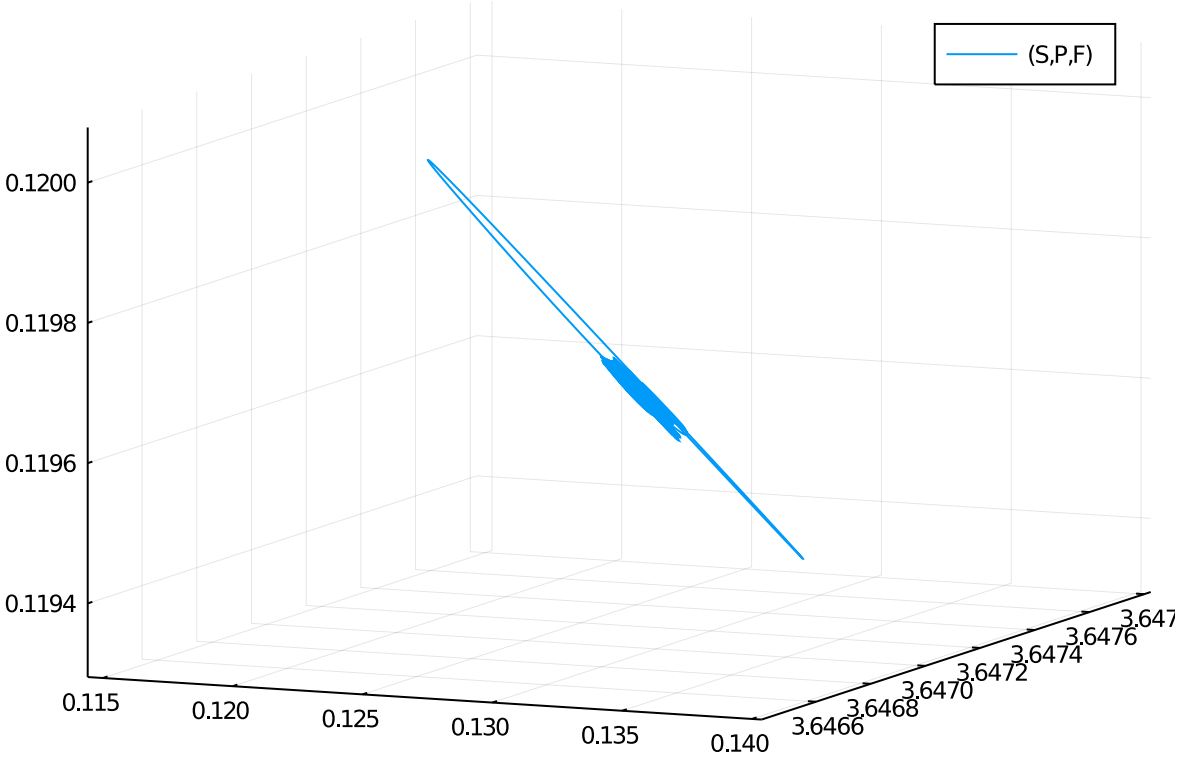
In [55]:
```
plot(odeSol, layout = (3,1))
```

Out[55]:



In [56]:
```
plot(odeSol,vars=(1,2,3),plotdensity=10000)
```

Out[56]:



Bifurcations

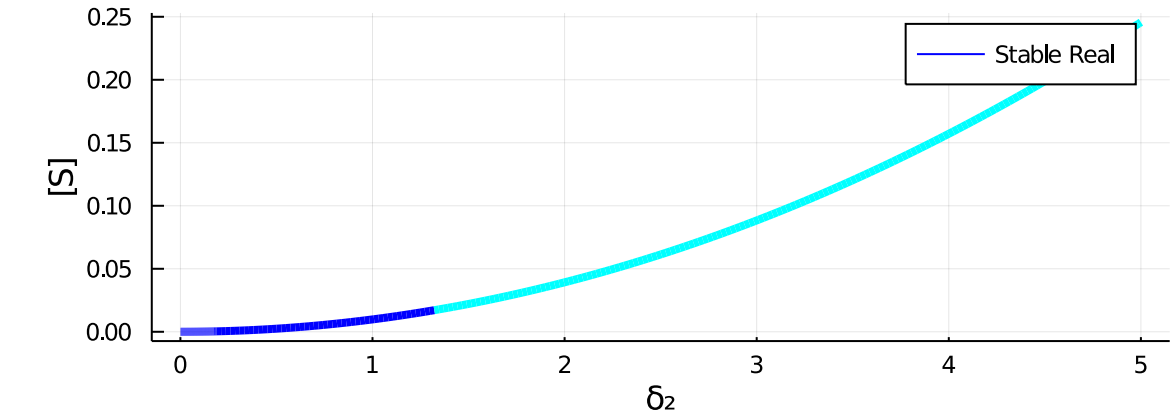
Variation of decay rate of patched receptor, or $\bar{\delta_P}$

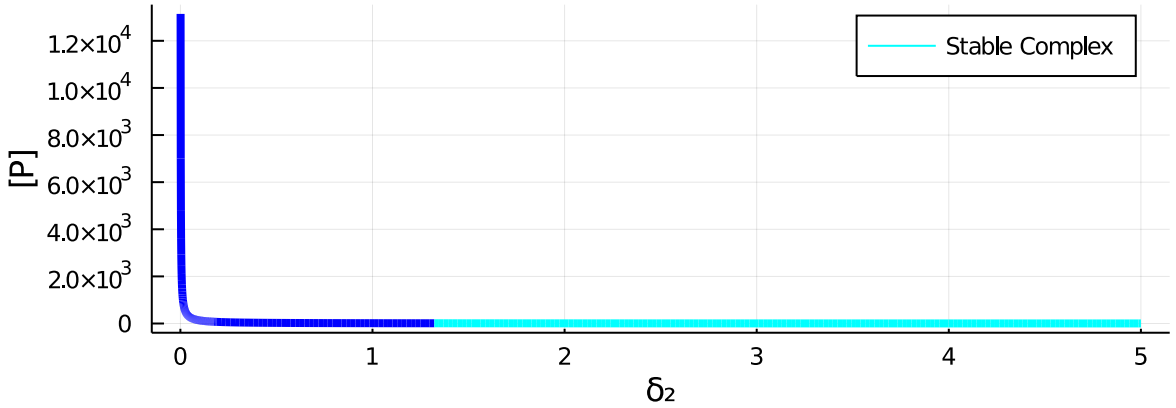
In [72]:
```
bif = bifurcations(rn, rnParam, :δ₂, (0.001,5.))
plt = plot(layout = (3,1), size = (600, 700))
plot!(plt, [[],[]],color=[:blue :cyan],label = ["Stable Real" "Stable Complex"])
plot!(plt[1], bif, 1, ylabel = "[S]")
plot!(plt[2], bif, 2, ylabel = "[P]")
plot!(plt[3], bif, 3, ylabel = "[F]")
```

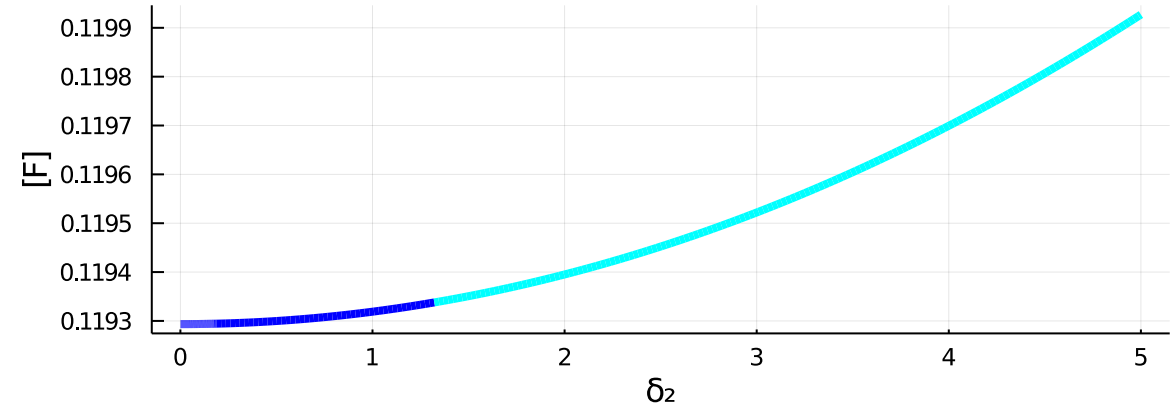
```
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
```

```
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
```

Out[72]:


Stable Real
[S]
0.25
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
5
δ2


Stable Complex
[P]
1.2×10^4
1.0×10^4
8.0×10^3
6.0×10^3
4.0×10^3
2.0×10^3
0
0
1
2
3
4
5
δ2


[F]
0.1199
0.1198
0.1197
0.1196
0.1195
0.1194
0.1193
0
1
2
3
4
5
δ2

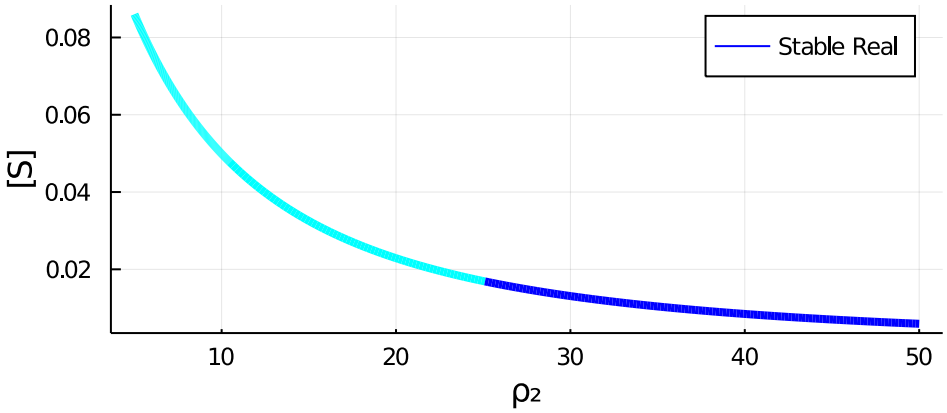
Variation of production rate of patched receptor, or $\bar{\rho}_P$

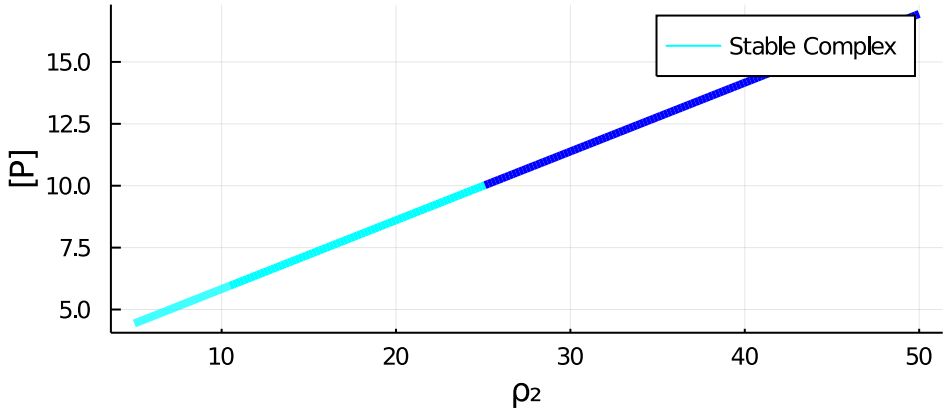
In [74]:

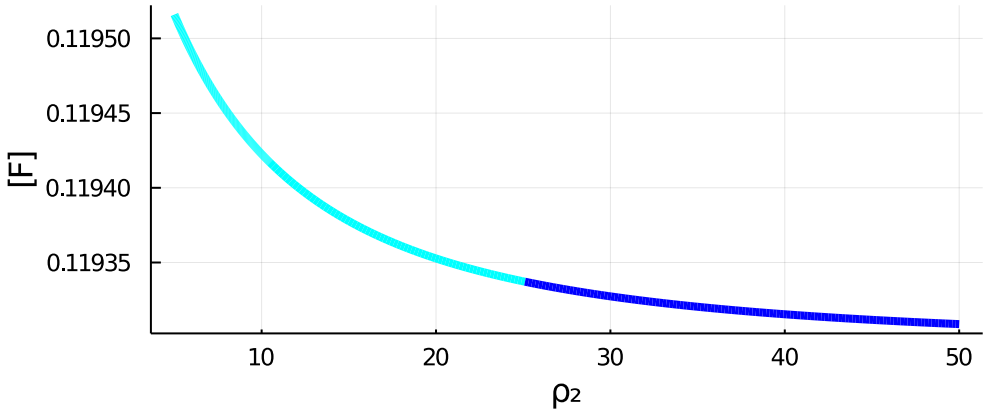
```
bif = bifurcations(rn, rnParam, :ρ₂, (5.0,50.0))
plt = plot(layout = (3,1), size = (500, 700))
plot!(plt[1], bif, 1, ylabel = "[S]")
plot!(plt[2], bif, 2, ylabel = "[P]")
plot!(plt[3], bif, 3, ylabel = "[F]")
plot!(plt, [[],[]],color=[:blue :cyan],label = ["Stable Real" "Stable Complex"])
```

```
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
```

Out[74]:


Stable Real
[S]
0.08
0.06
0.04
0.02
10
20
30
40
50
ρ2


Stable Complex
[P]
15.0
12.5
10.0
7.5
5.0
10
20
30
40
50
ρ2


[F]
0.11950
0.11945
0.11940
0.11935
10
20
30
40
50
ρ2

Variation of decay rate of FGF10, or $\bar{\delta_F}$

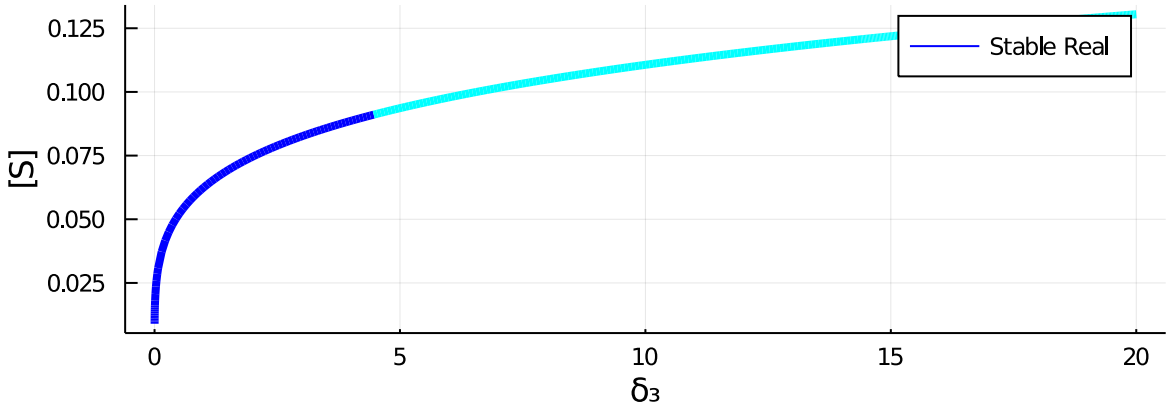
The variation is from 0.001 to 20

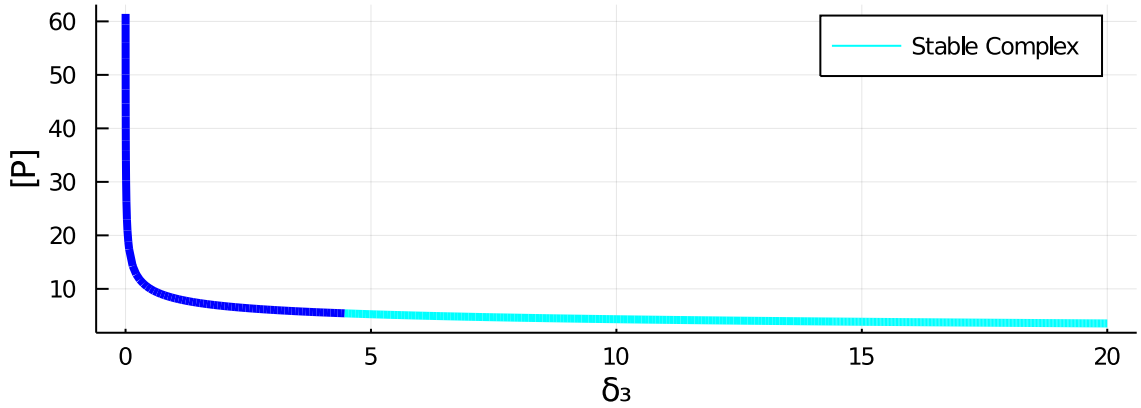
In [65]:

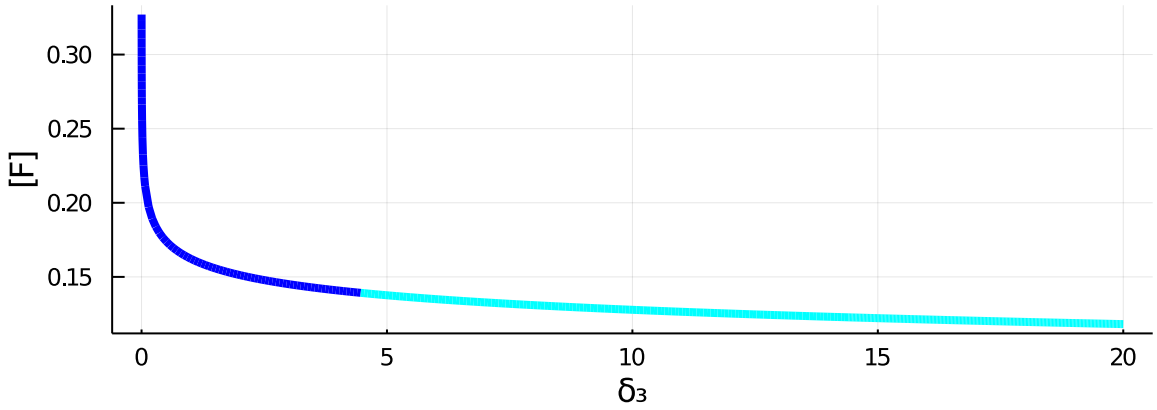
```
bif = bifurcations(rn, rnParam, :δ₃, (0.001,20.))
plt = plot(layout = (3,1), size = (600, 700))
plot!(plt, [[],[]],color=[:blue :cyan],label = ["Stable Real" "Stable Complex"])
plot!(plt[1], bif, 1, ylabel = "[S]")
plot!(plt[2], bif, 2, ylabel = "[P]")
plot!(plt[3], bif, 3, ylabel = "[F]")
```

```
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
```

Out[65]:


0.125
0.100
0.075
0.050
0.025
[S]
0
5
10
15
20
δ3
Stable Real


60
50
40
30
20
10
[P]
0
5
10
15
20
δ3
Stable Complex


0.30
0.25
0.20
0.15
[F]
0
5
10
15
20
δ3

In [ ]:

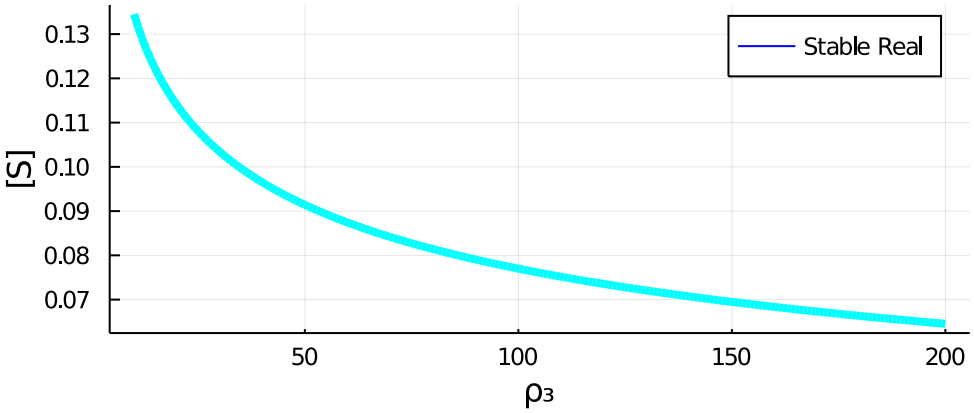
Variation of production rate of FGF10, or $\bar{\rho_F}$

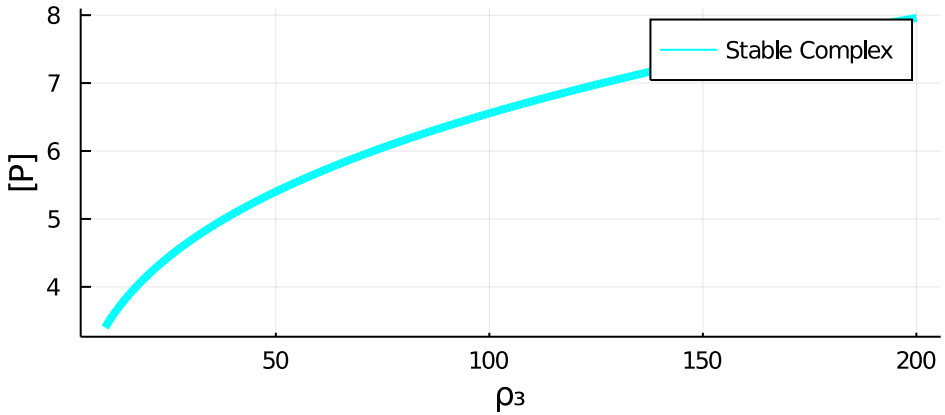
The variation is from 10 to 200

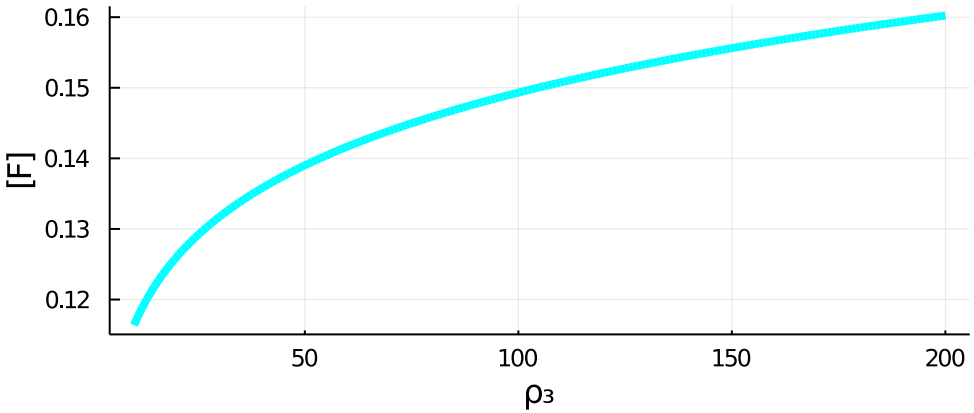
In [66]:
```
bif = bifurcations(rn, rnParam, :ρ₃, (10.0,200.0))
plt = plot(layout = (3,1), size = (500, 700))
plot!(plt[1], bif, 1, ylabel = "[S]")
plot!(plt[2], bif, 2, ylabel = "[P]")
plot!(plt[3], bif, 3, ylabel = "[F]")
plot!(plt, [[],[]],color=[:blue :cyan],label = ["Stable Real" "Stable Complex"])
```

```
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
```

Out[66]:


Stable Real
[S]
0.13
0.12
0.11
0.10
0.09
0.08
0.07
50
100
150
200
ρ3


Stable Complex
[P]
8
7
6
5
4
50
100
150
200
ρ3


[F]
0.16
0.15
0.14
0.13
0.12
50
100
150
200
ρ3

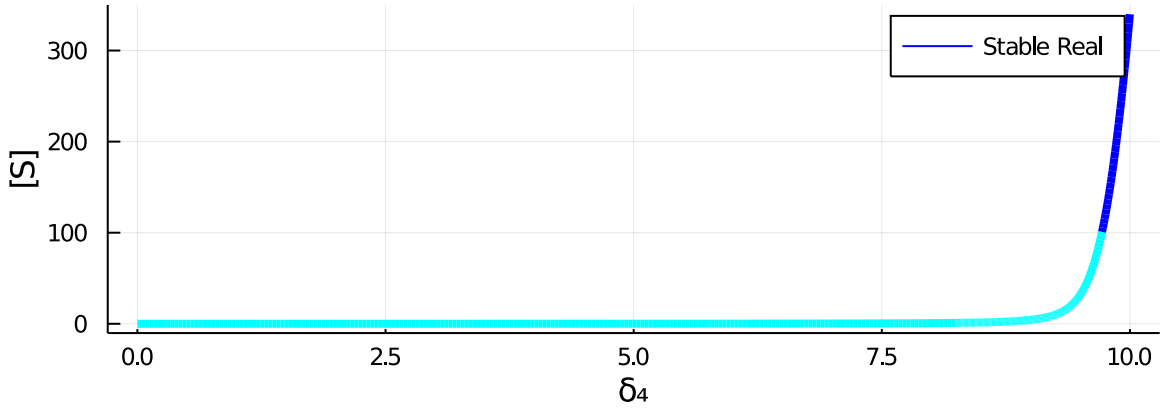
Variation of decay rate of complex SHH-Ptc, or $\bar{\delta_C}$

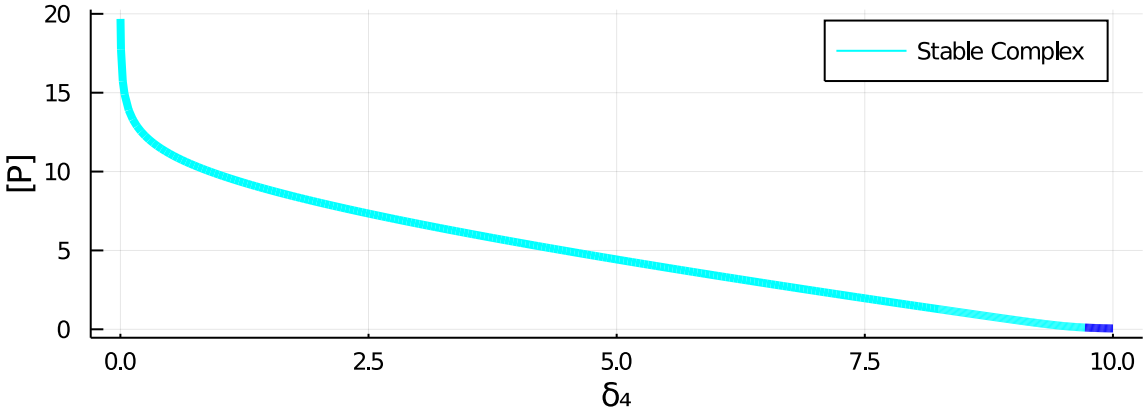
In [75]:

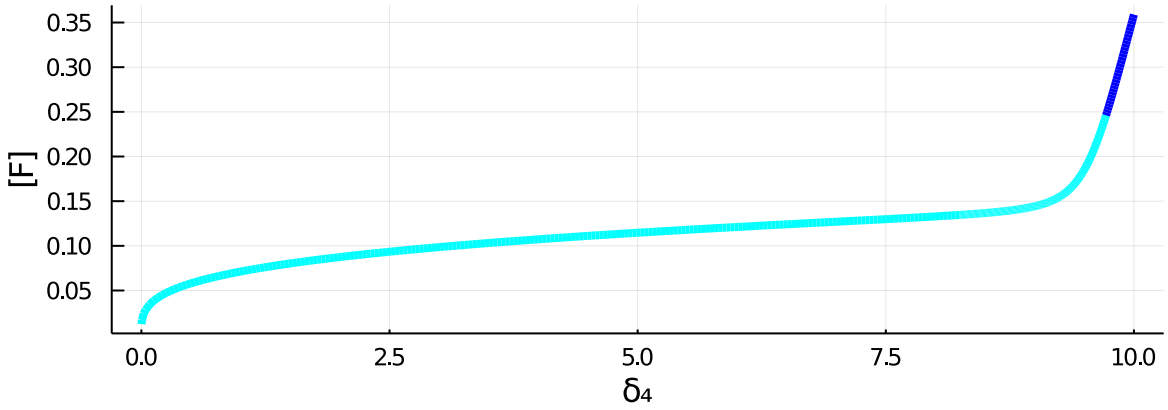
```
bif = bifurcations(rn, rnParam, :δ₄, (0.001,10.))
plt = plot(layout = (3,1), size = (600, 700))
plot!(plt, [[],[]],color=[:blue :cyan],label = ["Stable Real" "Stable Complex"])
plot!(plt[1], bif, 1, ylabel = "[S]")
plot!(plt[2], bif, 2, ylabel = "[P]")
plot!(plt[3], bif, 3, ylabel = "[F]")
```

```
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `xlabel` detected in the user recipe defined for the signature (::DiffEqBiological.Bifurcation
Diagram, ::Int64). To ensure expected behavior it is recommended to use the default attribute `xguide`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
┌ Warning: Attribute alias `color` detected in the user recipe defined for the signature (::DiffEqBiological.BifurcationP
ath, ::Int64). To ensure expected behavior it is recommended to use the default attribute `seriescolor`.
└ @ Plots C:\Users\hmngu\.julia\packages\Plots\hyS17\src\pipeline.jl:15
```

Out[75]:


Stable Real
[S]
300
200
100
0
0.0
2.5
5.0
7.5
10.0
δ4


Stable Complex
[P]
20
15
10
5
0
0.0
2.5
5.0
7.5
10.0
δ4


[F]
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.0
2.5
5.0
7.5
10.0
δ4