Proof of stability of the G-protein signalling model

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$$\frac{dx_1}{dt} = -k_{RL}x_1u + k_{RLm}x_2 - k_{Rd0}x_1 + k_{Rs}$$

$$\frac{dx_2}{dt} = k_{RL}x_1u - k_{RLm}x_2 - k_{Rd1}x_2$$

$$\frac{dx_3}{dt} = -k_{Ga}x_2x_3 + k_{G1}(G_{total} - x_3 - x_4)(G_{total} - x_3)$$

$$\frac{dx_4}{dt} = k_{Ga}x_2x_3 - k_{Gd}x_4$$

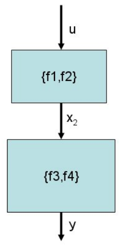
The four-state model of G-protein signalling can be shown to be stable within a region containing one of its fixed points.

Preliminaries: The above system has two fixed points.

Consider the two subsystems {f(1),f(2)} and {f(3),f(4)}. The first, which describes the evolution of $x_1$and x_2 is linear, with one fixed point. The fixed point is away from the origin for k_{Rs}nonzero. At that fixed point, that is with x_2 fixed, $x_{3,equil}$ and $x_{4,equil}$ are linearly independent. See that the second subsystem has two fixed points by substituting in 'f(3)=0' and solving the resulting quadratic equation in one variable.

Note the cascade configuration of this model, in that the first subsystem does not depend on the second, but drives the second through the coupling in

x_2.



The system is constrained to have at most G_{total} G-proteins in the activated or undissociated state. Recall that the state equations allow for the original number G_{total} to be transformed between activated $G_\alpha : GTP$, undissociated $G\alpha\beta\gamma$, and a third form $G_\alpha : GDP$.

By analyzing the linearized system, we observe that one of the fixed points is stable, while the other is unstable.

$u(M)$	stable fixed point: x_1, x_2, x_3, x_4	eigenvalues
10^{-10}	9333, 66.7, 9933, 66.2	-66.4, -0.100, -0.014, -0.0004
10^{-9}	5833, 417, 9599, 400	-400, -0.104, -0.014,-0.00065
10^{-8}	1228, 877, 9193, 806	-806, -0.109, -0.022, -0.002
10^{-7}	138.1, 986, 9102, 898	-898, -0.111, -0.110, -0.0037
10^{-6}	14.0, 998.6, 9092, 908	-908, -1.01, -0.110, -0.004
10^{-5}	1.40, 999.9, 9091, 909	-909, -10.01, -0.110, -0.004

Also insert unstable fixed point data?

It is always the case in this example that the unstable fixed point is outside the region $x_3 + x_4 \leq G_{total}$ and outside the region $x_3 \leq G_{total}$.

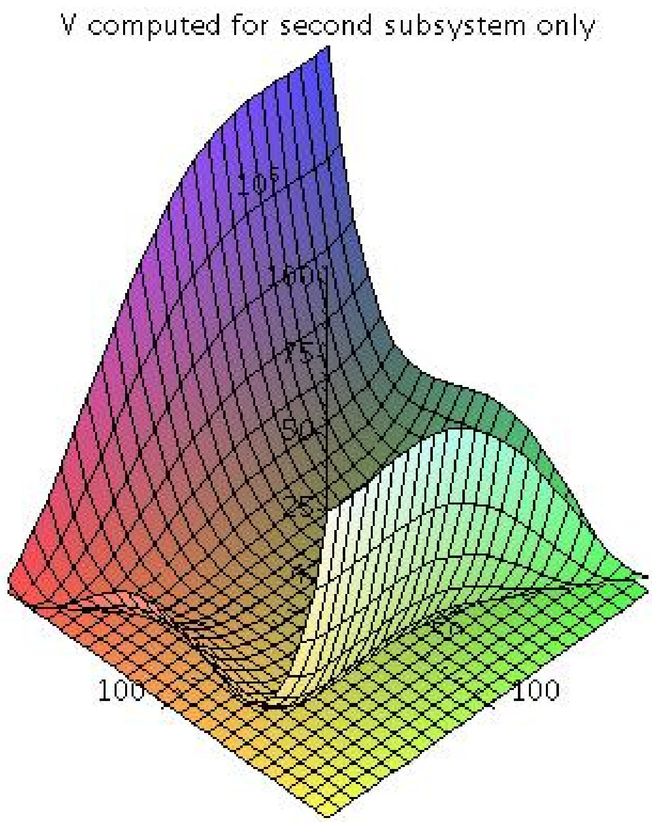
Proof: Note that at $x_3 + x_4 = G_{total}$, or at $x_3 = G_{total}$, $\dot{x_3}$ is negative, that is, x_3 is decreasing. Thus in state space we have hyperplane barriers that shows that the unstable fixed point lies to the right of the plane. (I need to do this properly.)

1. The first subsystem is stable: I searched for a second-order polynomial V, SOS, such that $-\dot{V}$ is SOS. Result: Found Lyapunov function $0.0042038x_1^2 + 0.027463x_2^2$.

2. A three-state reduced-order model is stable: I justify a three-state, reduced-

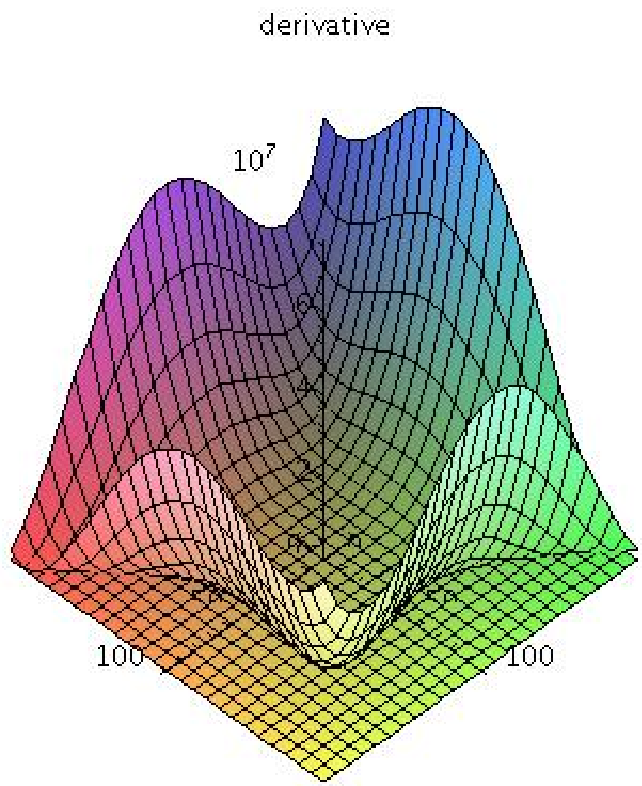
order model by noting from simulations that $G_\alpha : GDP$ is maintained at near-zero concentrations, which implies that $(G_{total} - \dot{x_3} - x_4) = -k_{G1}(G_{total} - x_3 - x_4)(G_{total} - x_3) + k_{Gd}x_4 \approx 0$. Then the second subsystem can be replaced by $\frac{dx_4}{dt} = k_{Ga}x_2(G_{total} - x_4) - k_{Gd}x_4$ for short times. Physically, this happens because of the fast dynamics of $G_\alpha : GDP$; the value of $k_{G1}$is so large that any available $G_\alpha : GDP$ is quickly converted to $G_\alpha : GTP$. We investigate the stability of its single fixed point. By searching over some polynomials of degree 2 in x_1,$x_2$and x_4, I found the Lyapunov function $V \approx 0.61x_1^2 + 1.9x_2^2 - 0.17x_2x_4 + 0.19x_4^2$.

3. Experiment: Since the given model can be separated naturally into two subsystems in a cascade, and given that the first sub-system is stable, we seek a Lyapunov function in x3 and x4 alone that shows that a 2D-slice of phase-space (x1=x10,x2=x20) converges to the fixed point. Then, by continuity of the vector field, there is a stable region around the fixed point. The above argument holds even when the 2-D slice is a disc and not all of x10×x20×x3×x4. Result: Found Lyapunov function. Although this proves stability of the fixed point {x10,x20,x30,x40}, this procedure doesn't give a lower bound on the size of the basin of attraction of the fixed point. (details: above radius^2=60, numerical error code goes from 0 to 1(fragile). We plot the program output for much larger radii to see that we can actually prove stability for much larger radii using SOSTOOLS. We expect the radius to be at least 482 (max{the distance to x3=10^4,the distance to x3+x4=10^4}, see barrier described above) and at most 568(the distance between from this to the unstable fixed point), shown below is the Lyapunov function for radius^2=6000, radius about 77,

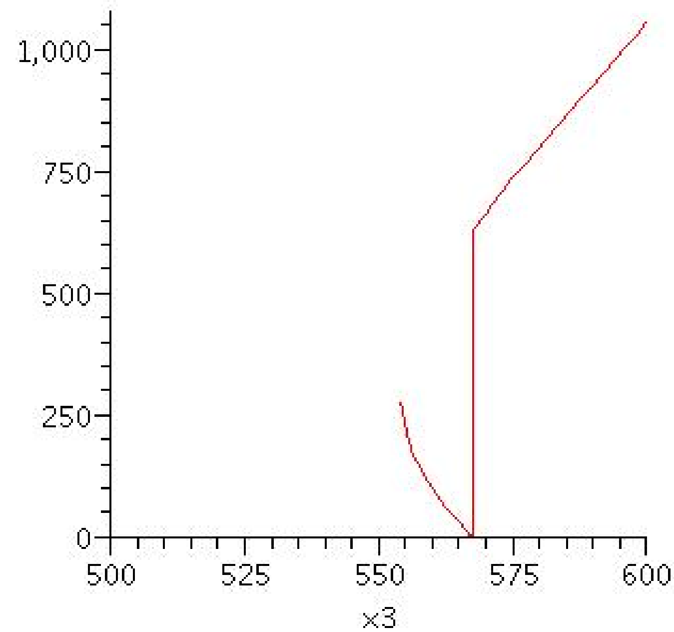


and

we see by plotting that the Lyapunov criteria are not met for the output



when radius = 1000; in



fact, the boundary is shown here

4. Experiment: The original system, requiring only semidefinite "Lyapunov functions." INSERT PLOTS of this as well. Discuss FRAGILITY of solutions: Lyapunov functions are barely definite as they have close-to-zero gradients in some radial directions, also, this proves stability for only small radius (<10) with numerical error flag appearing early. The first problem justifies imposing strict definiteness as in 5. The second problem suggests that we don't do the four-state proof directly, but use outline in 6.

5. Impose strict definiteness. No results yet.

6. Future work: Can I find a Lyapunov function like this one, but independent of the value of x1 and x2? This will help me state the radius of

attraction. Experiment: The second subsystem, with a constraint on x2, such as x2 in (-n,+n).

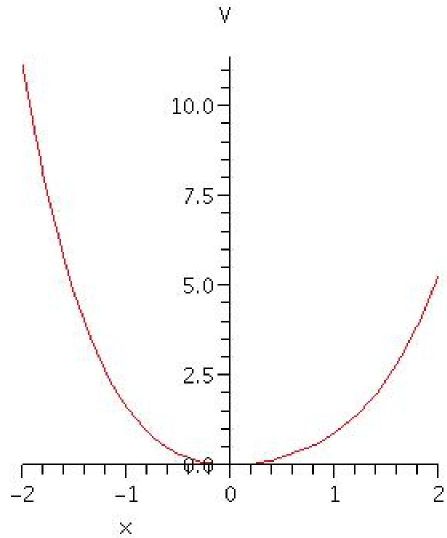
7. Parameter estimation / Model invalidation results

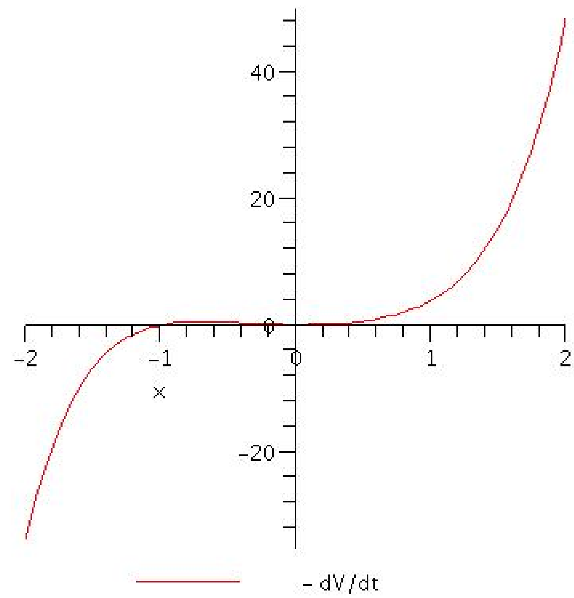
8. Exclude: Scaling experiment: I'll like to explore how scaling the problem affects the conditioning of the SOS solution. By conditioning, I mean, V=a^2 + 10^-9*b^2 is a non-negative function, but we have less confidence in its strict definiteness than in one in which the coefficients of a^2 and b^2 are closer in magnitude. The experiment in scaling was done to see if we can use this trick to guard against false positives (and possibly against false negatives if the time-scale variation in the given problem makes the program's work harder.)TO DO:WRITE UP SCALING STEPS. Results: Lyapunov function found. (INSERT) Scaling the problem by its eigenvalues did NOT improve the conditioning of the results. (Reconcile with the following results:

a	V
1	$0.61x^2 + 0.61y^2$
10	$0.095x^2 + 0.61y^2$
100	$0.00995x^2 + 0.61y^2$

for the test vector field $\begin{matrix} \dot{x} = -a * x \\ \dot{y} = -y \end{matrix}$) which show a significant dependence of the Lyapunov function conditioning on the ratio of the eigenvalues. Comment: The problem is with the way scaling is done here, which does not in fact change the system eigenvalues. The dilation in fast states could be useful in some contexts, but I don't know which.

9. Exclude: The original system has a phase portrait topologically equivalent to this one $\dot{x} = -x - x^2$, $\dot{y} = -y$, $\dot{z} = -z$, and$\dot{w} = -w$. (TO DO: Justify this. The brute-force way is to find the Jordan Normal form of the original system. QUICK COMMENT: Actually the normal form is not the right transformation to look for here; the near-identity transformation in a normal form establishes topological conjugacy (same qualitative behaviour in a neighbourhood of the origin) and not topological equivalence in a global sense, for which we need a linear transfomation (or perhaps just a continuous transformation? why or why not?) A not-so-brute-force way is to think about the phase portraits: in each we have two fixed points, one stable in all directions, and the other unstable in one direction. I would like to say that they're neccesarily topoligically equivalent. I can draw pictures to suggest this, but I will like to prove it.) Anyway, it's interesting to try to prove stability of this test system $\dot{x} = -x - x^2$. Although it's considerably simpler than the original problem, it has the following important features: it's quadratic in x, so we'll need to search Lyapunov functions of order higher than two, and it has an unstable fixed point, so I'll need to find V valid only in a subregion of phase-space. It has fixed points at x=0(stable) and x= -1(unstable), so I chose to search for a Lyapunov function valid on $x \in (-0.9, 0.9)$. The resulting fourth order Lyapunov function is $\approx 0.99x^2 - 0.37x^3 + 0.27x^4$.


V
10.0
7.5
5.0
2.5
0.0
−2
−1
0
1
2
x


40
20
0
−20
−2
−1
0
1
2
x
– dV/dt