Report on Sensitivity Analysis

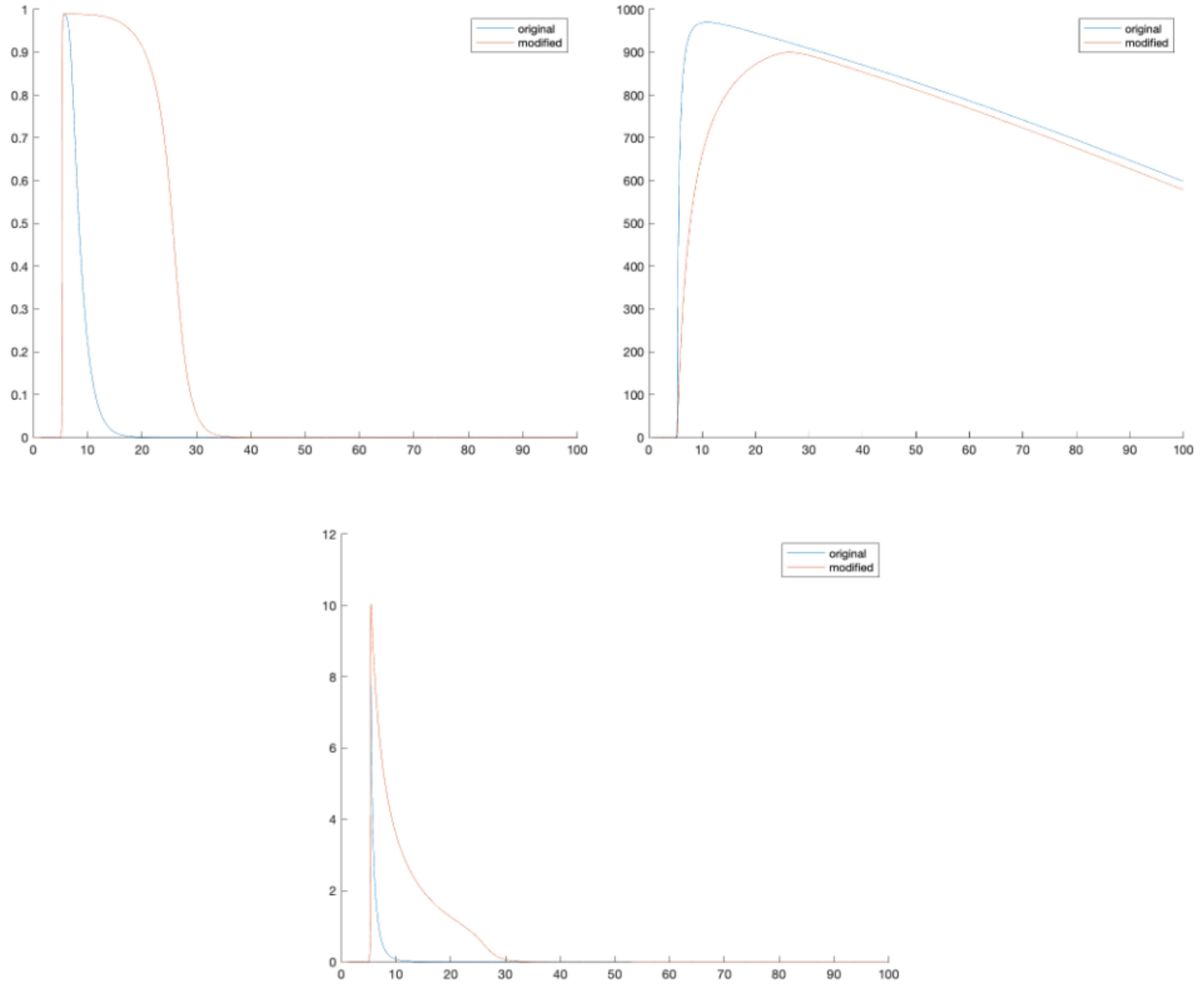
Zihan Zhang, Apr 16th 2022

Brute-force Approach

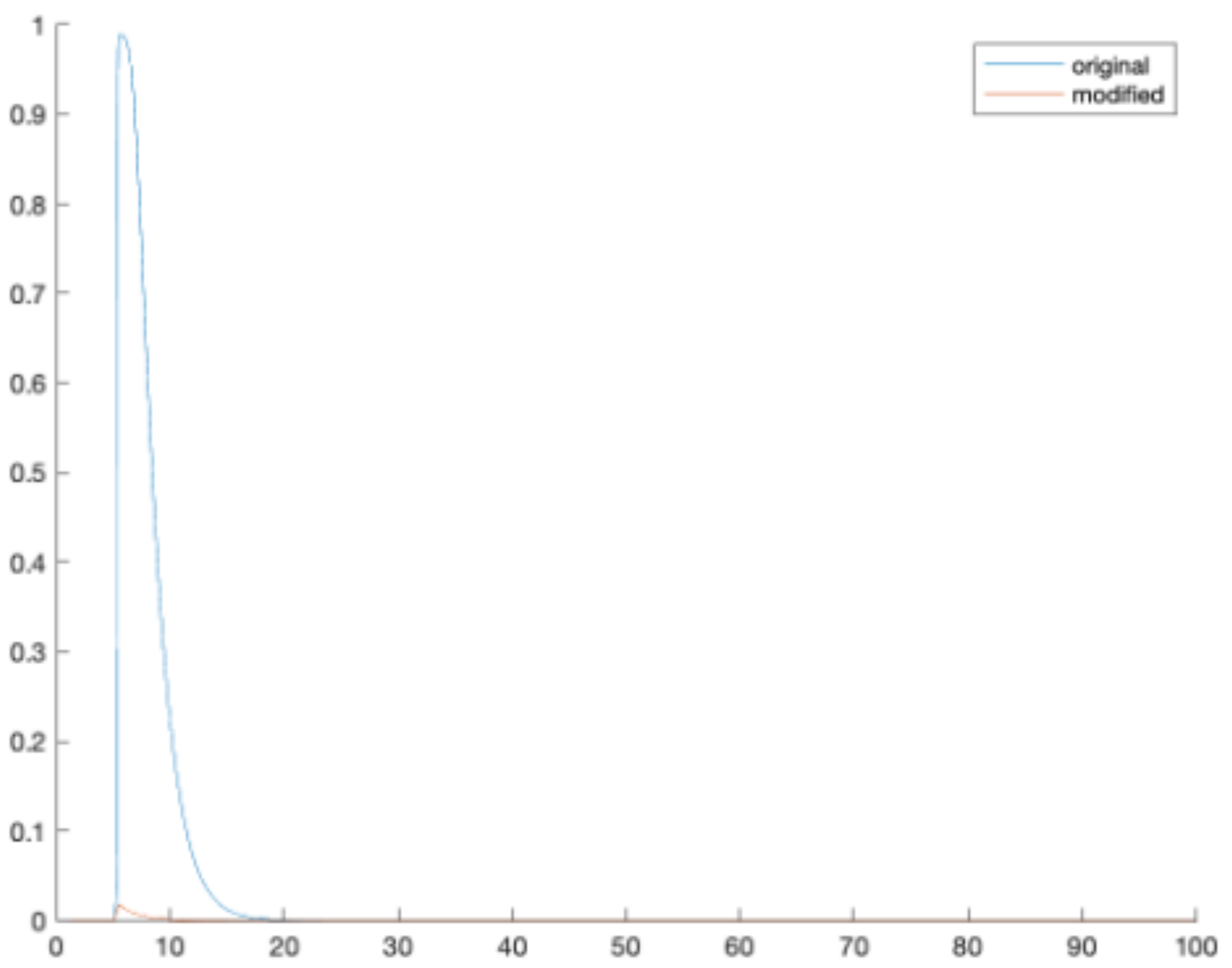
Parameter	
alpha	RyR luminal dependence factor
dryr	RyR Permeability constant
nryr	Number of RyR channels in a
csq	total concentration of CSQ
efflux	SS efflux time constant
refill	JSR refilling time constant
V_JSR	JSR volume
V_SS	Subspace volume
[BSL]Total	Total SL membrane buffer

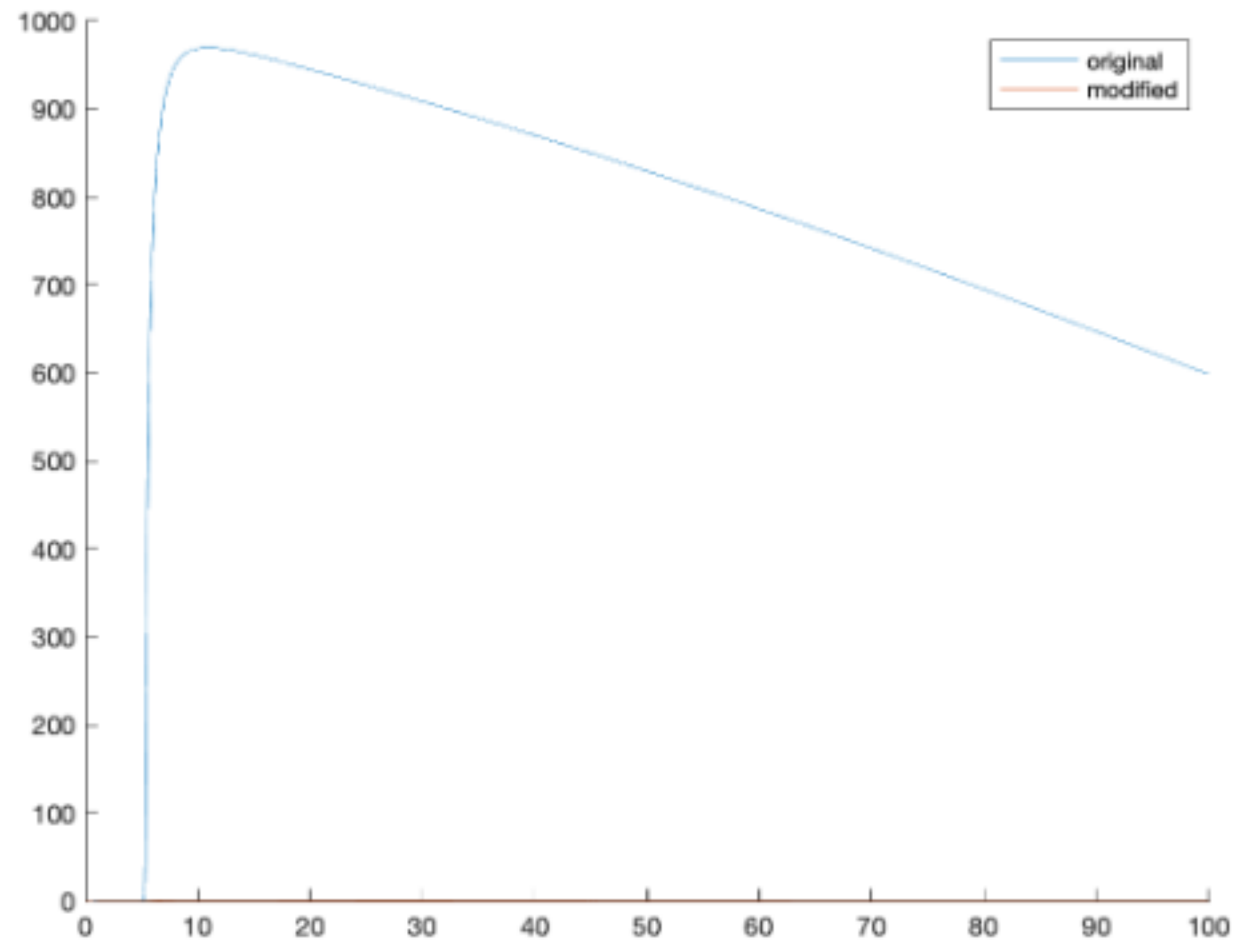
		2011 Model using 2002 Parameter				
		Change of Parameter (\times the original value)	Open Prob	Ca2+ Lumenal	Release Flux Subspace	
alpha	alpha1	6.86	0.01	0.00	0.00	
	alpha2		0.31	0.02	0.44	
dryr	alpha1	0.18	0.98	0.97	0.98	**Similar to nryr**
	alpha2		0.97	0.97	0.97	
nryr	alpha1	1.79	0.07	0.03	0.04	
	alpha2		0.10	0.04	0.40	
csq	alpha1	0.33	0.28	0.37	0.60	
	alpha2		0.27	0.41	0.54	
kmax	alpha1	0.86	0.05	0.01	0.01	
	alpha2		0.14	0.01	0.16	
efflux	alpha1	0.39	1.00	1.00	1.00	
	alpha2		0.96	0.99	0.60	
refill	alpha1	1.54	0.00	0.08	0.01	
	alpha2		0.02	0.09	0.05	
V_JSR	alpha1	10.00	4.61	0.07	8.39	**Opposite direction to V_ss**
	alpha2		103.22	0.07	52.45	
V_SS	alpha1	0.10	4.61	0.07	8.39	
	alpha2		103.22	0.07	52.45	
[BSL]Total	alpha1	1.25	0.00	0.00	0.00	
	alpha2		0.29	0.01	0.30	

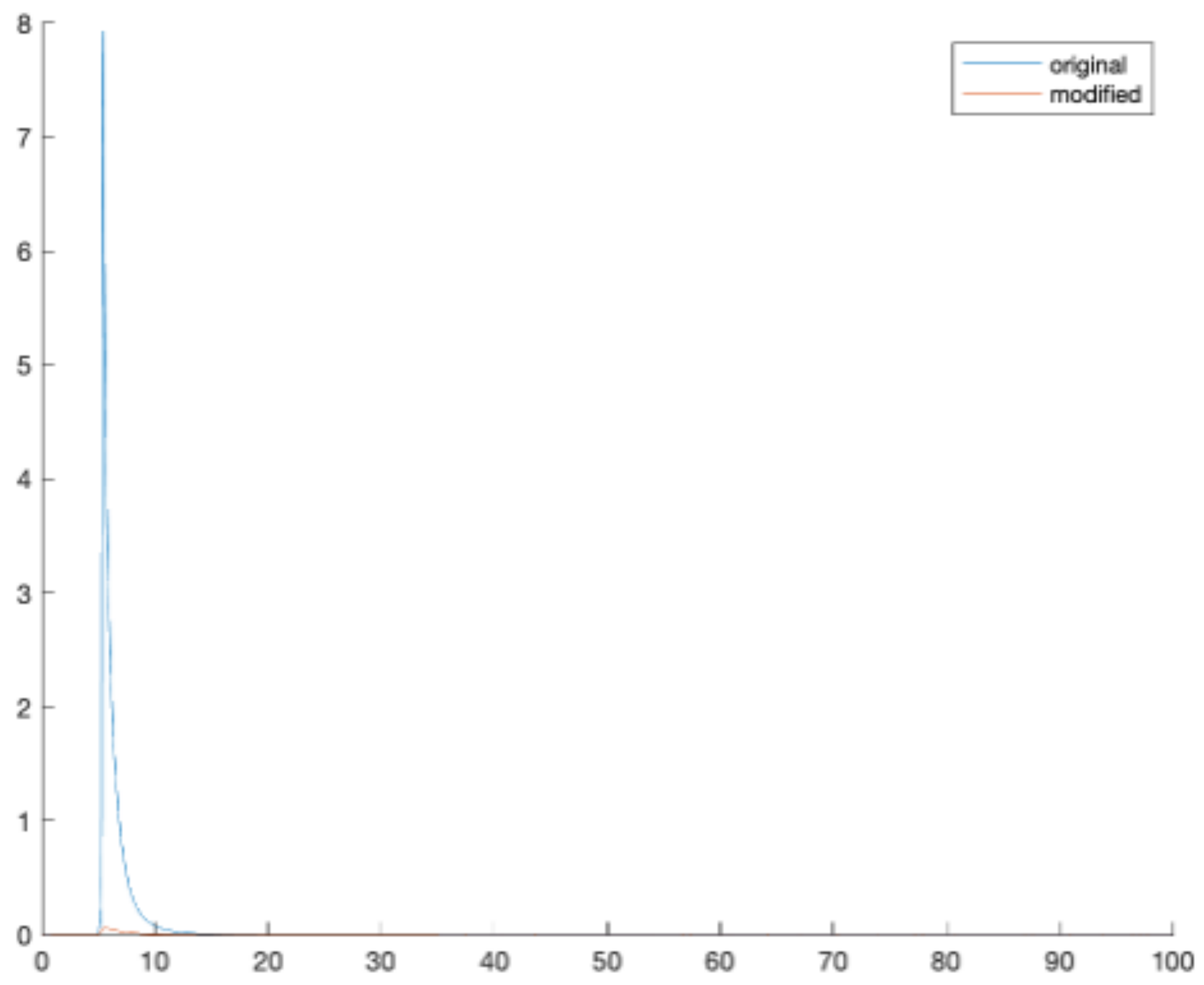
- Ex: V_jsr Graph



Use 2002 Parameter run 2011 Model			
alpha1	**0.99**	**1.00**	**0.98**
alpha2	0.65	1.00	1.83

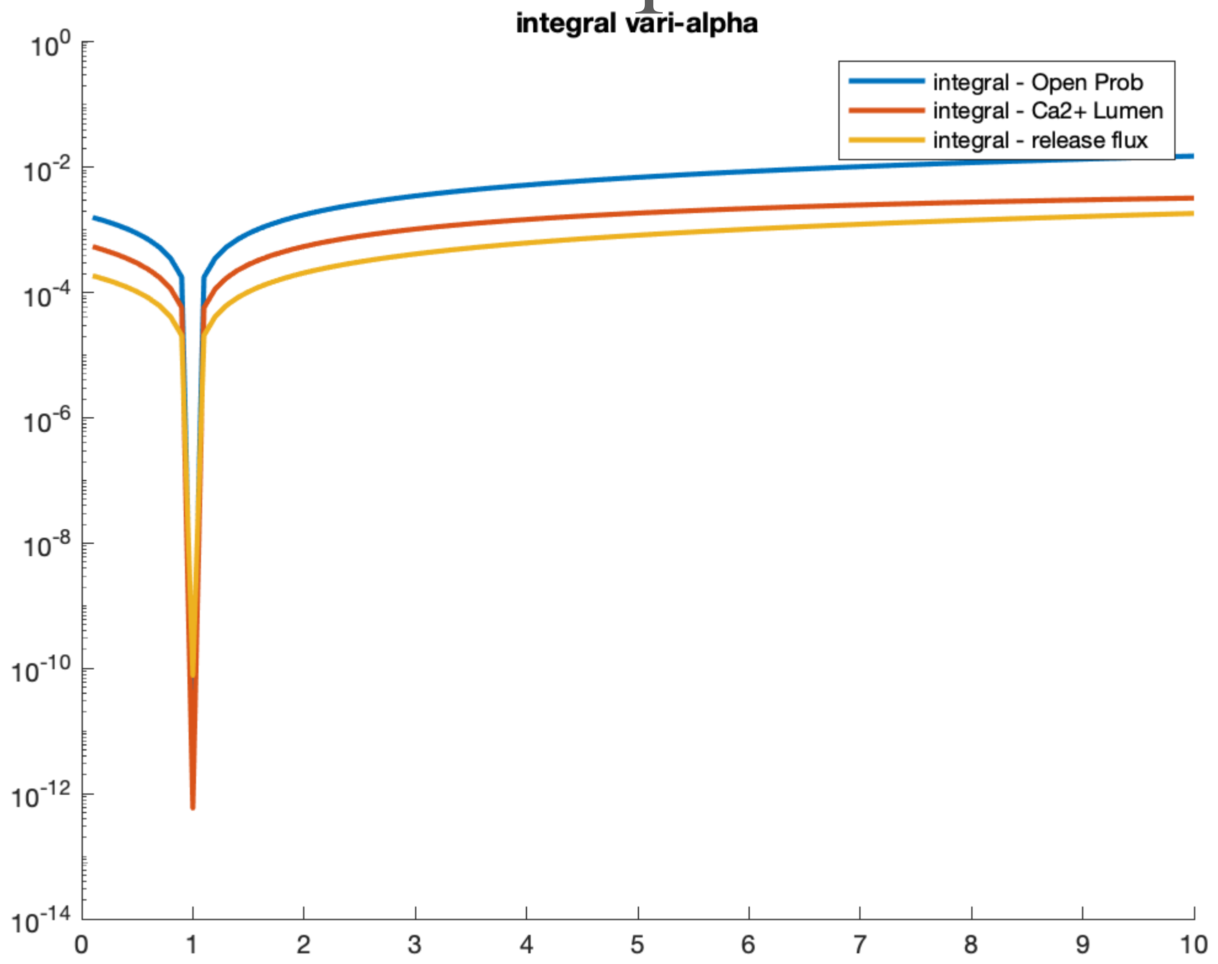




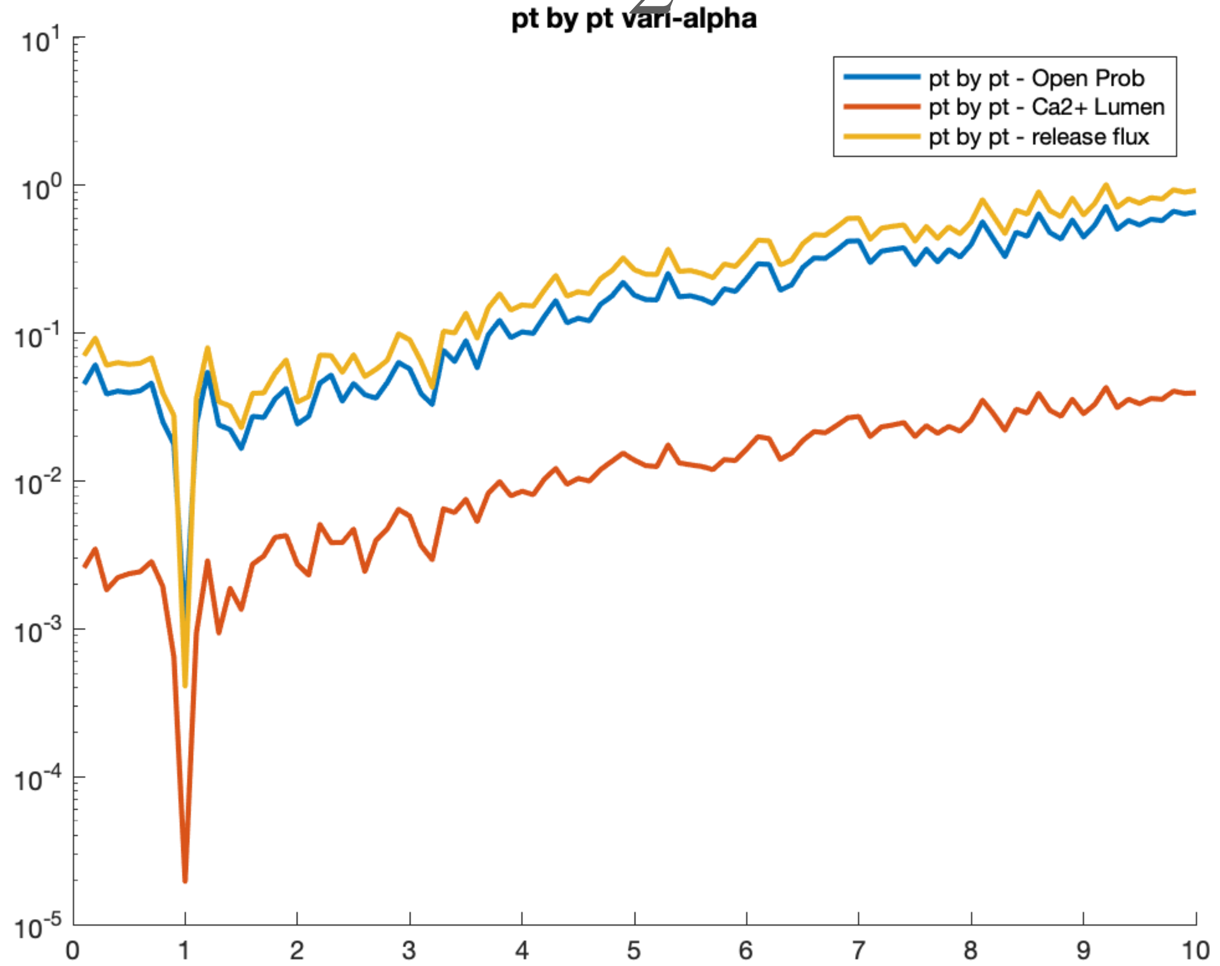


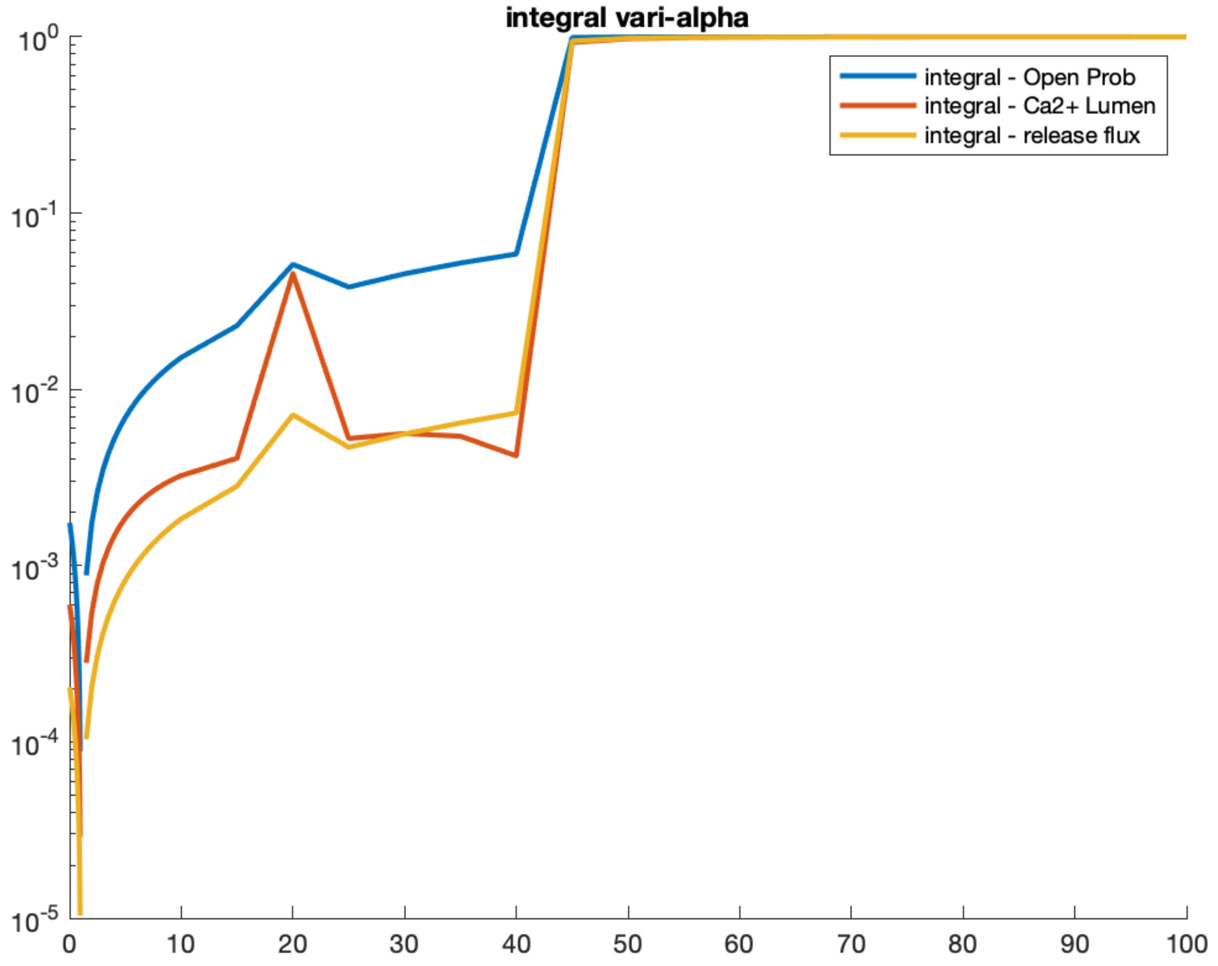
α

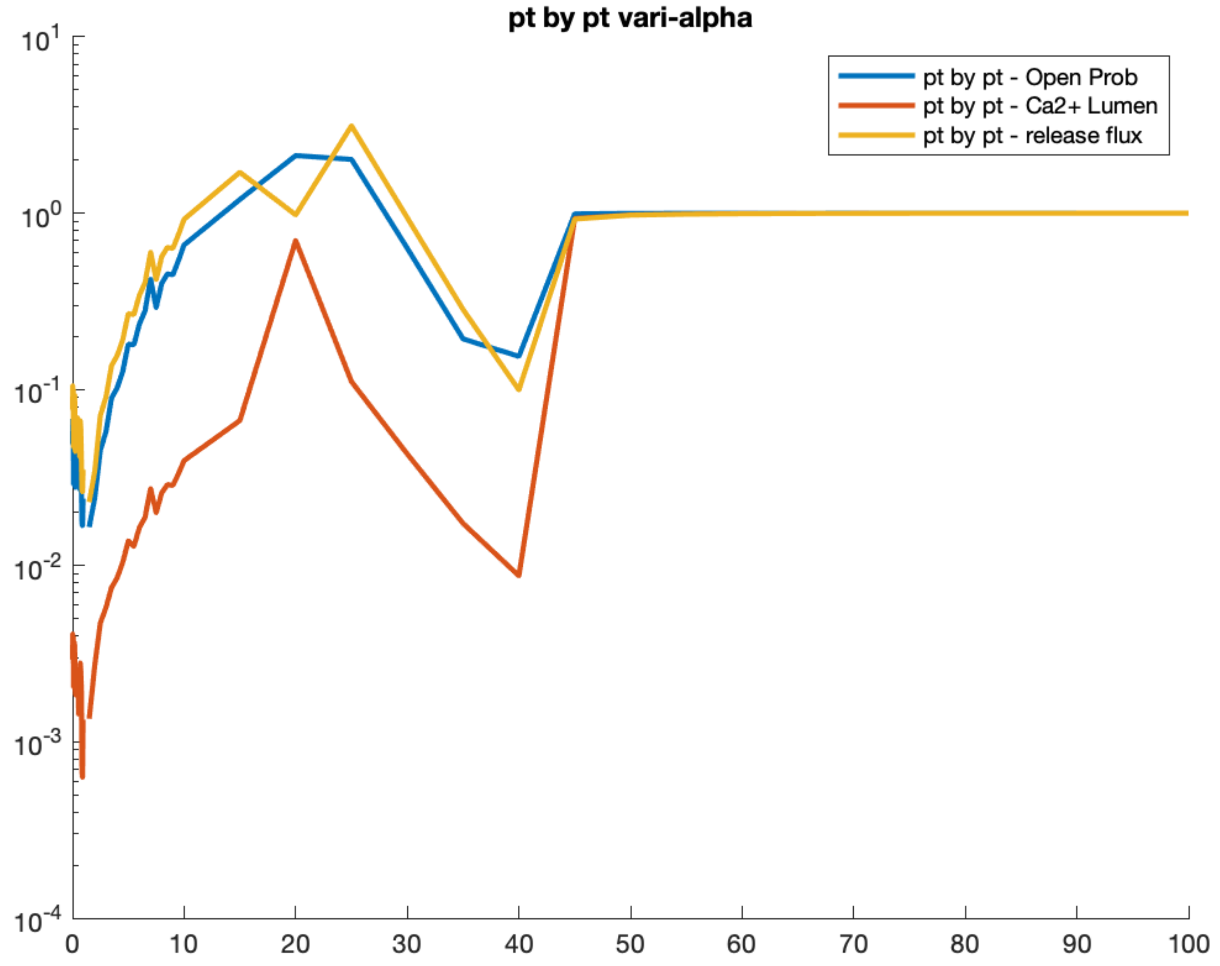
α_1



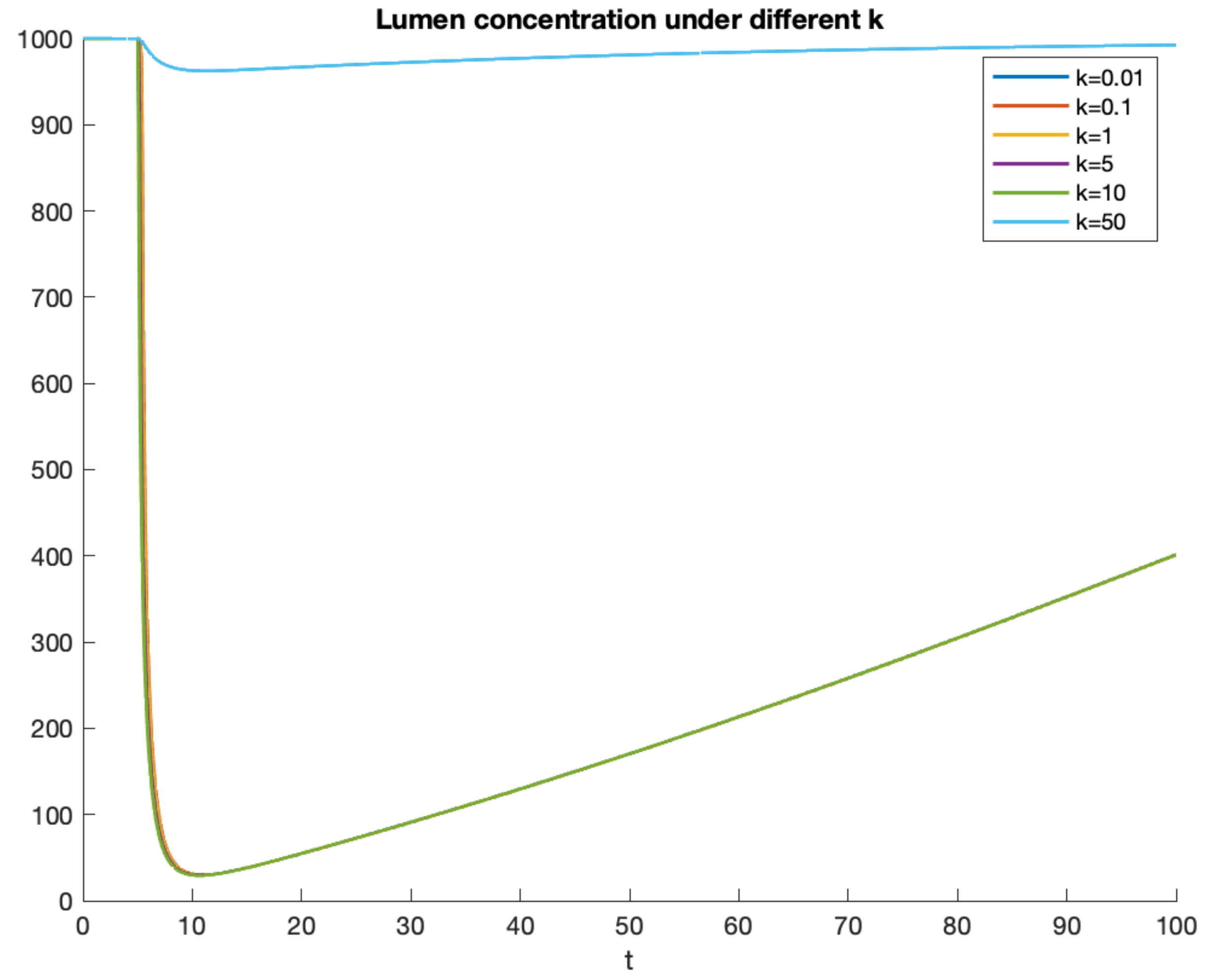
α_2







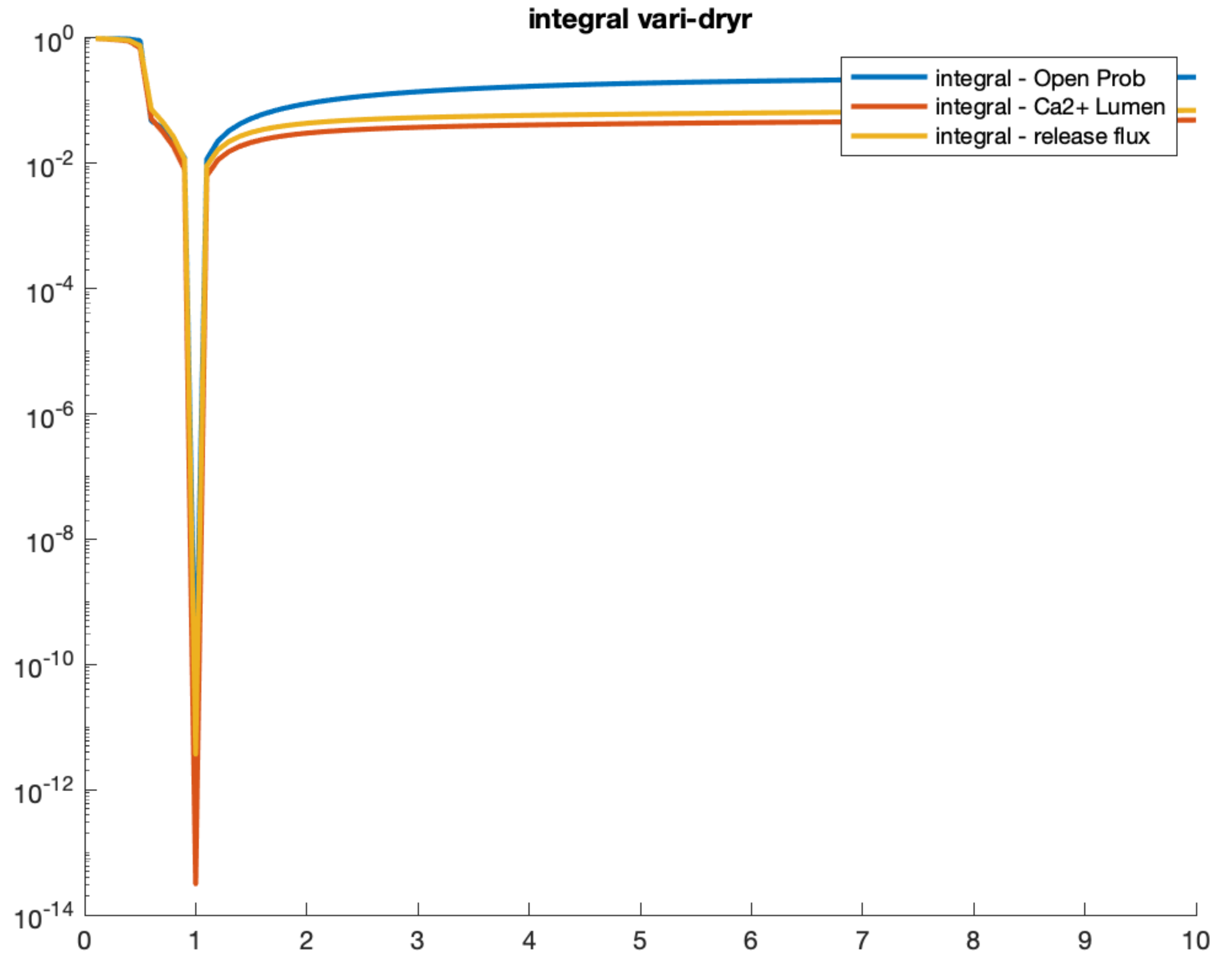
- Insensitive in when k is 0.01~10.
- Achieve local minimum of error when k≈40 (not monotonic).

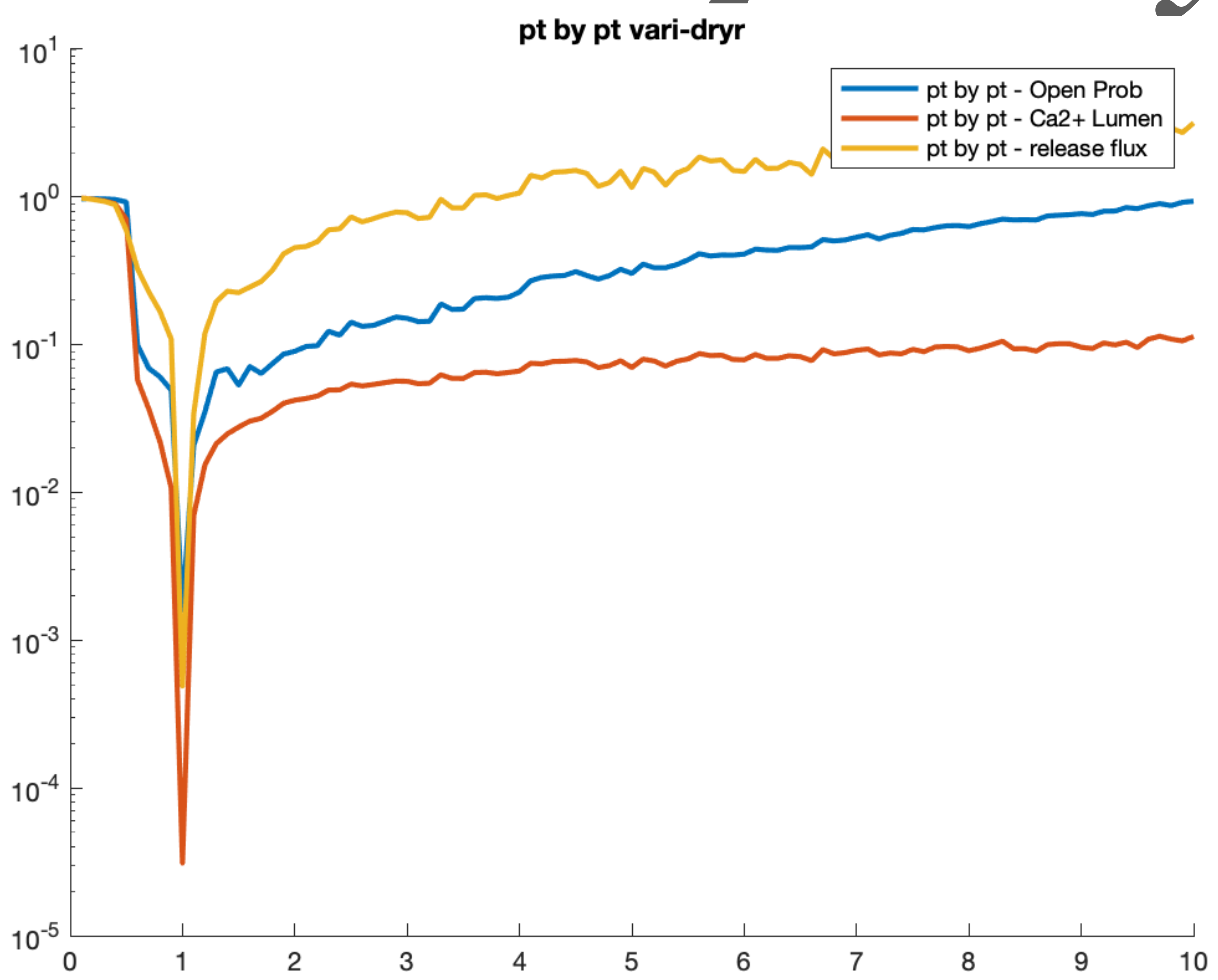


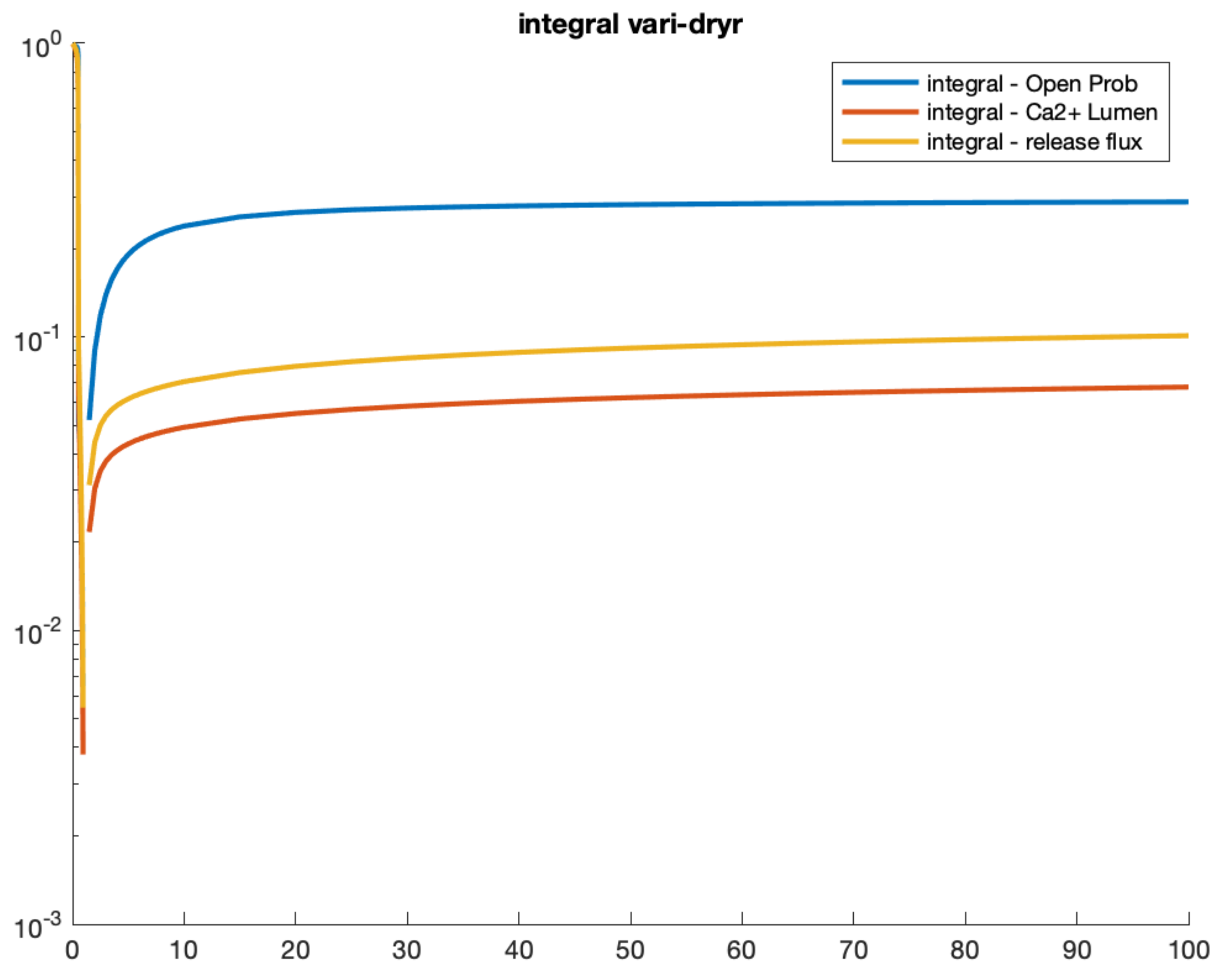
- Indistinguishable (very stable) at beginning, but blows up (shrinks to 0) when k≈50.

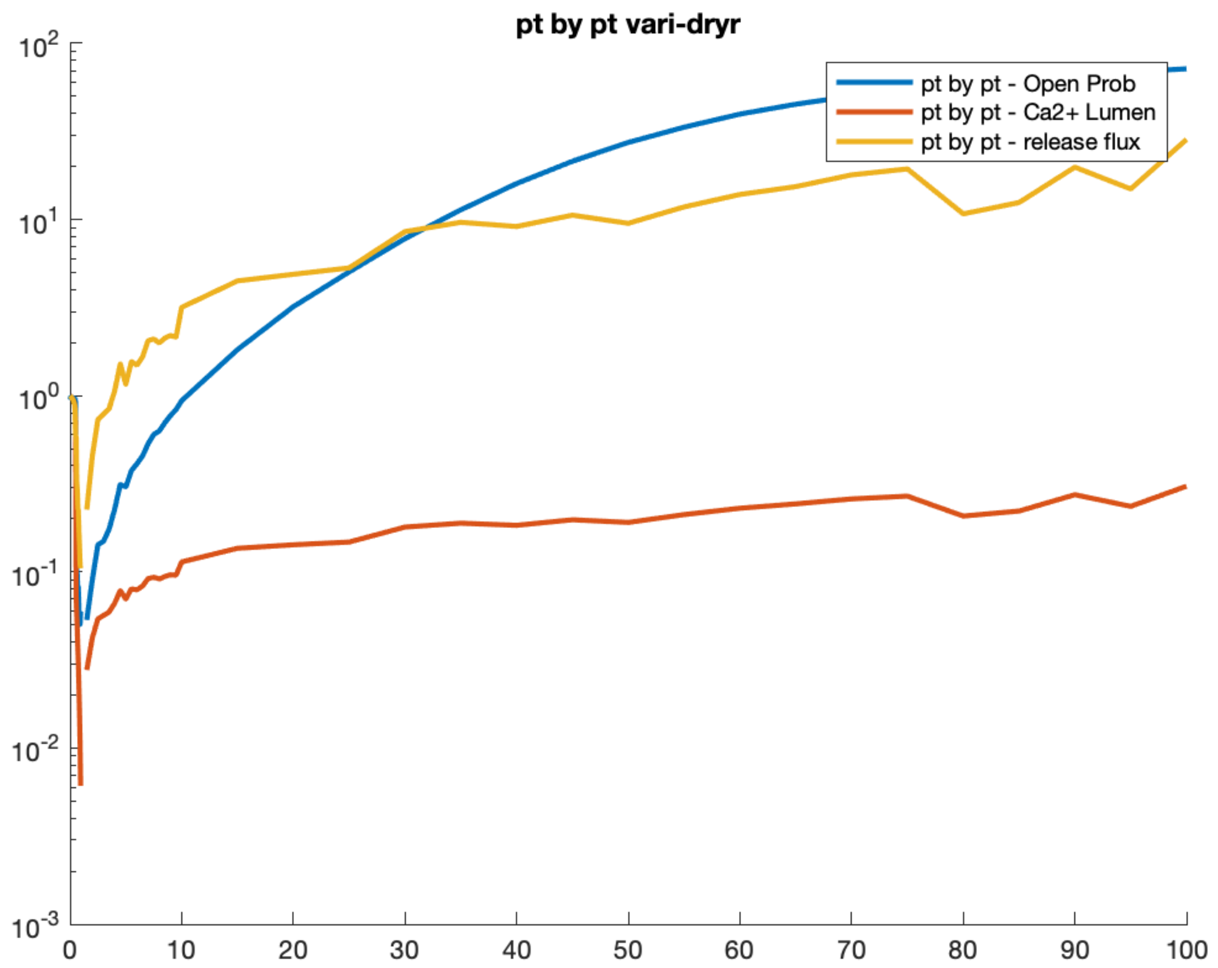
D_{RyR}

α_1 α_2

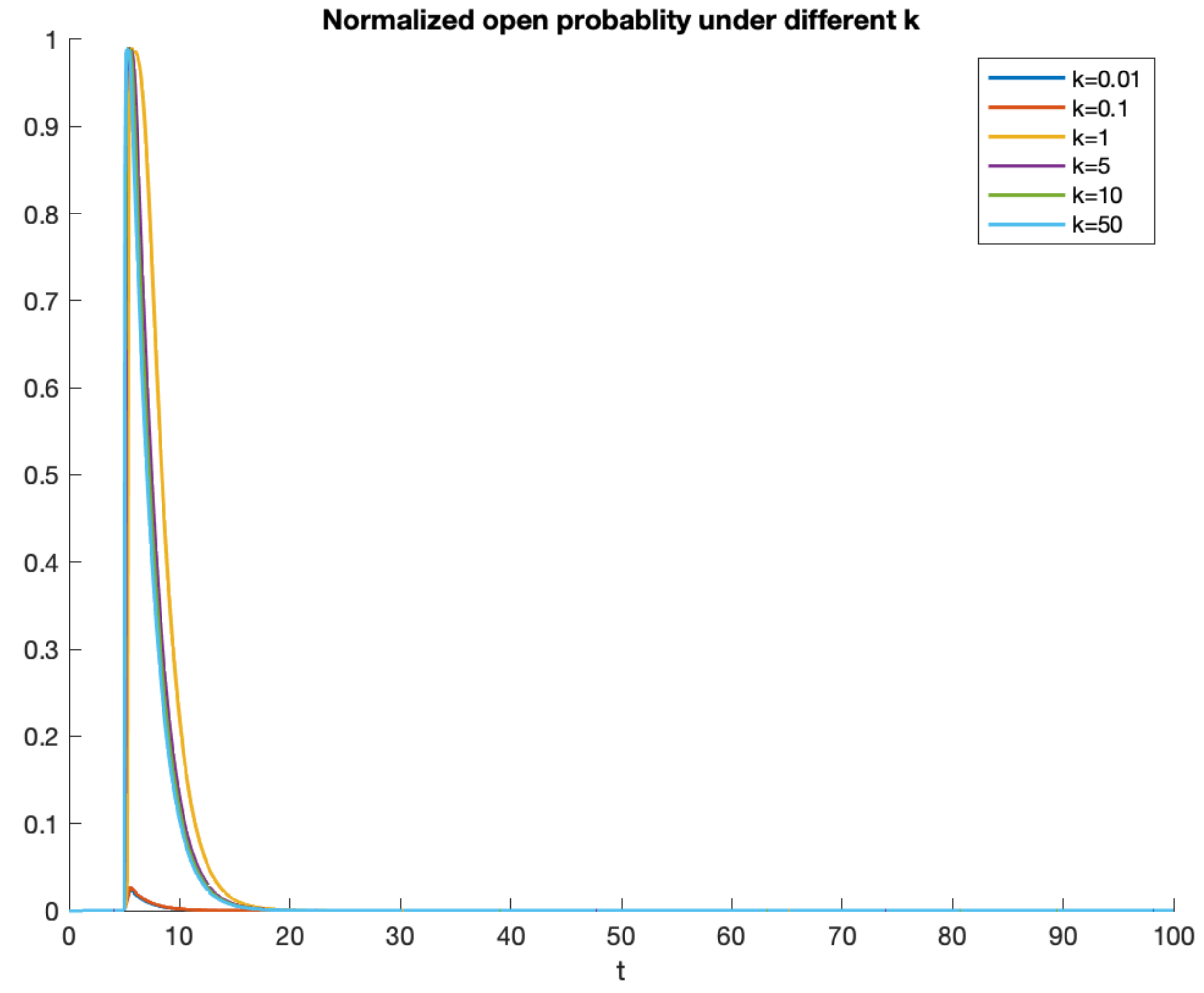






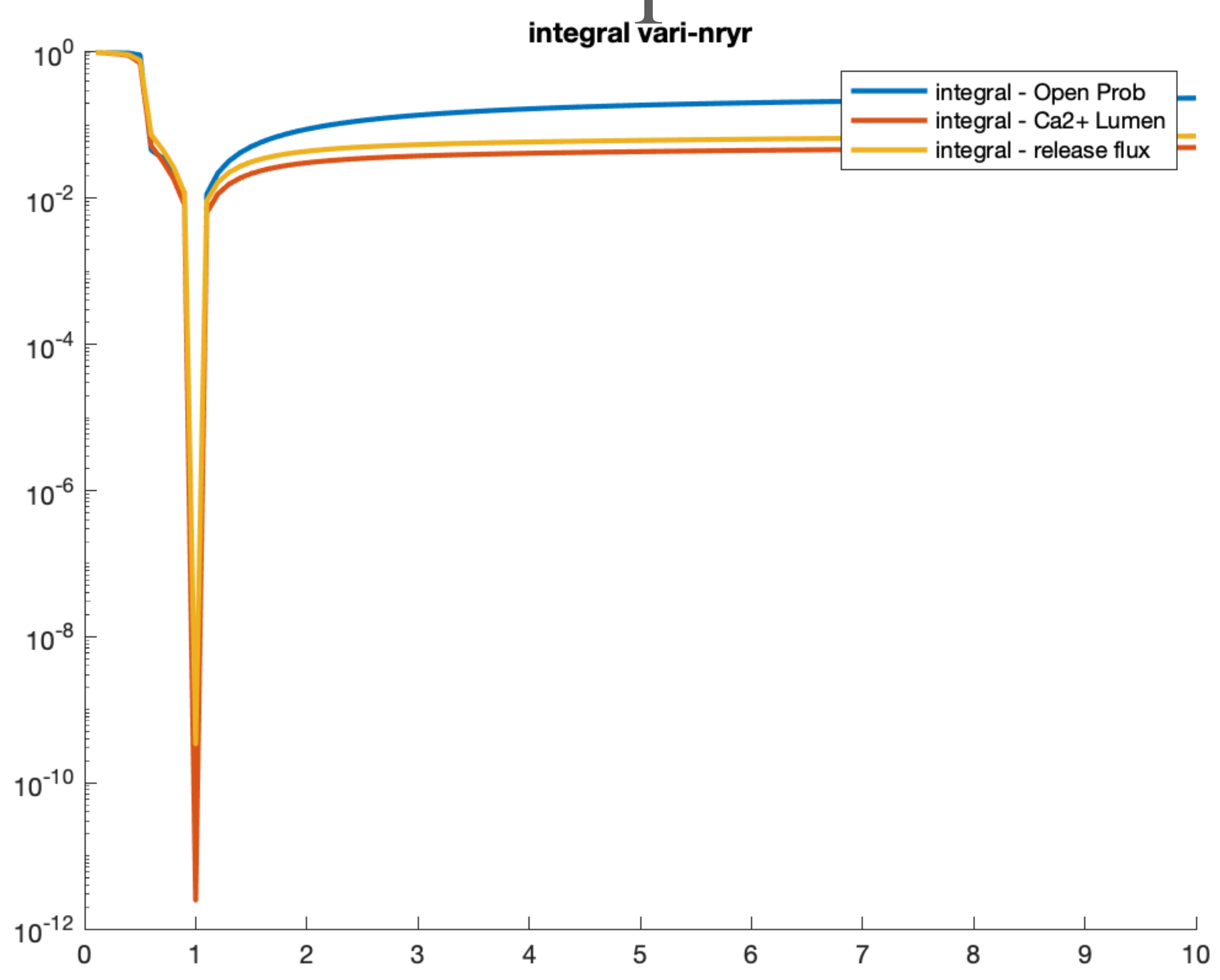


- Sensitive except when k≈1. When k grows, the contour gradually expands and then shrinks. For instance, the outermost boundary is when k≈1 for the normalized open probability.

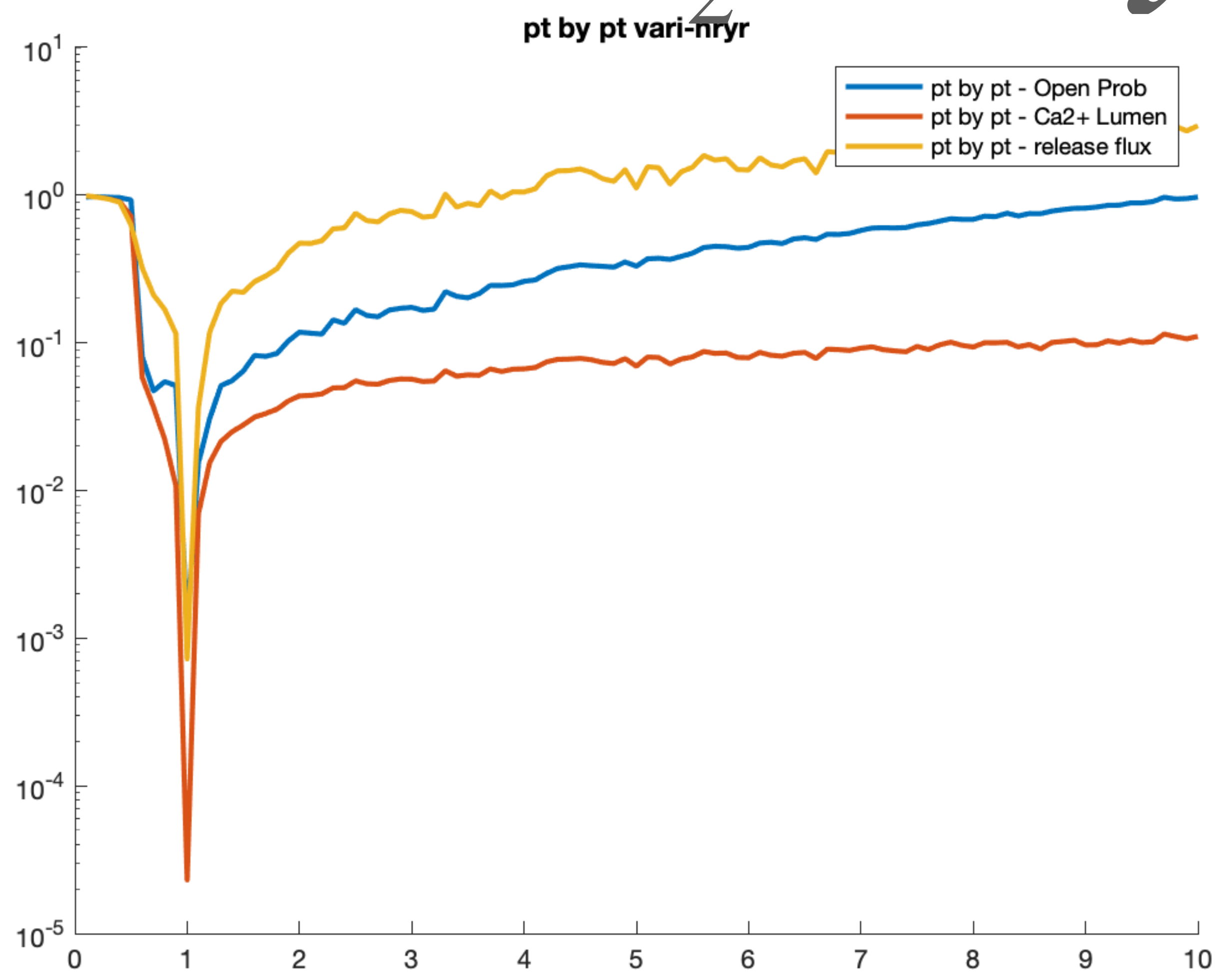


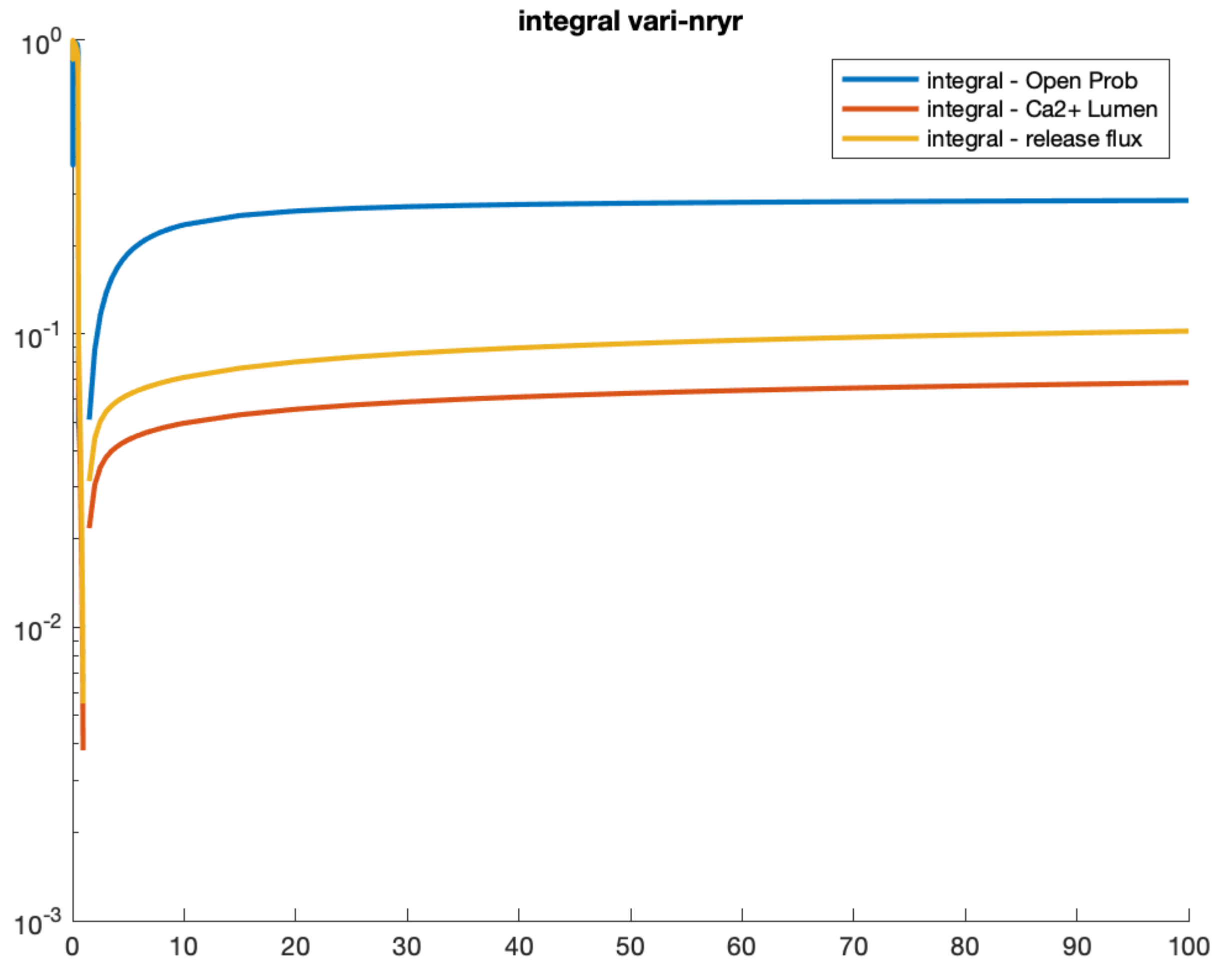
N_{RyR}

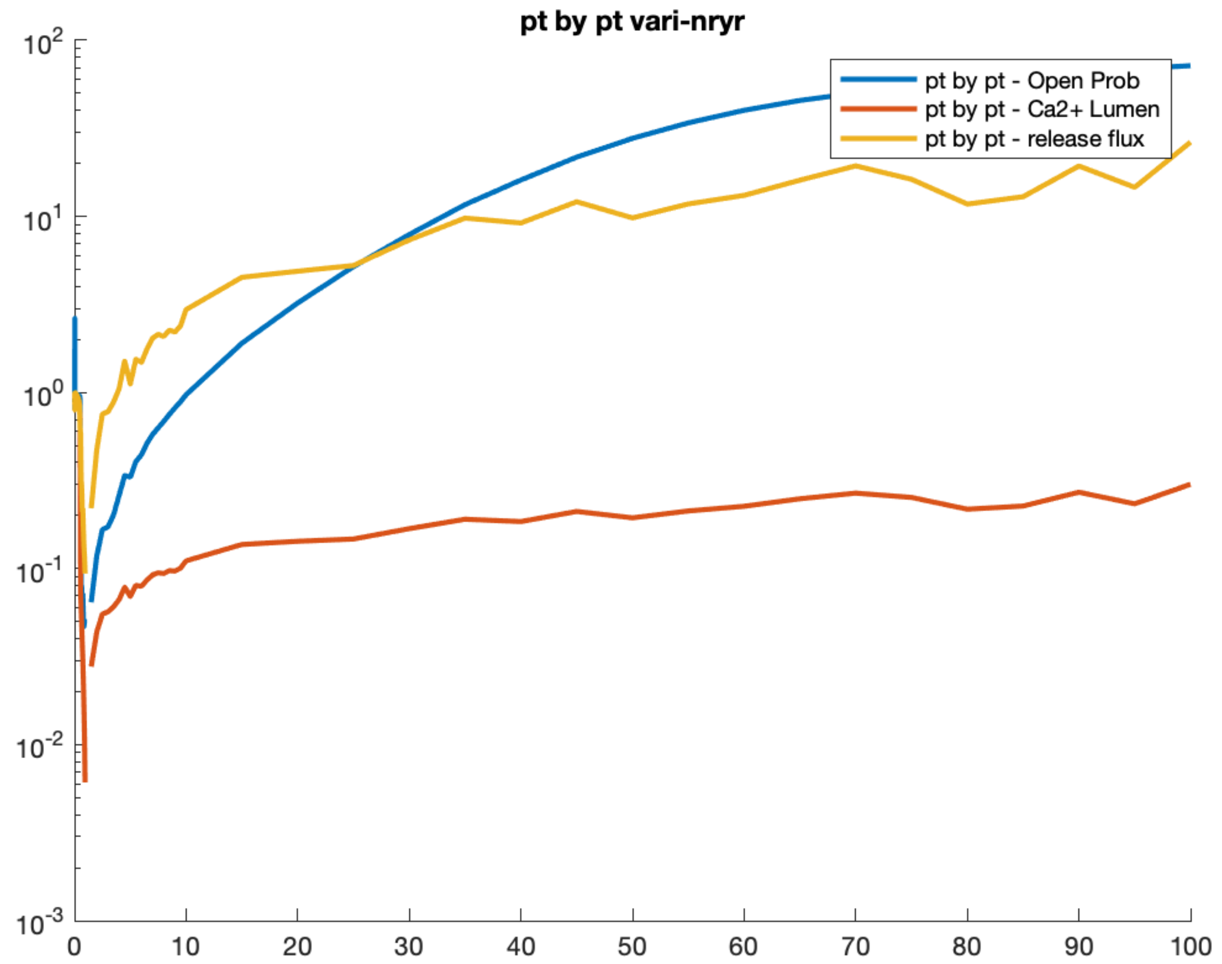
α_1



α_2







- Have a very similar pattern to D_{RyR} (RyR Permeability constant). Both involved in calculation:

$$J_{release} = \sum_{j-1}^{N_{RyR}} RyR_{open}^{j} J_{RyR}$$

$$J_{RyR} = \frac{D_{RyR}}{V_{SS}}([Ca^{2+}]_{JSR} - [Ca^{2+}]_{SS})$$

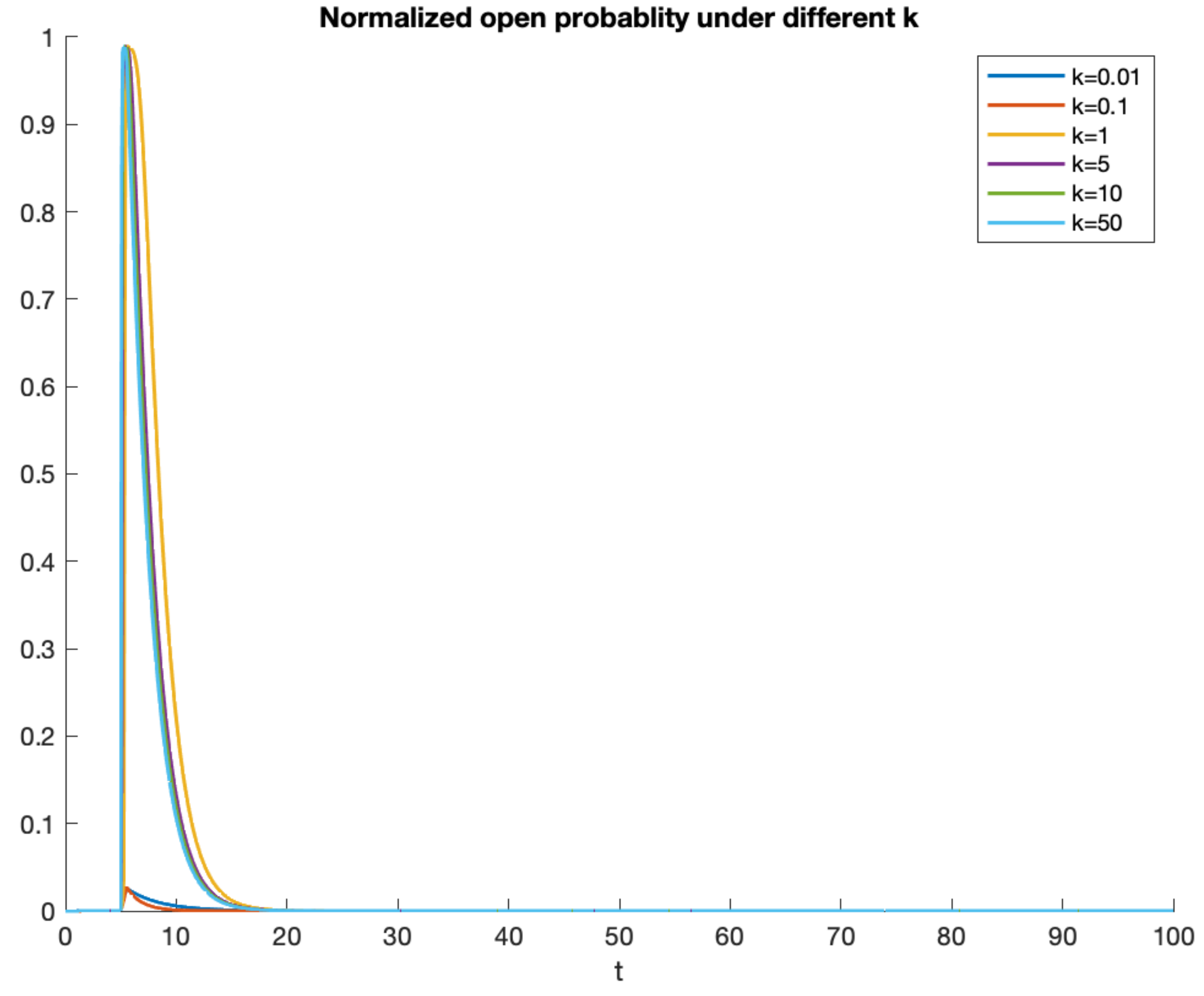
- However, not exactly identical, since N_{RyR} also involves in the calculation of allosteric coupling and the time derivative of open probability:

$$CF_{open} = K_{coup}^{(2N_{open}+1-N_{RyR})}$$

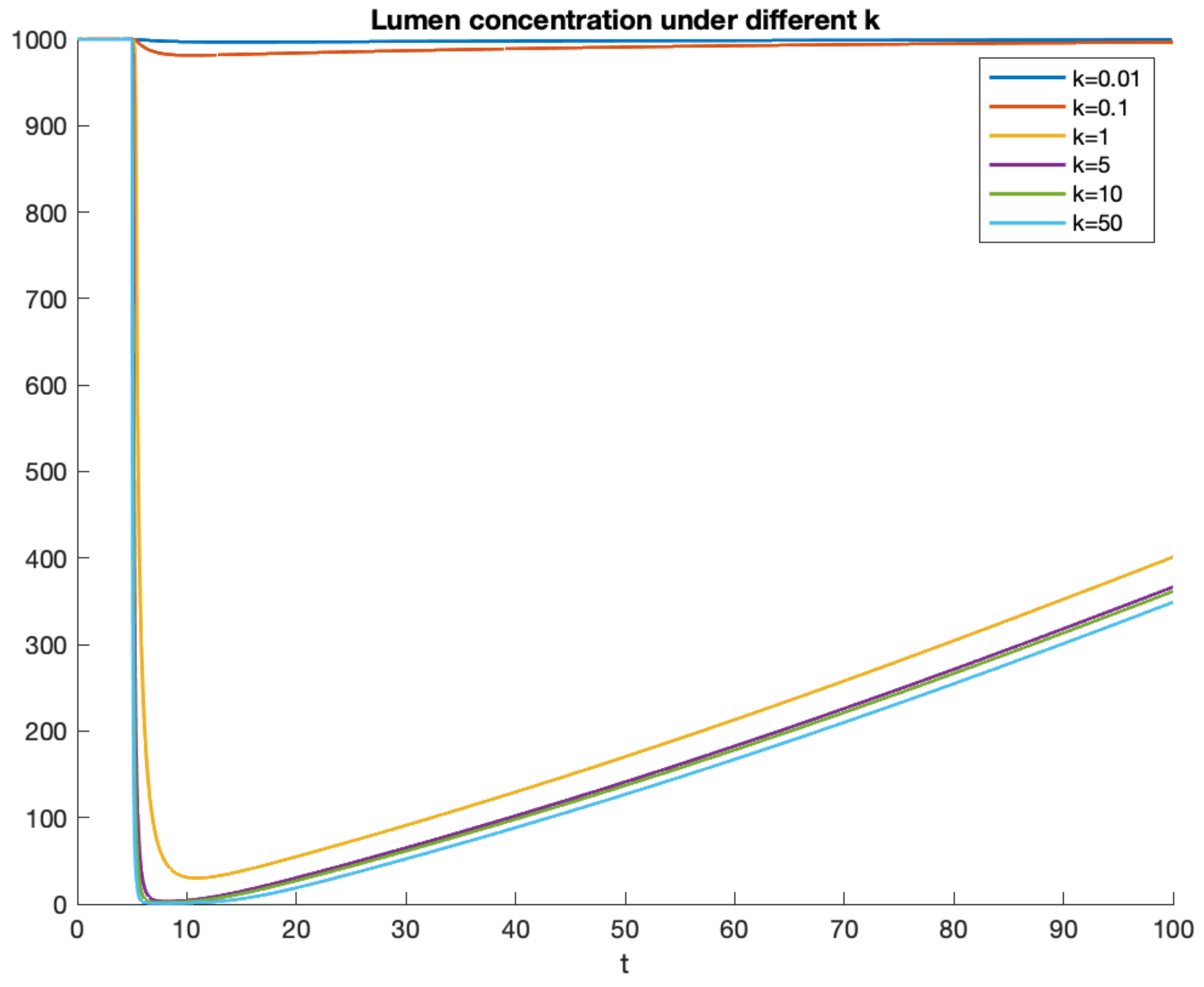
$$CF_{close} = K_{coup}^{(2N_{closed}+1-N_{RyR})}$$

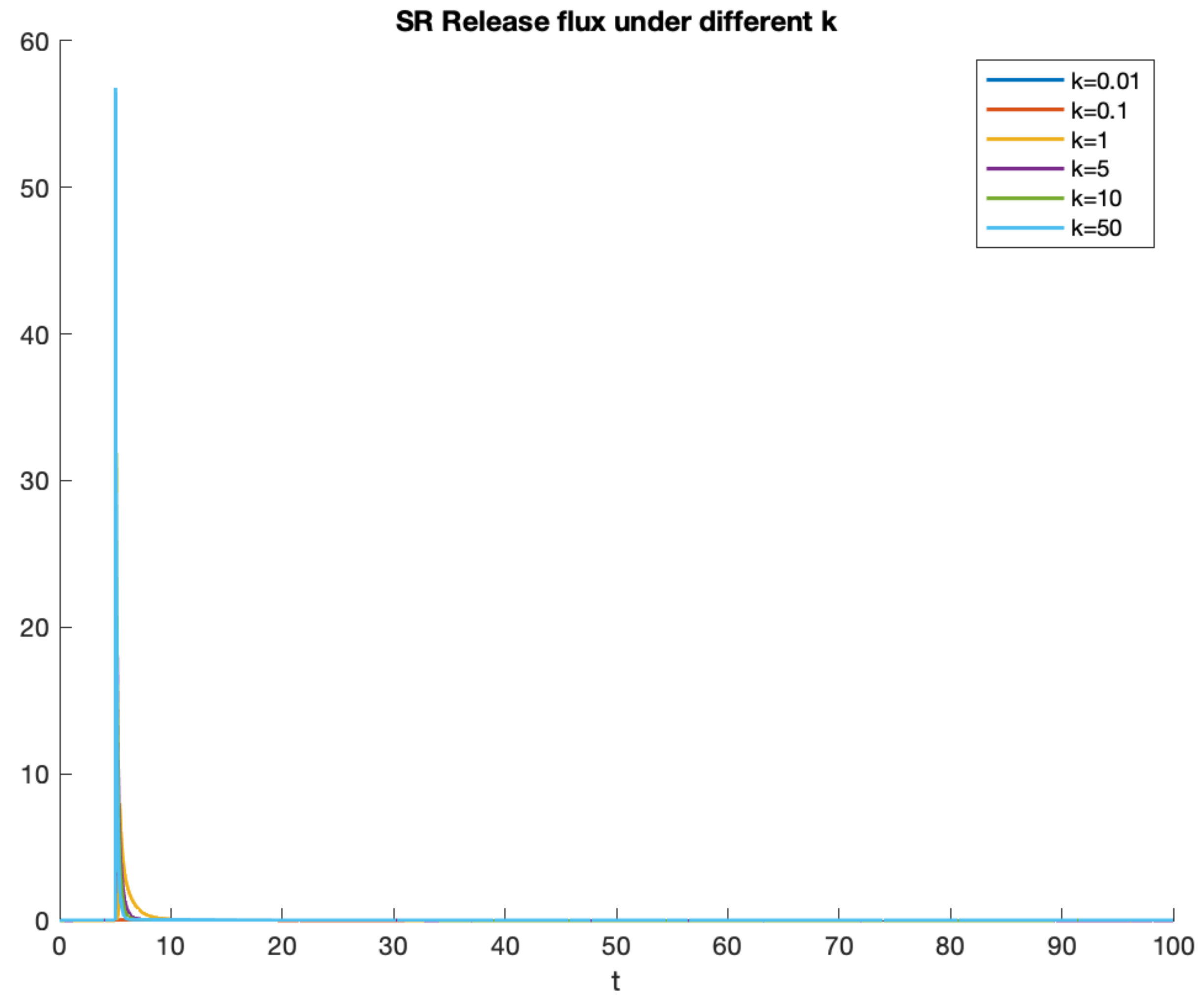
N_{RyR}

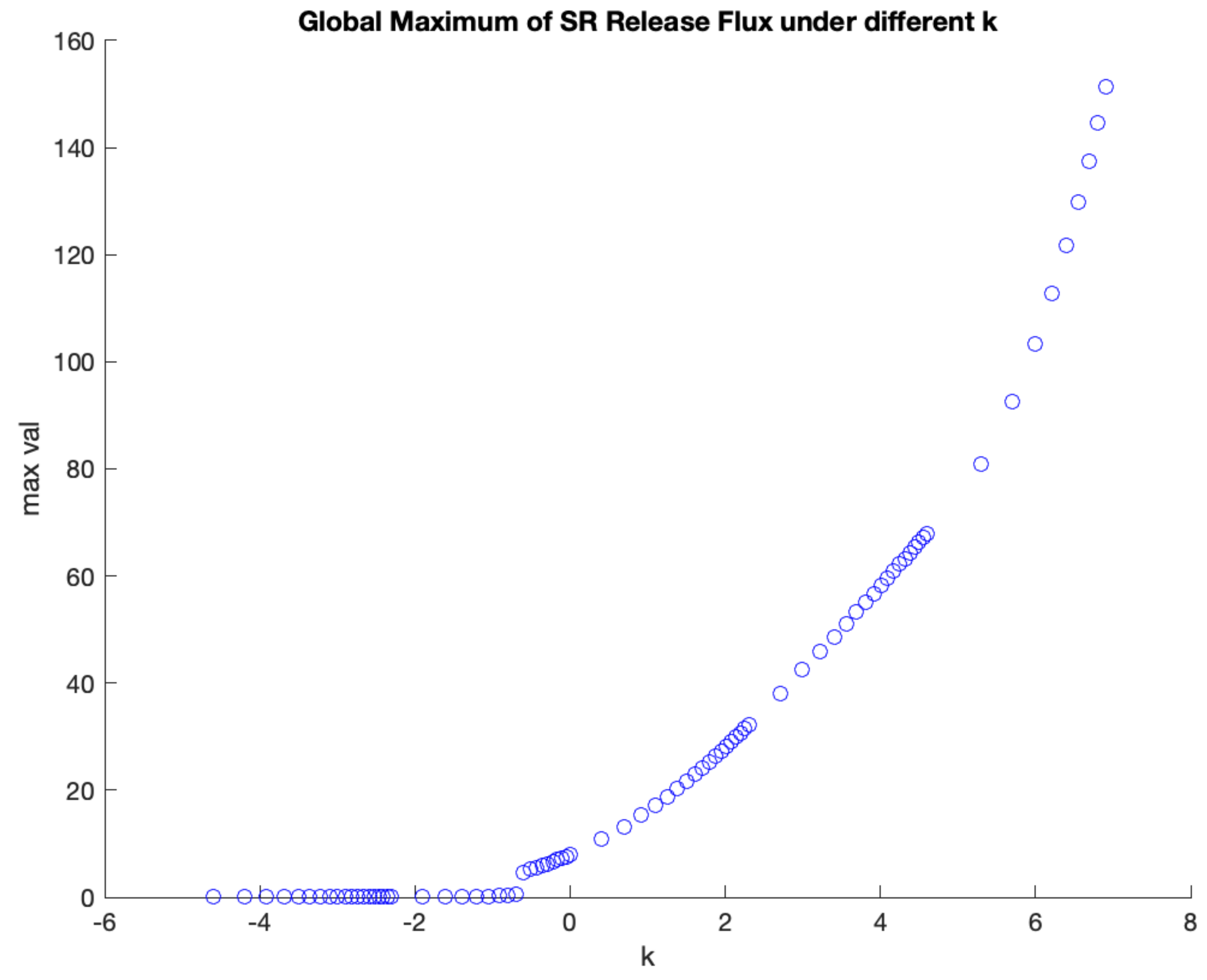
α_1



α_2



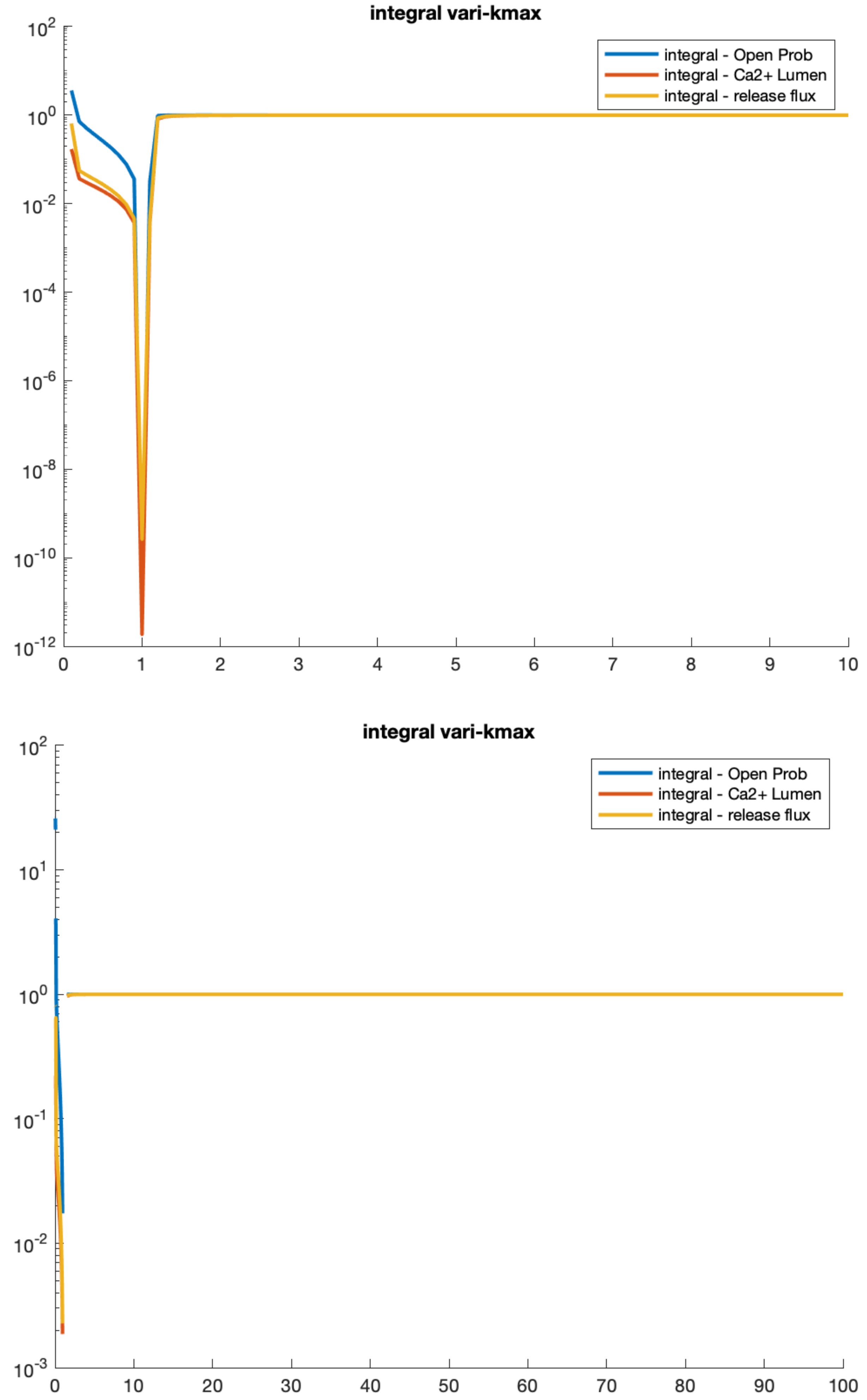




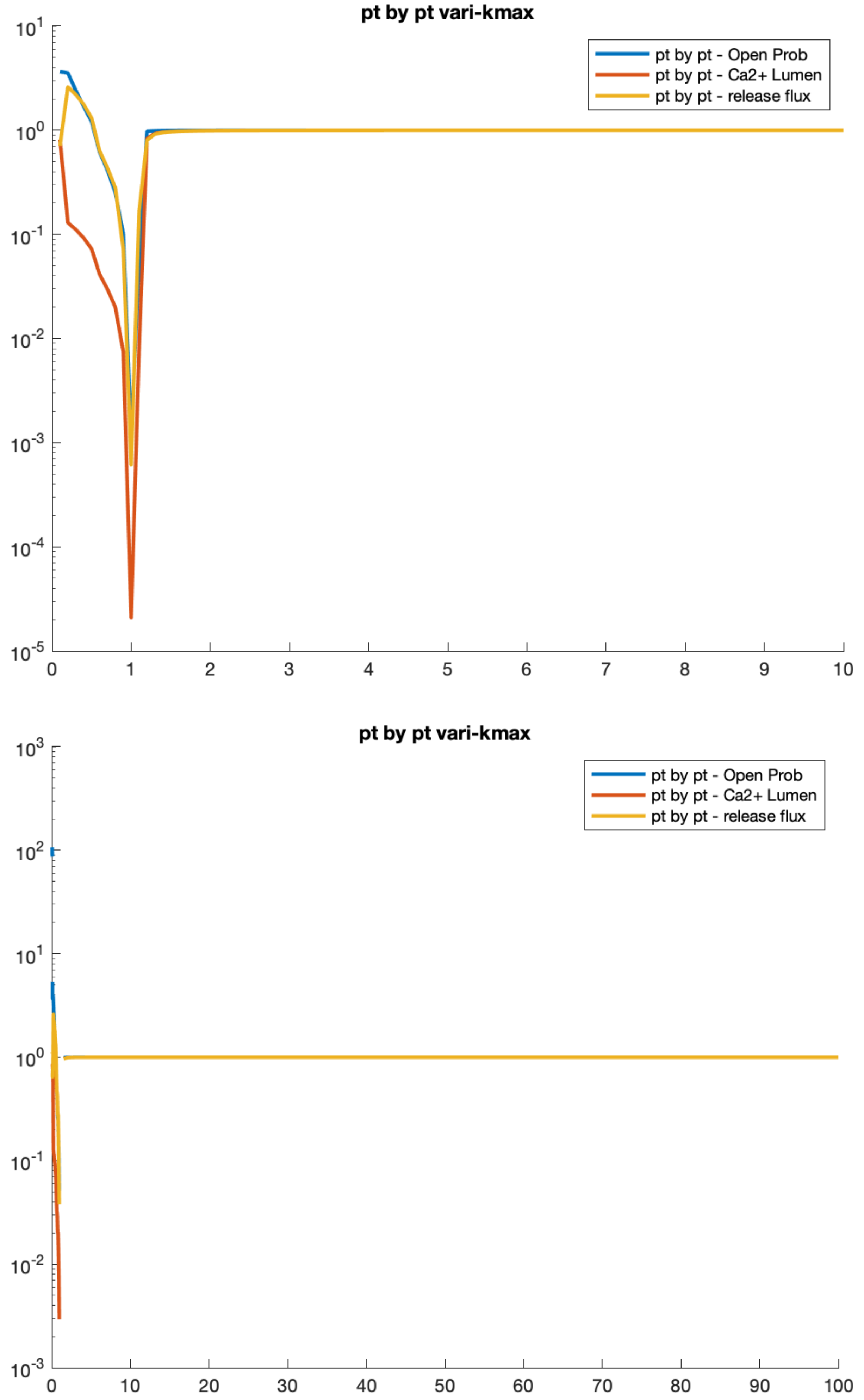
- k≈1 is the outermost frontier for open probability, but not for lumenal Ca2+ concentration, which could reduce to 0 if k is large enough.
- The global maximum of SR release flux does not converge when k (>1) increases, but the overall termination time decreases, so the total flux is genuinely consistent.

K_{max}

α_1



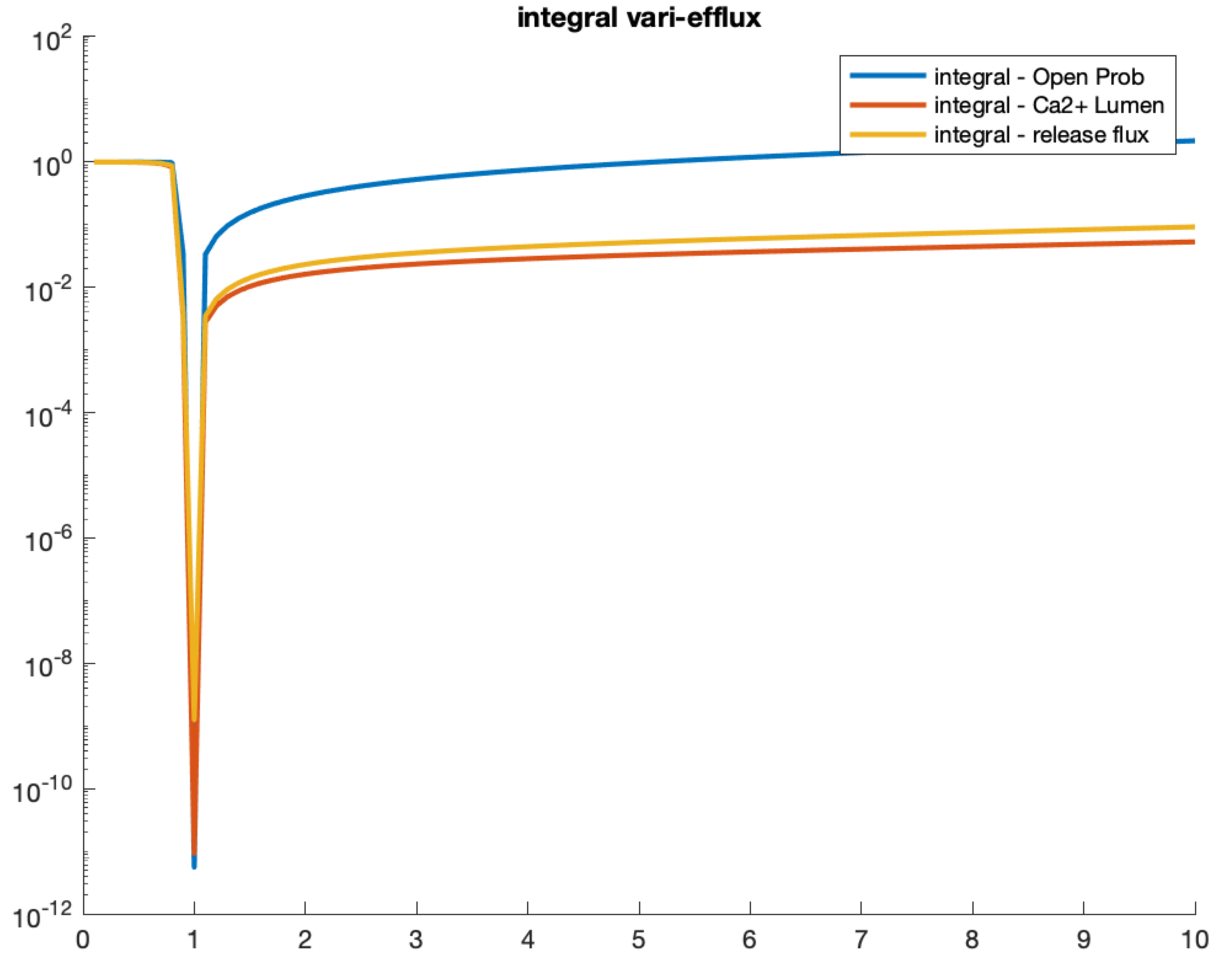
α_2

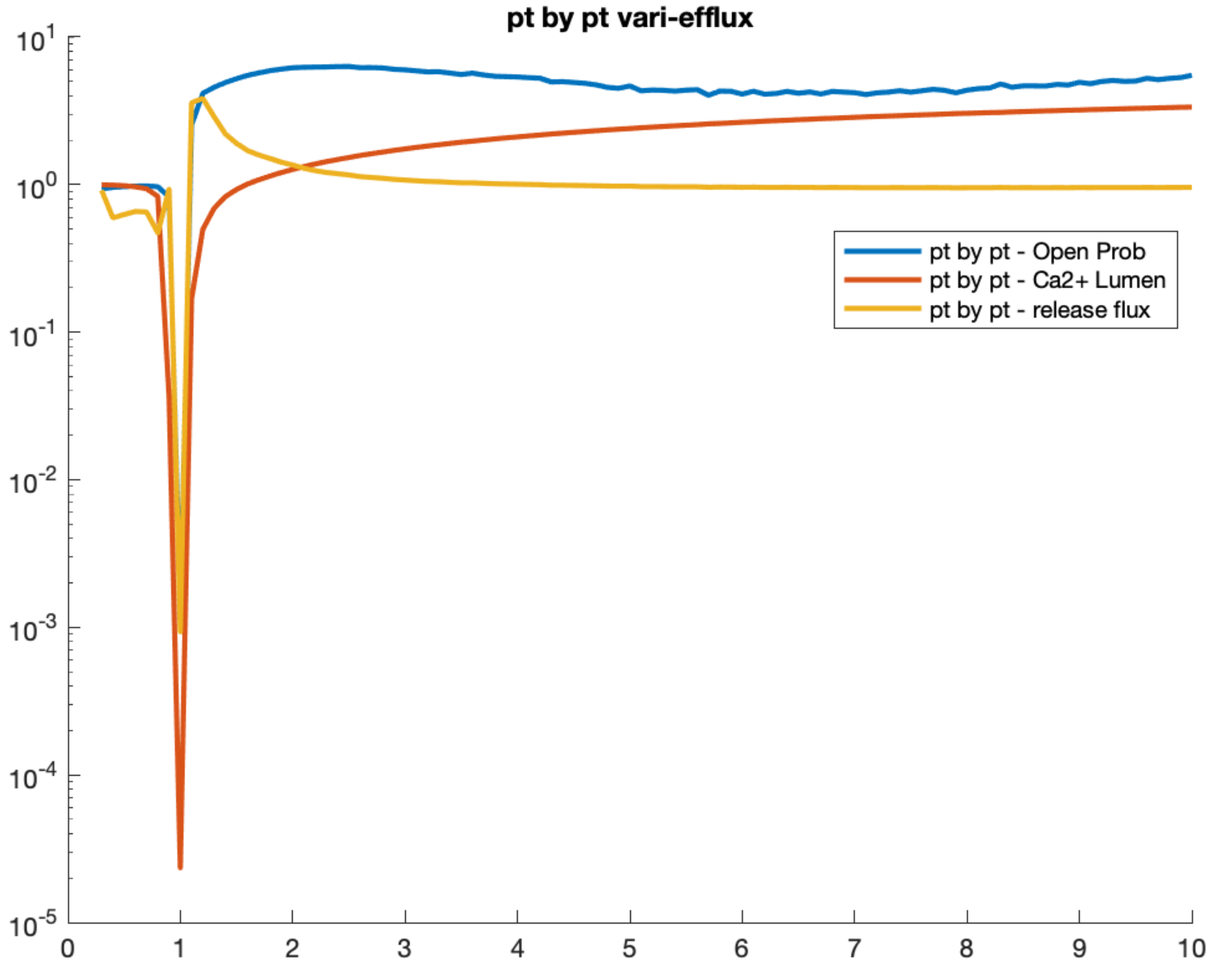


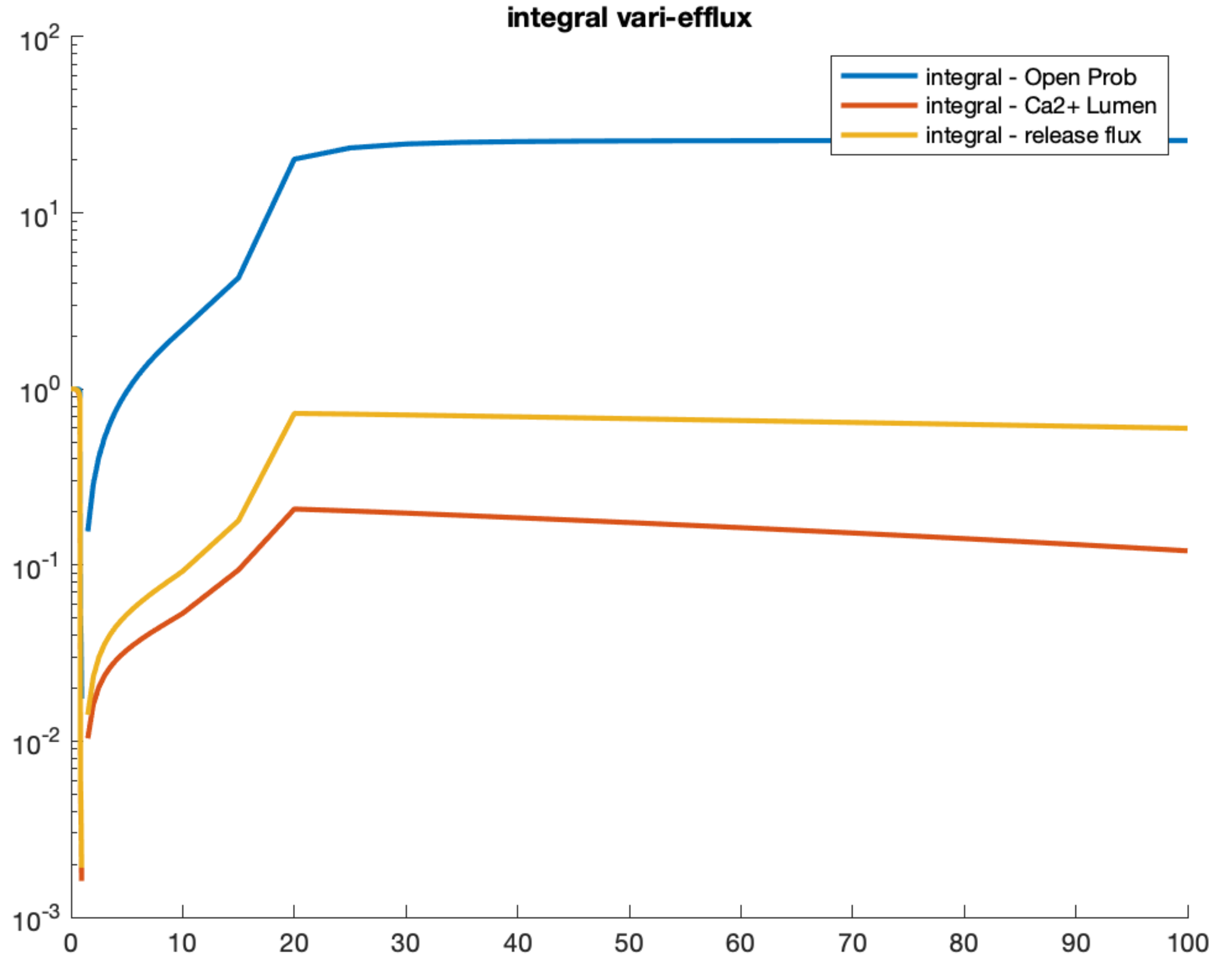
- Very sensitive. Results easily blow up when k is not around 1. Consistent with its definition as *sensitivity of opening to subspace [Ca]*.

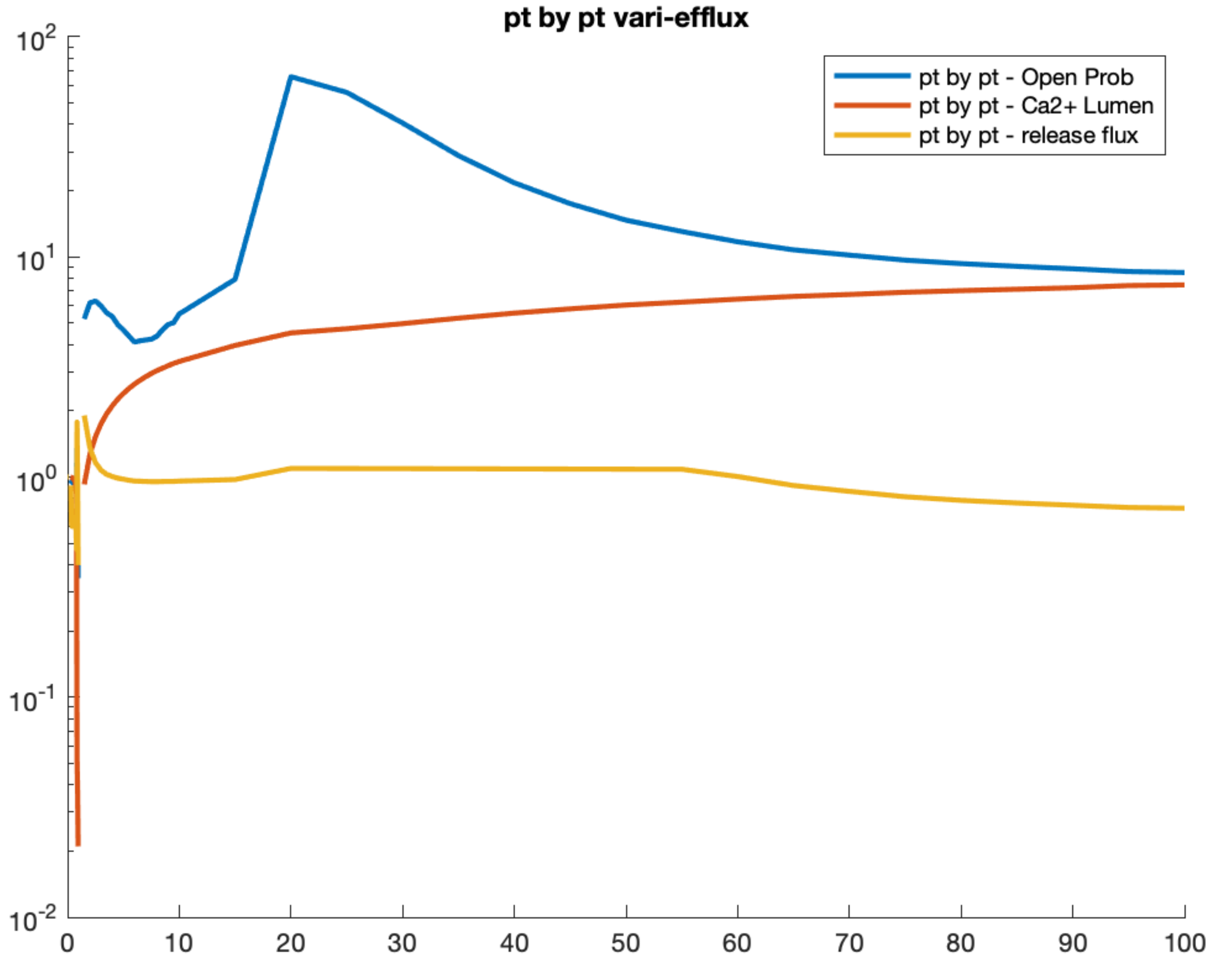
τ_{efflux}

α_1 α_2

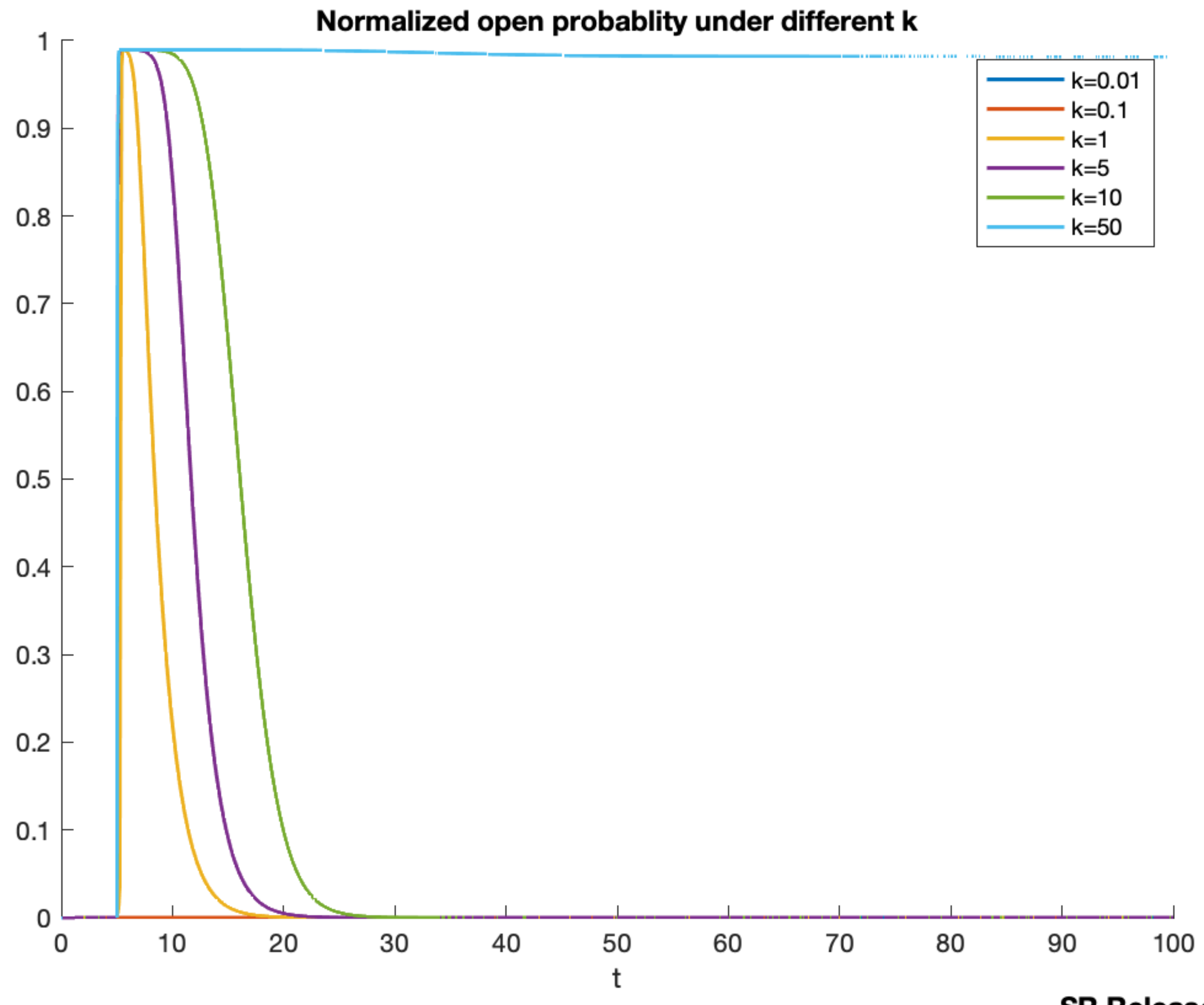


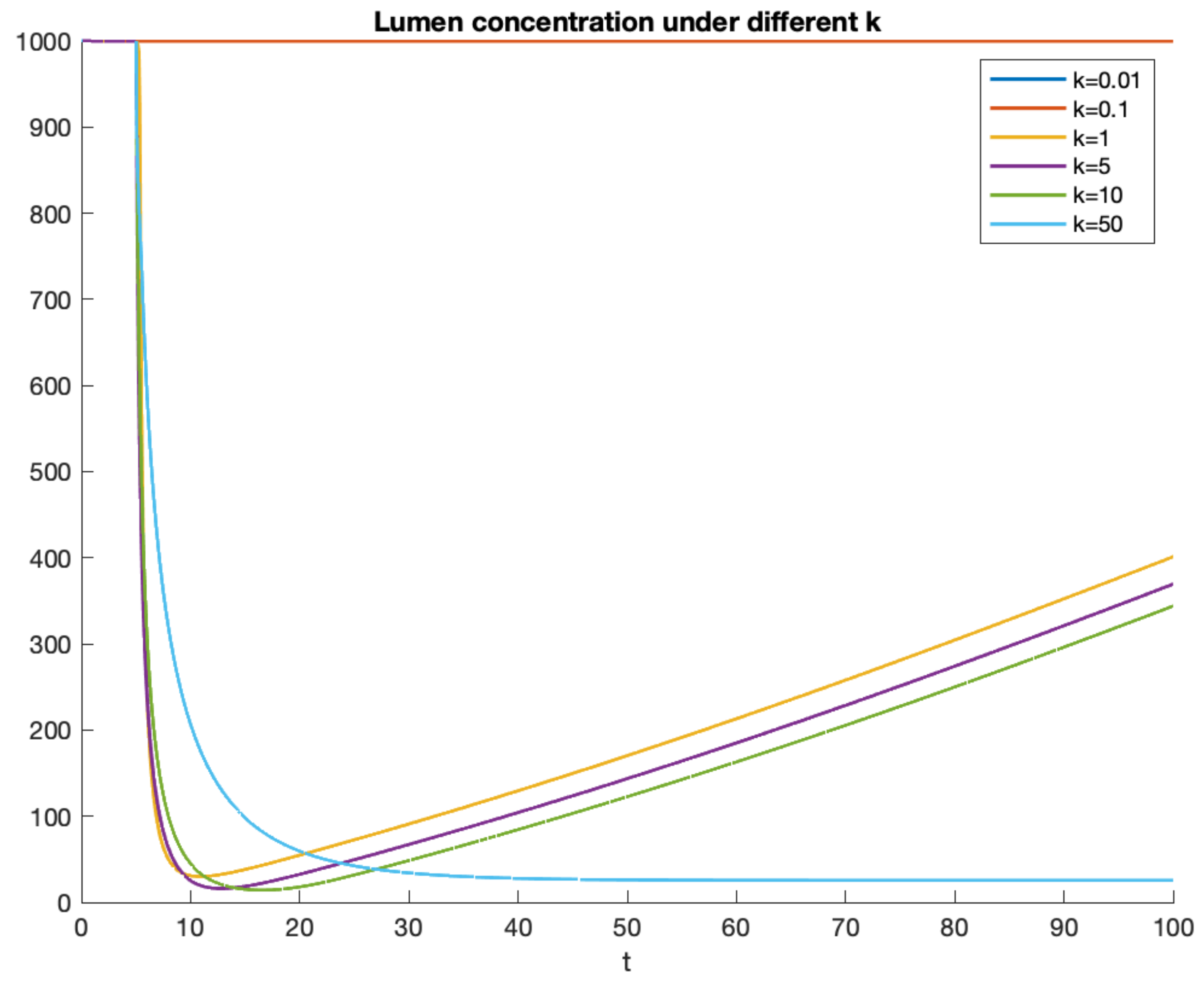


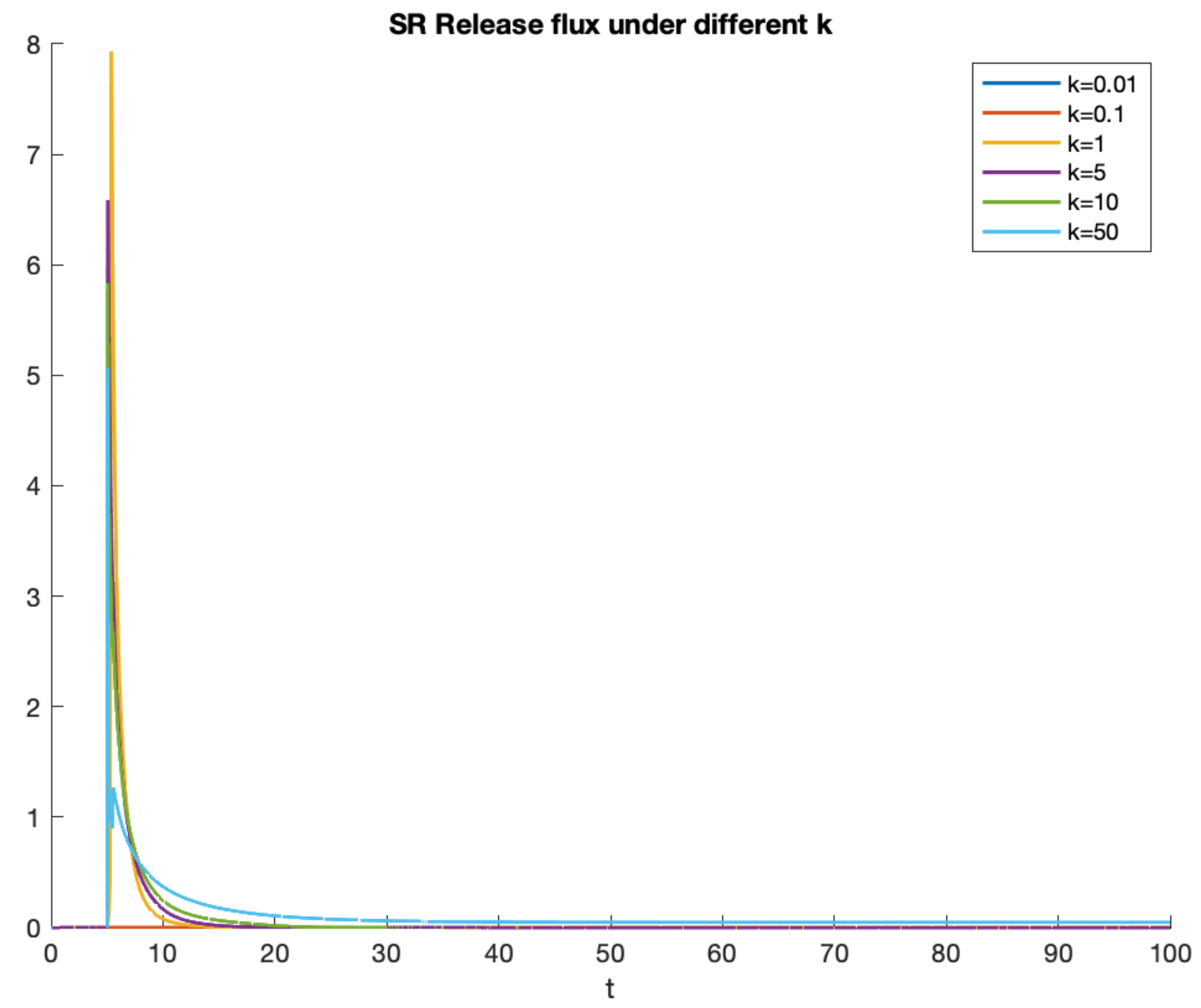




- Very sensitive. Completely diverge when $k \lessapprox 0.7$.



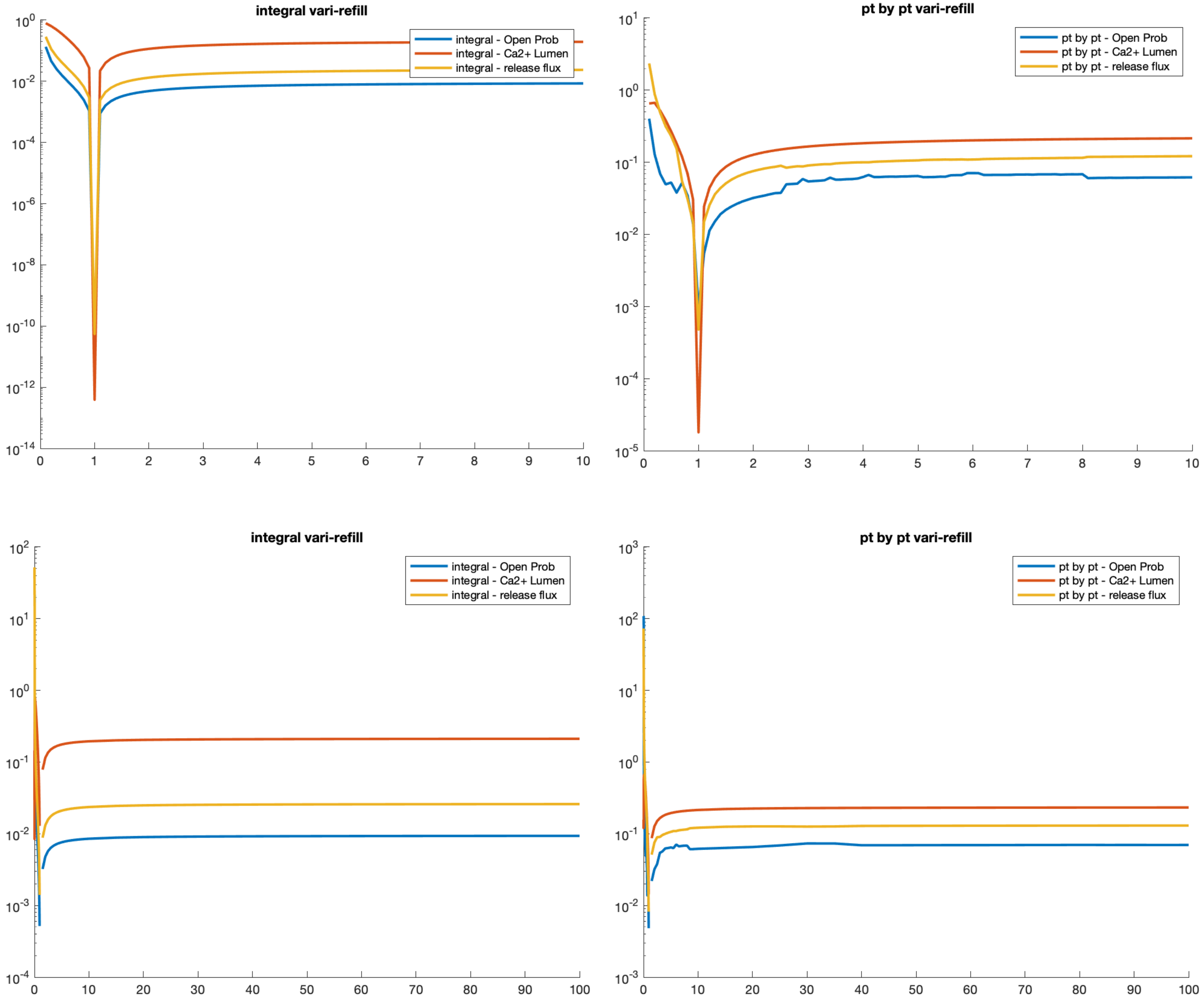


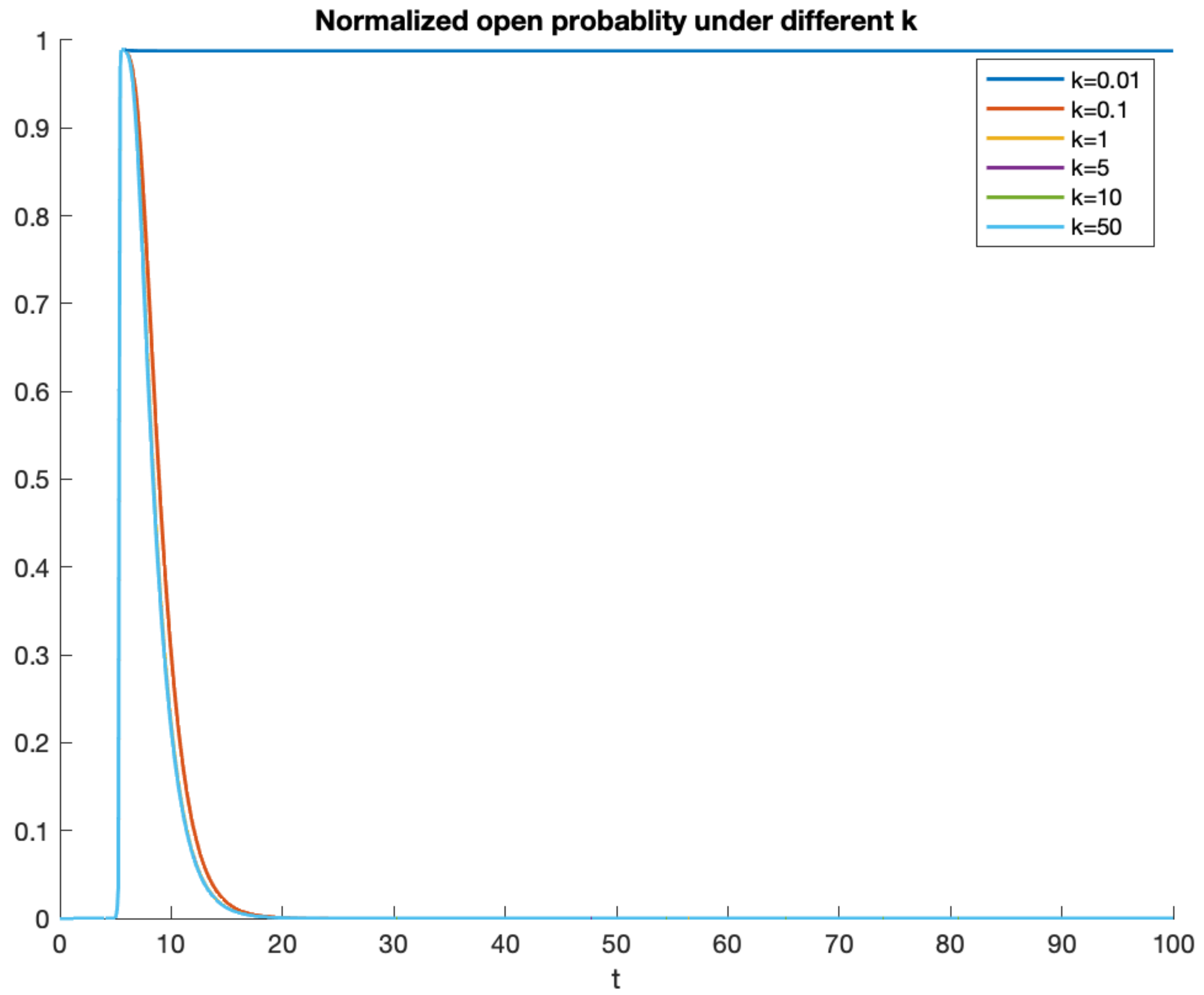


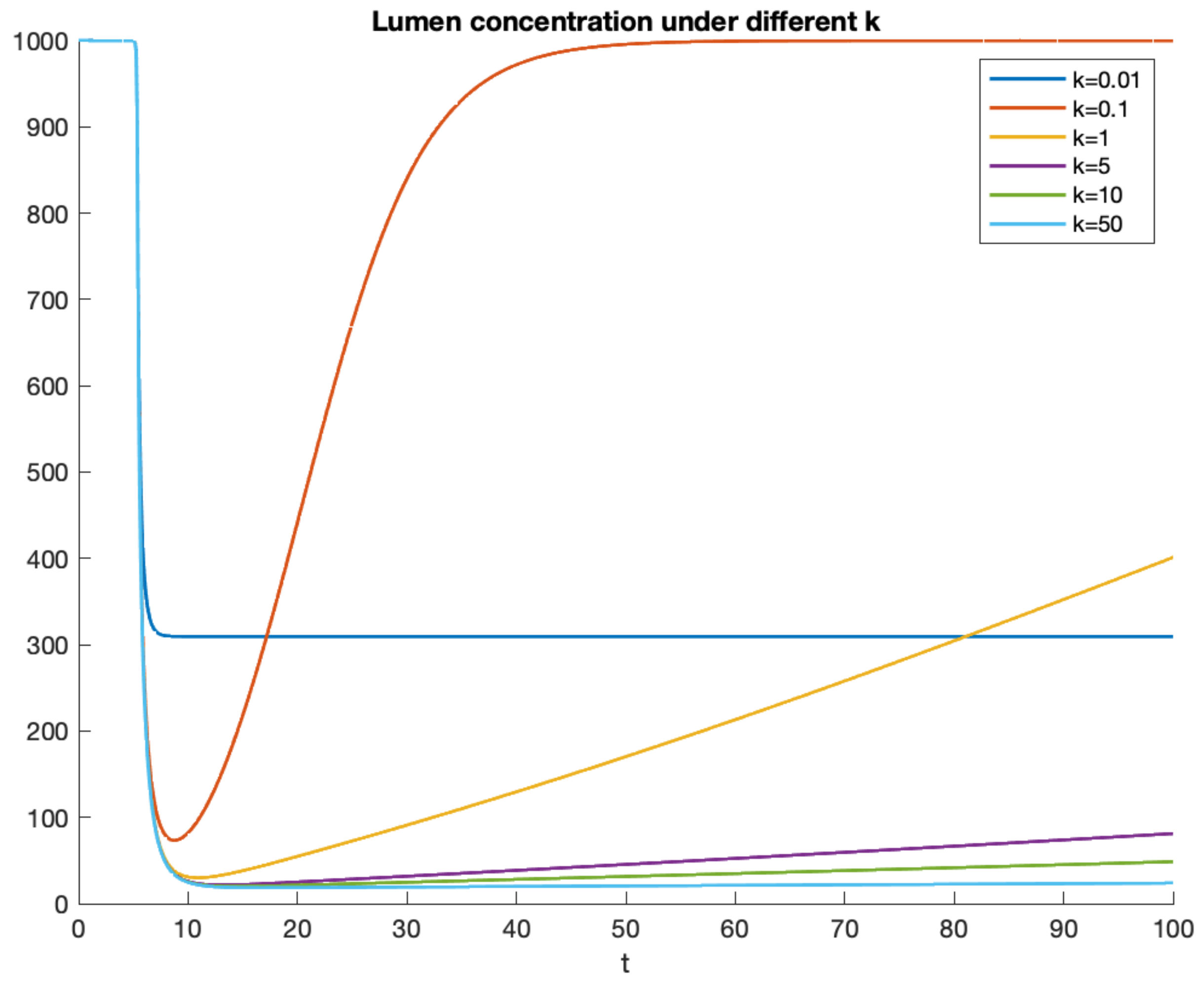
τ_{refill}

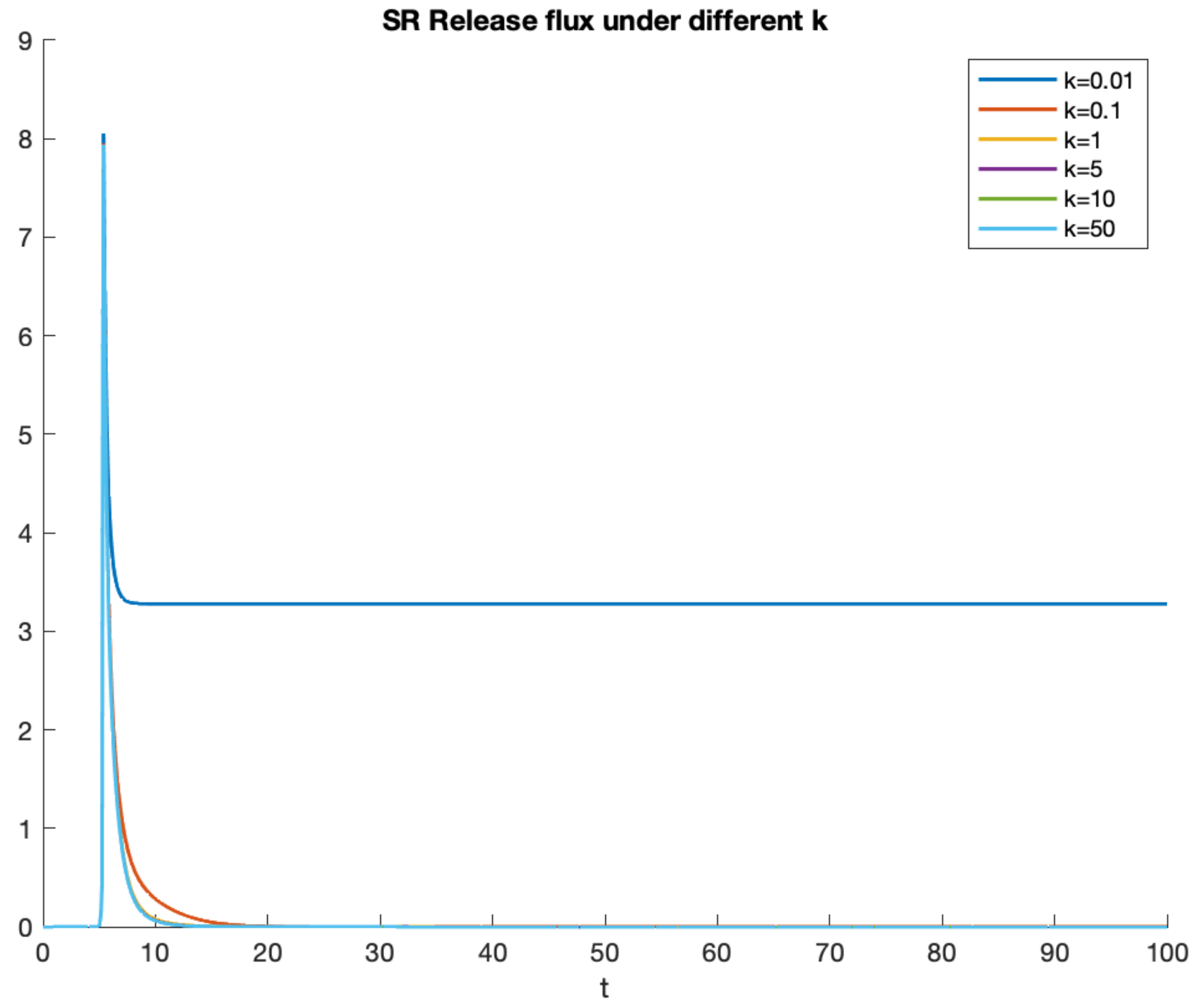
- Comparatively more stable comparing to τ_{efflux} (using the same scales of k but the variations are smaller).

α_1 α_2









τ_{efflux} & τ_{refill}

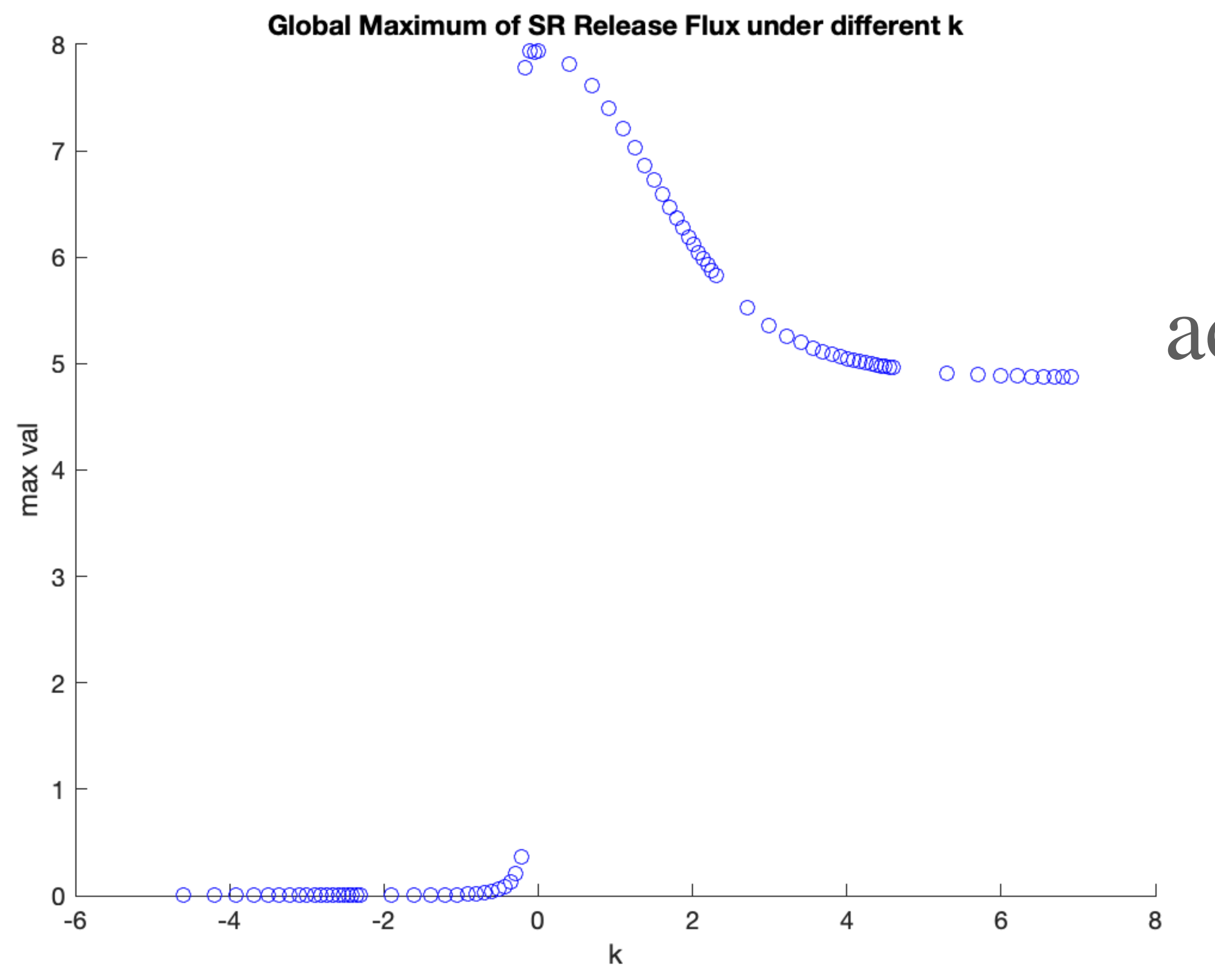
$$J_{refill} = \frac{([Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR})}{\tau_{refill}} \qquad J_{efflux} = \frac{([Ca^{2+}]_{myo} - [Ca^{2+}]_{SS})}{\tau_{efflux}}$$

- J_{efflux} is directly involved in the calculation of time derivative of $[Ca^{2+}]_{SS}$ as the main function

$$\frac{d[Ca^{2+}]_{SS}}{dt} = J_{release} + J_{efflux} + J_{buffer}$$

- but J_{refill} is involved in the intermediate parameter of time derivative of $[Ca^{2+}]_{lumen}$. The nonlinear system may reduce its impact.

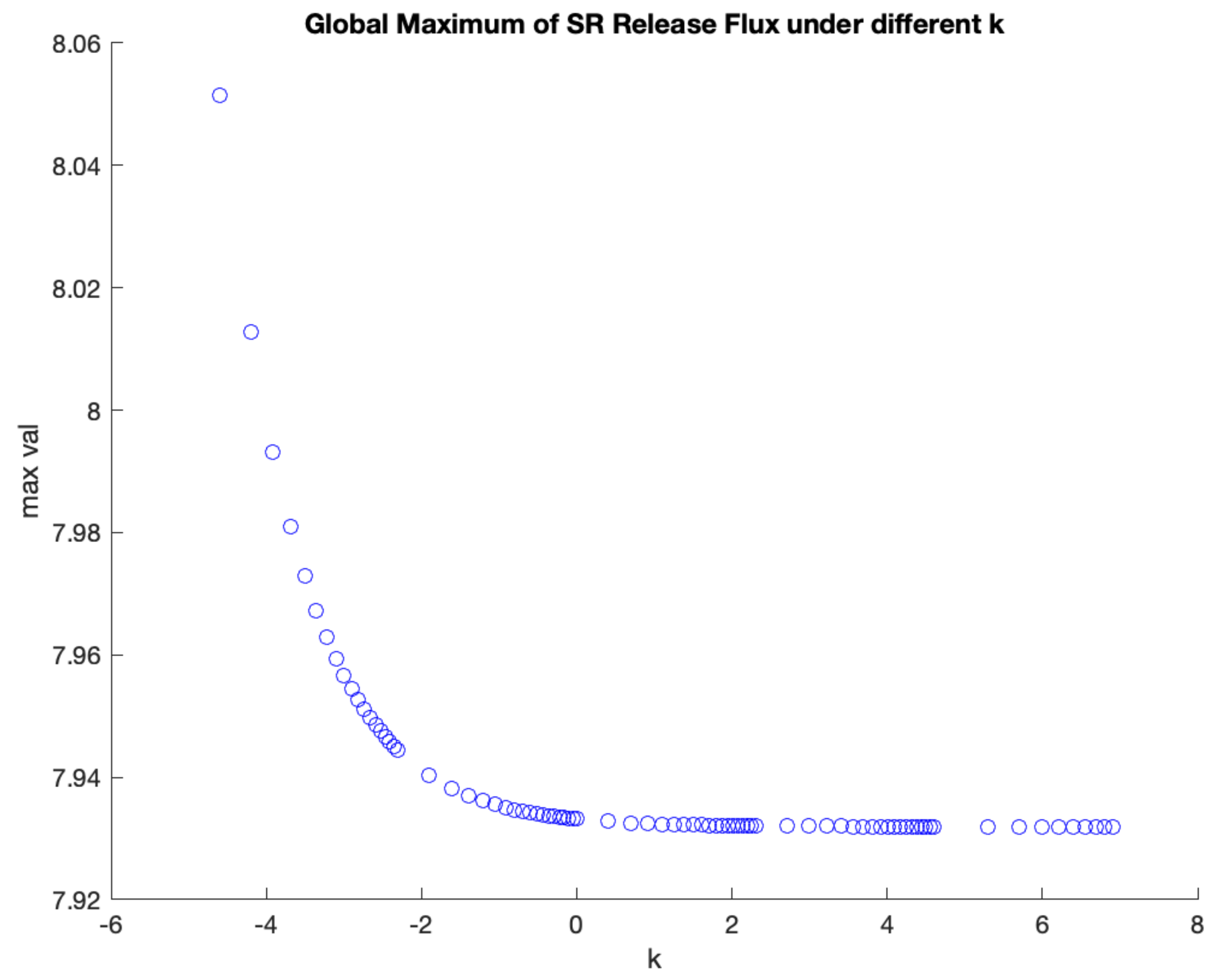
$$\frac{d[Ca^{2+}]_{JSR}}{dt} = \beta_{JSR}(-J_{RyR}\frac{V_{SS}}{V_{JSR}} + J_{refill})$$



τ_{efflux}

Not continuous; achieves maximum when k≈1

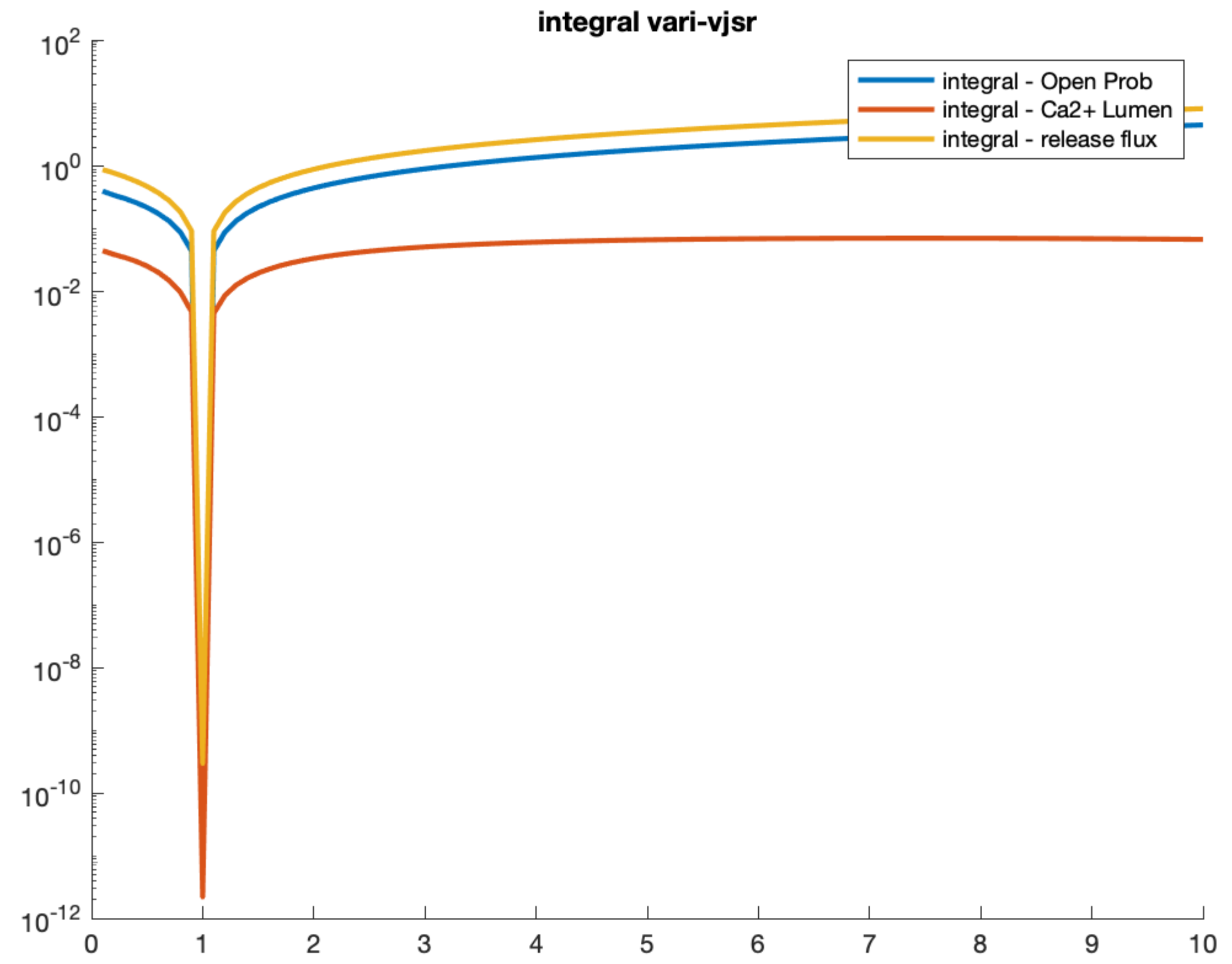
Log scale for x



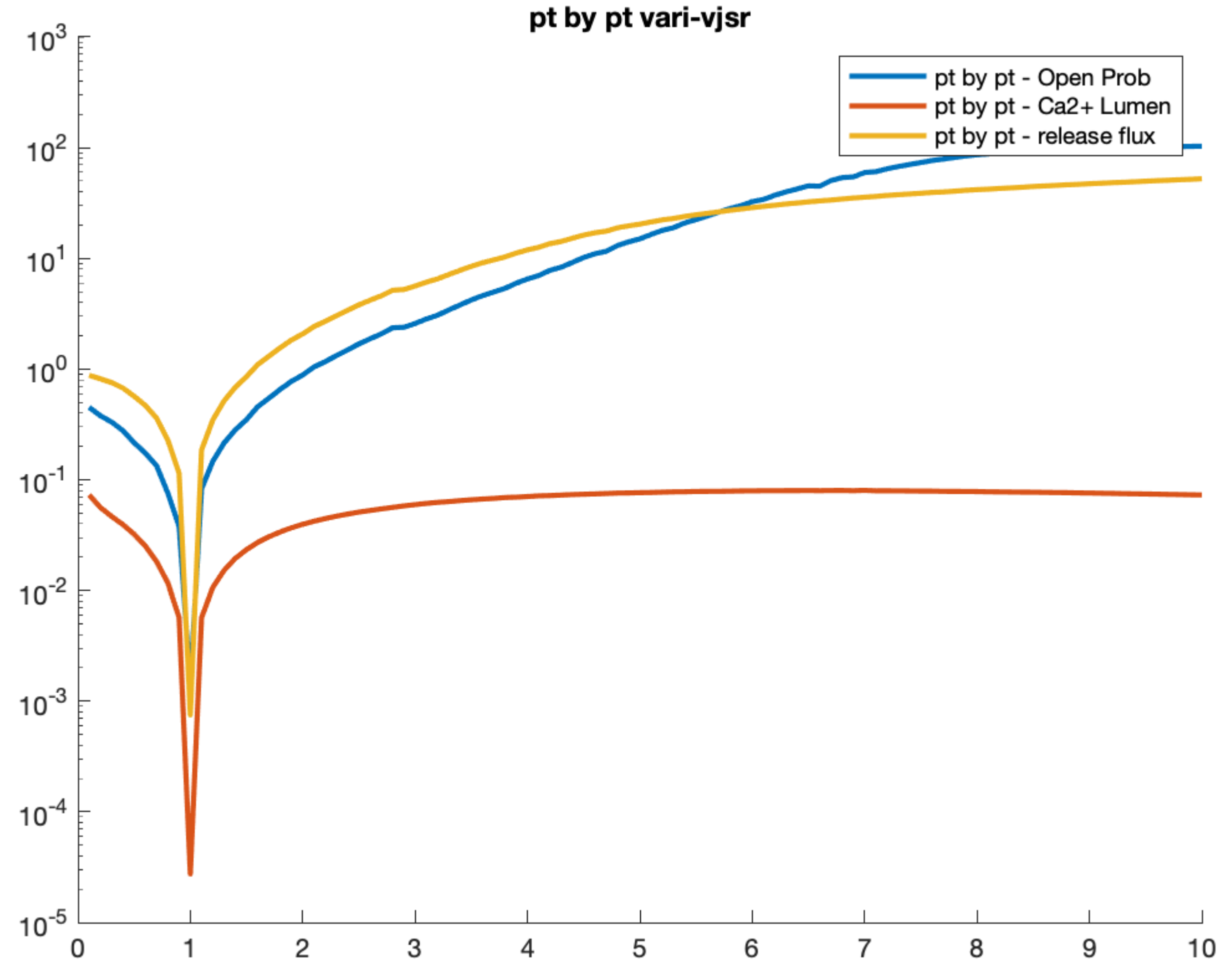
τ_{refill}

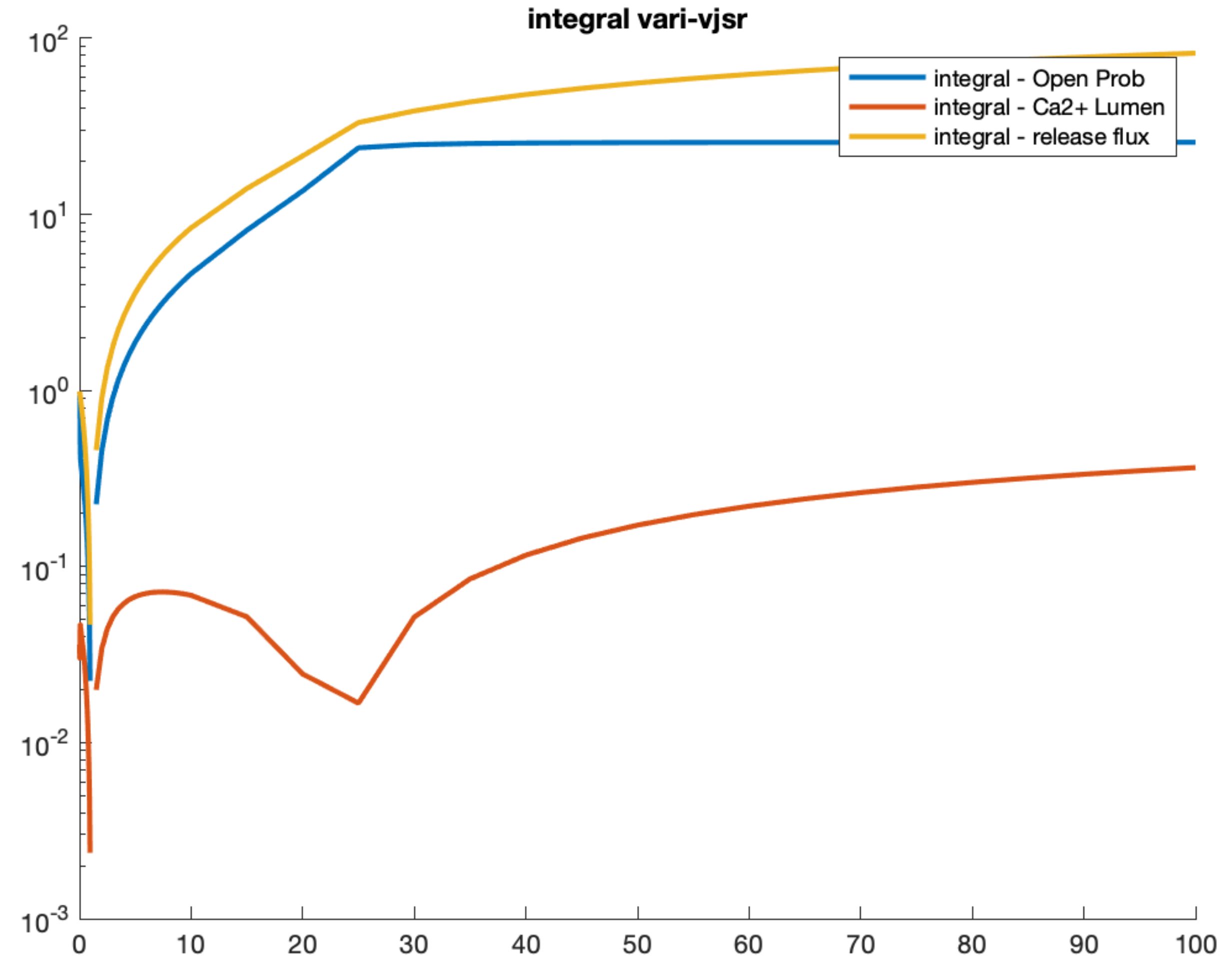
V_{JSR}

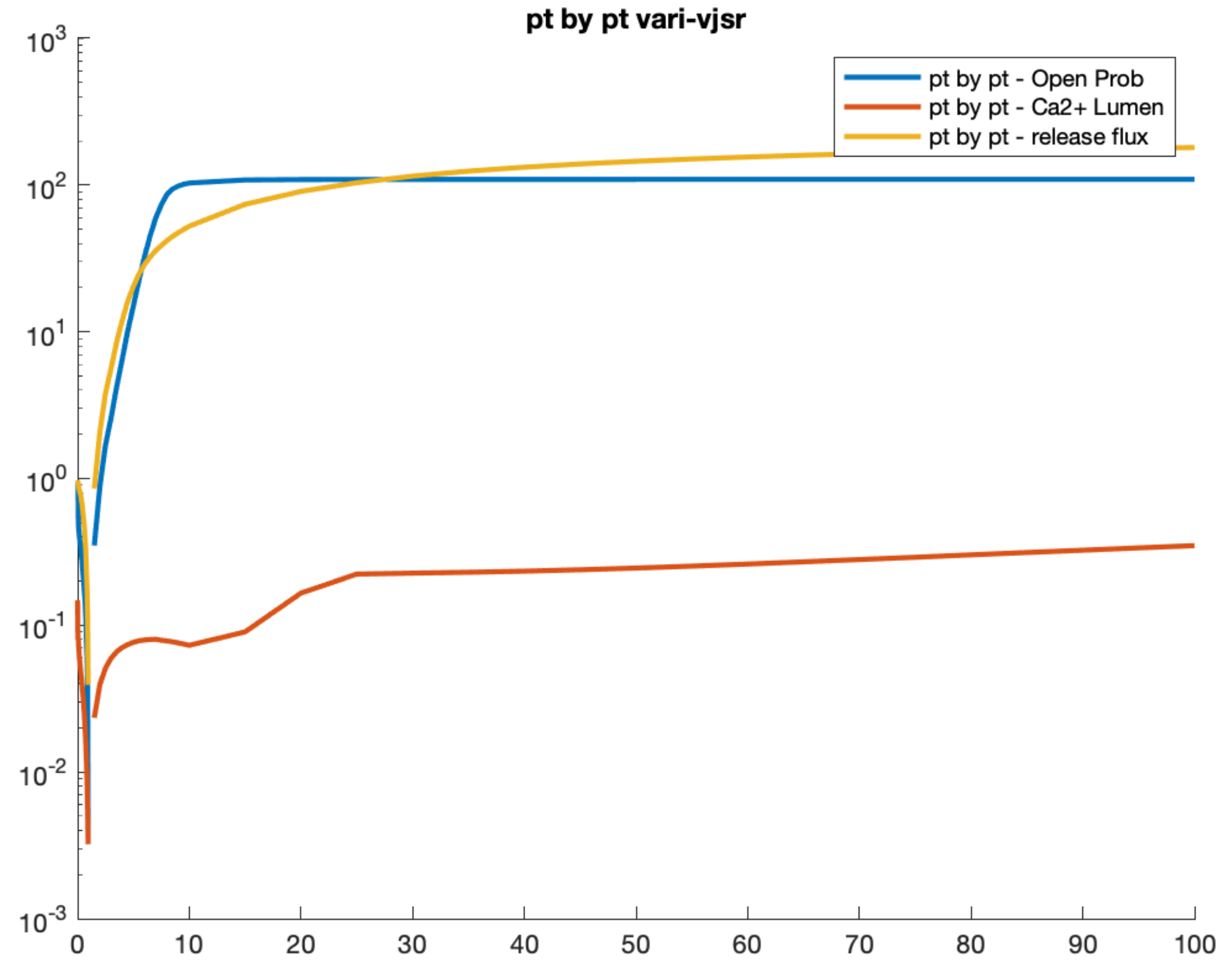
α_1



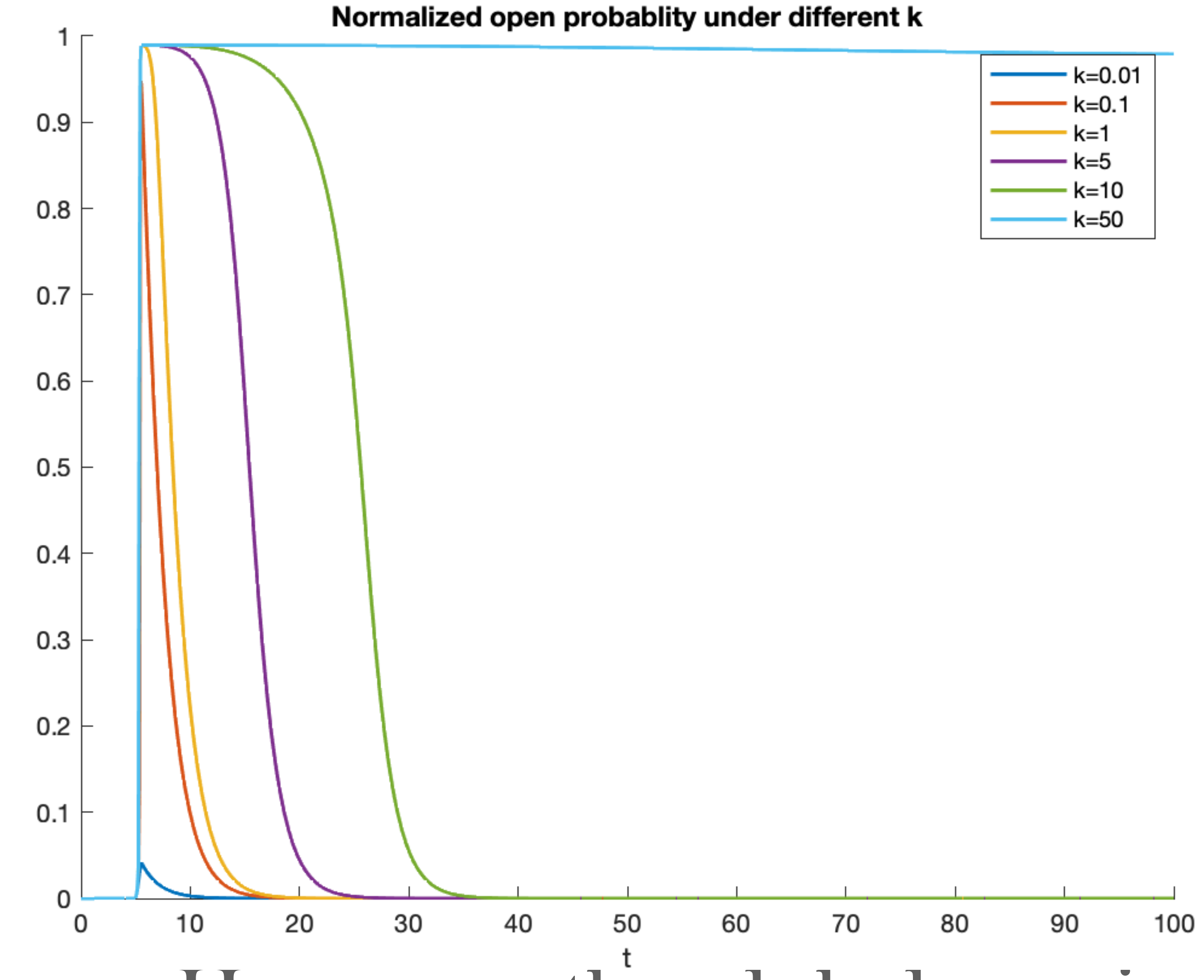
α_2

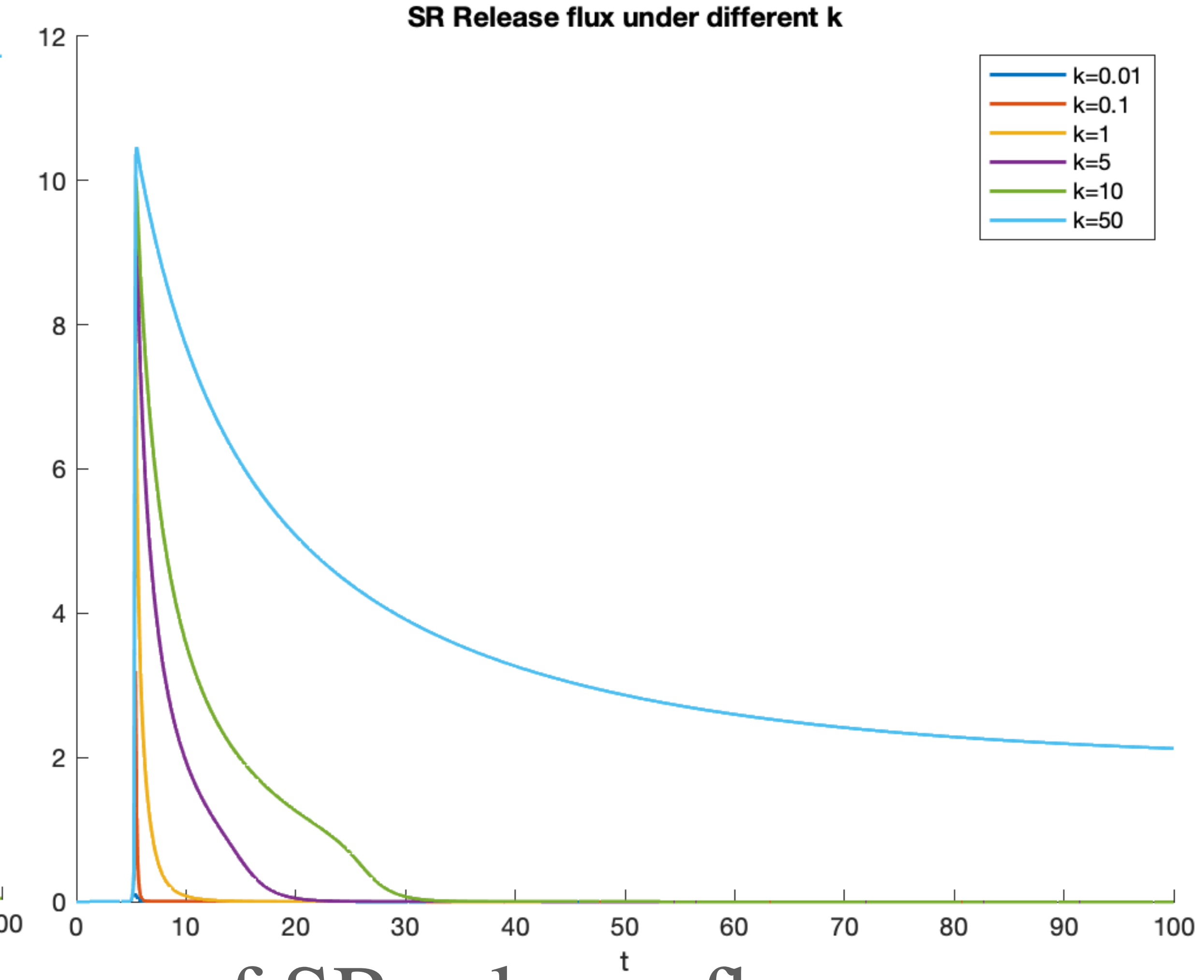




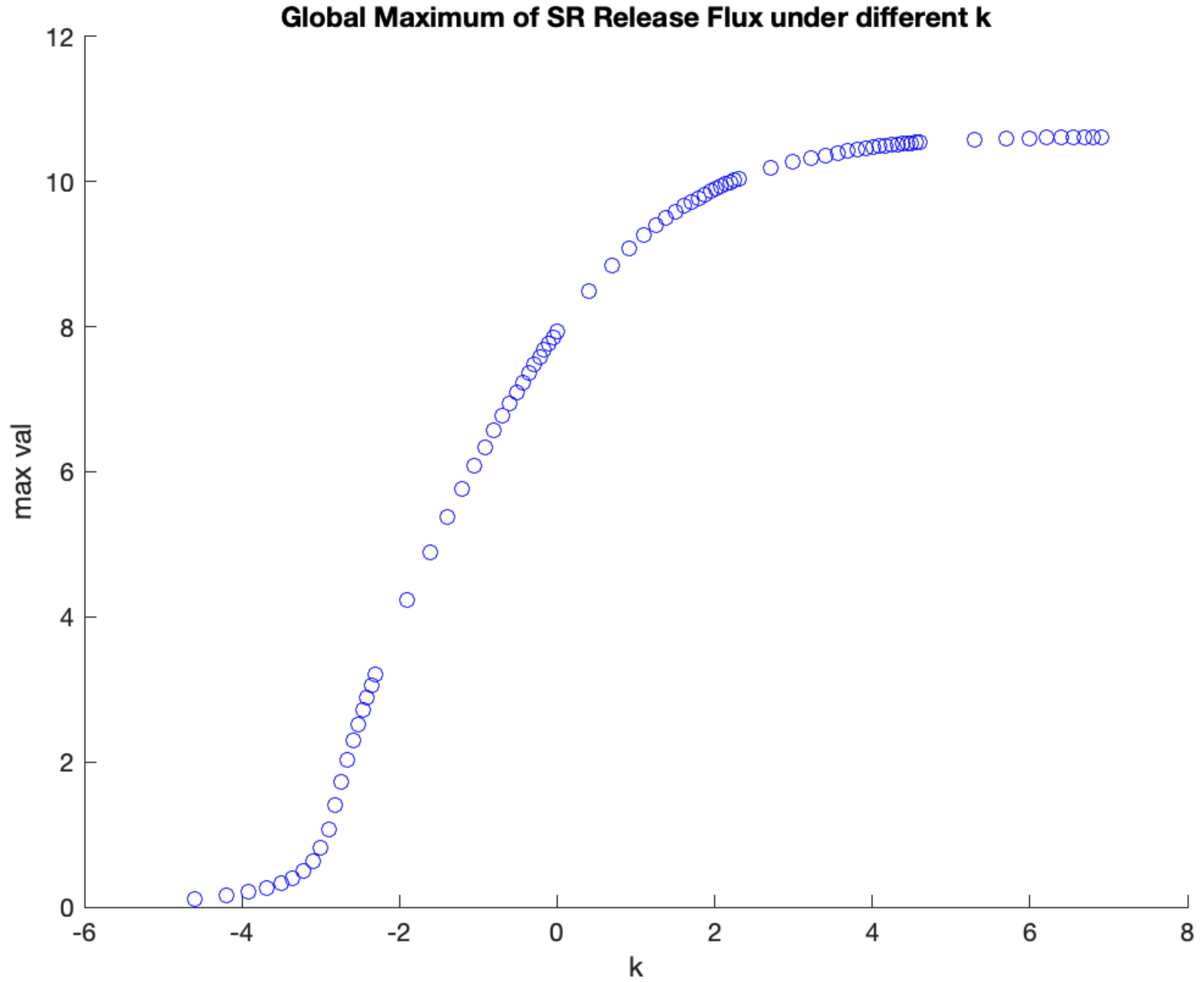


- Monotonically outward expansion of frontier when k increases, meaning that the process takes longer time to terminate.





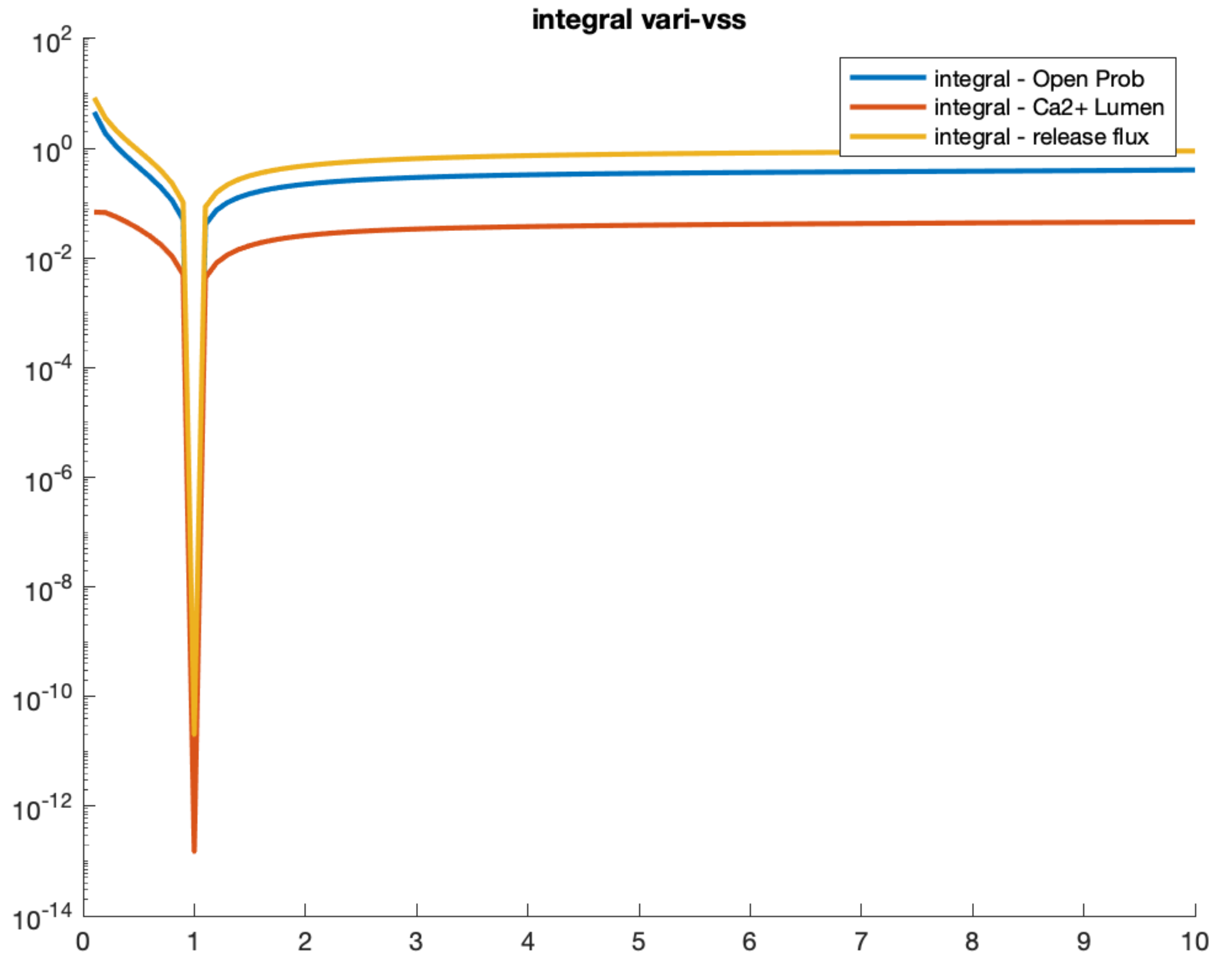
- However, the global maximum of SR release flux converges, unlike N_{RyR}.

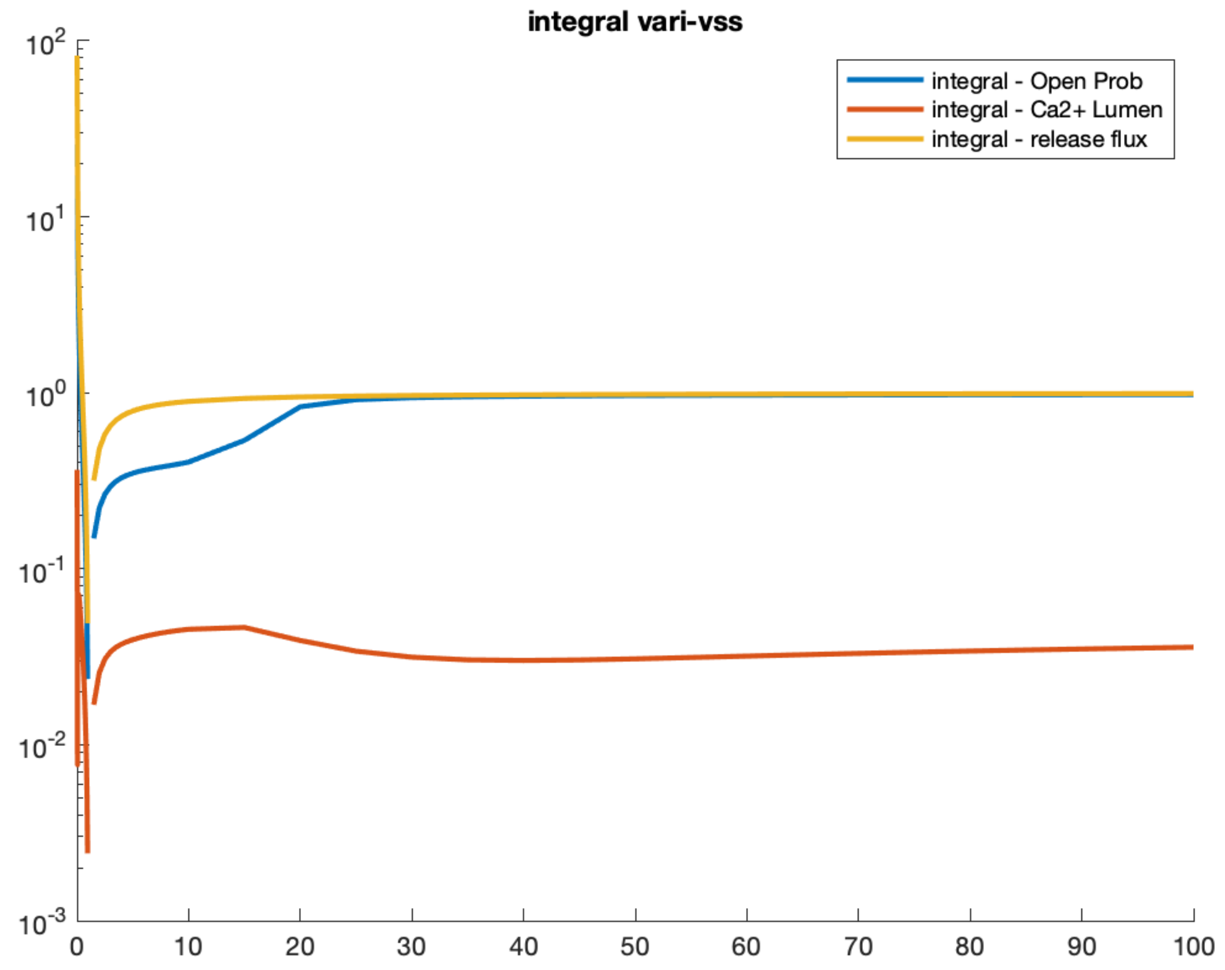


Log scale for x

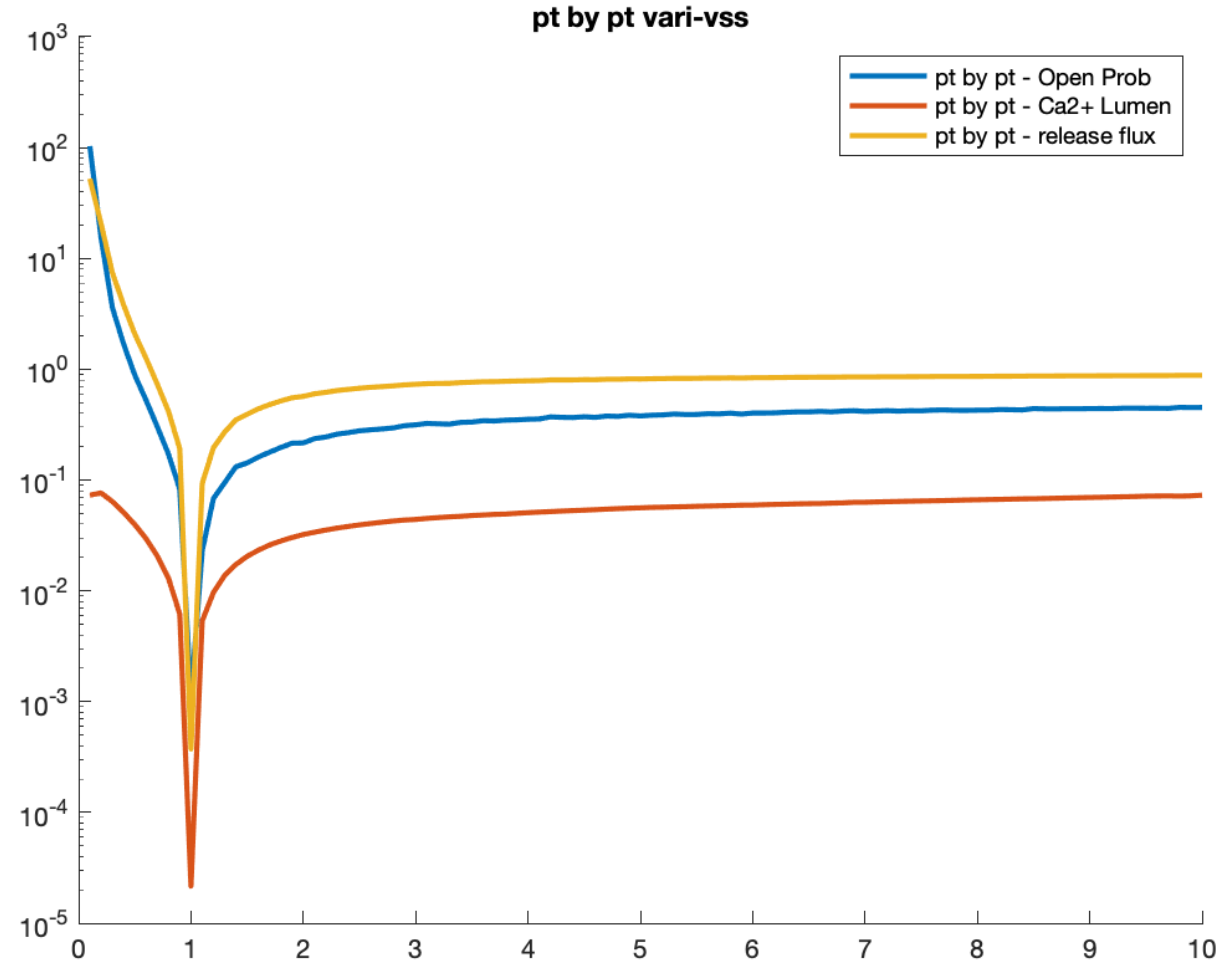
V_{SS}

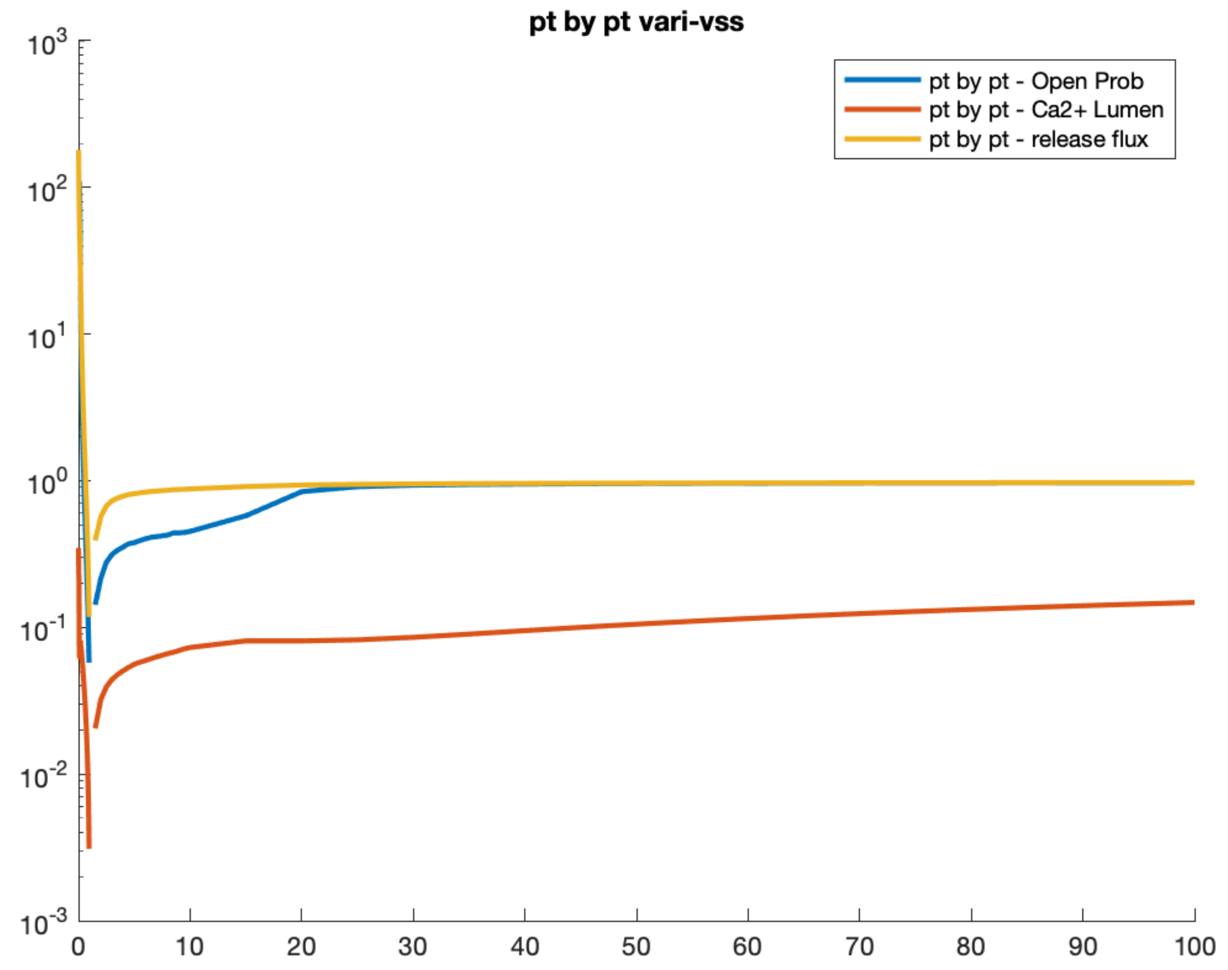
α_1





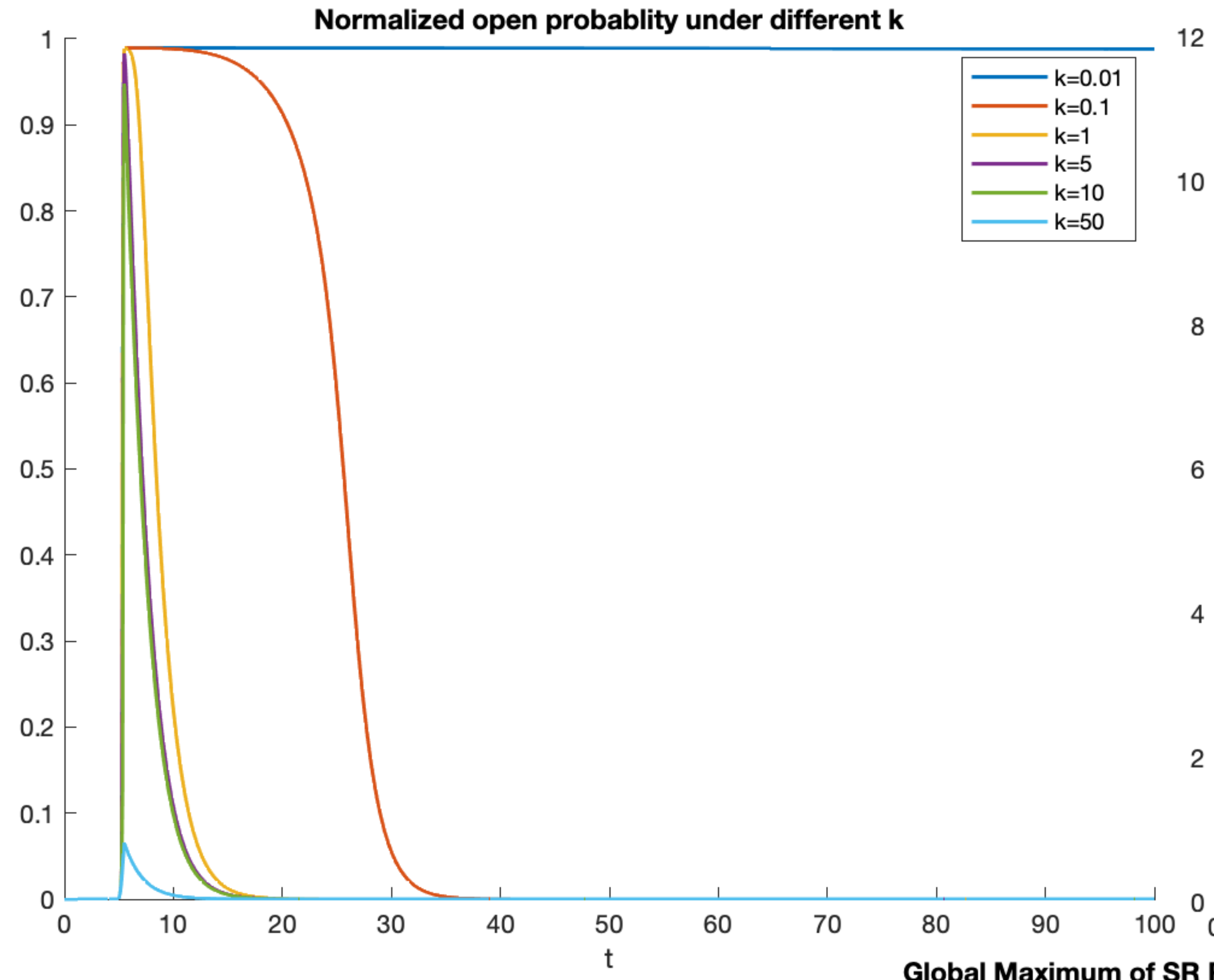
α_2

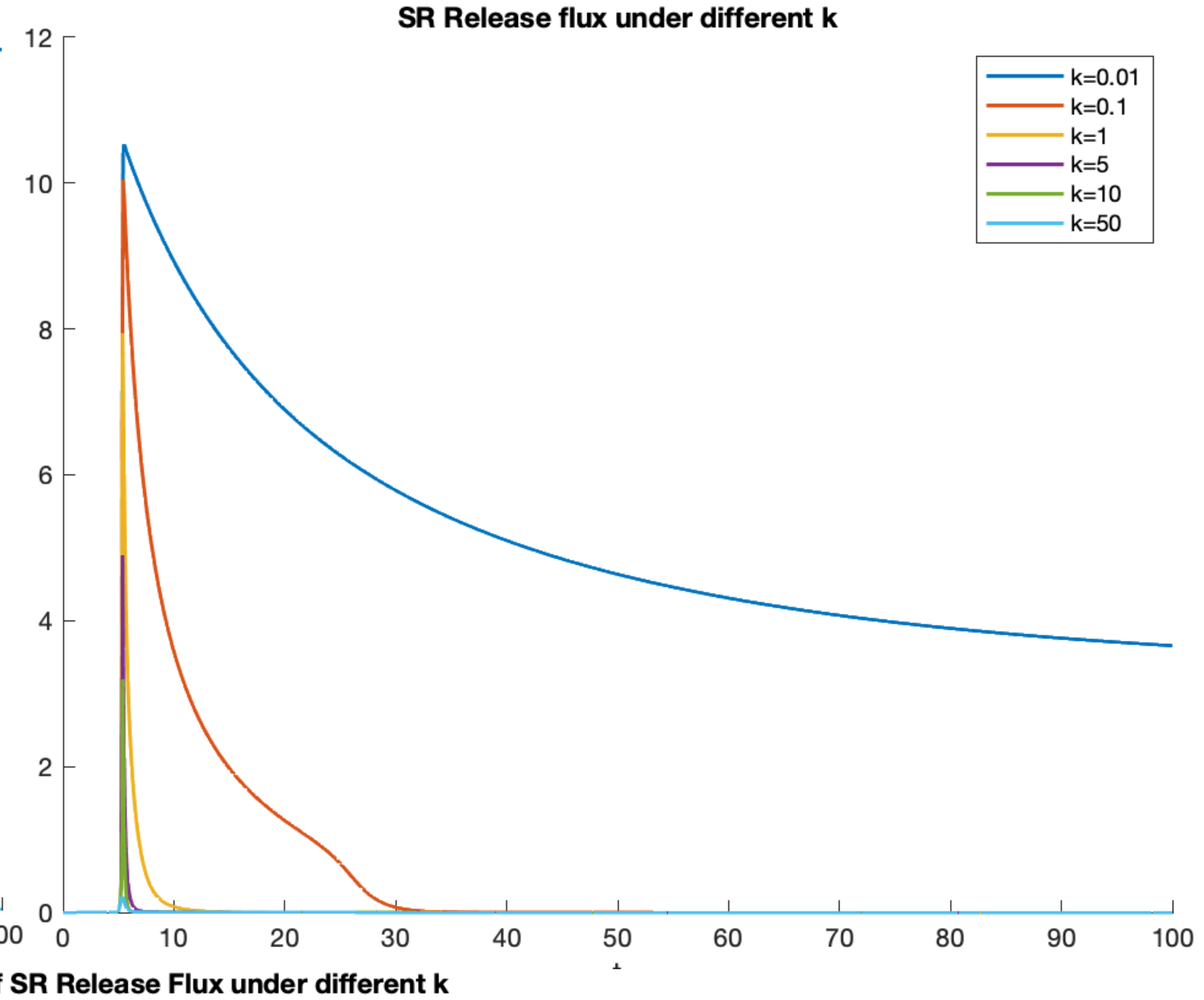


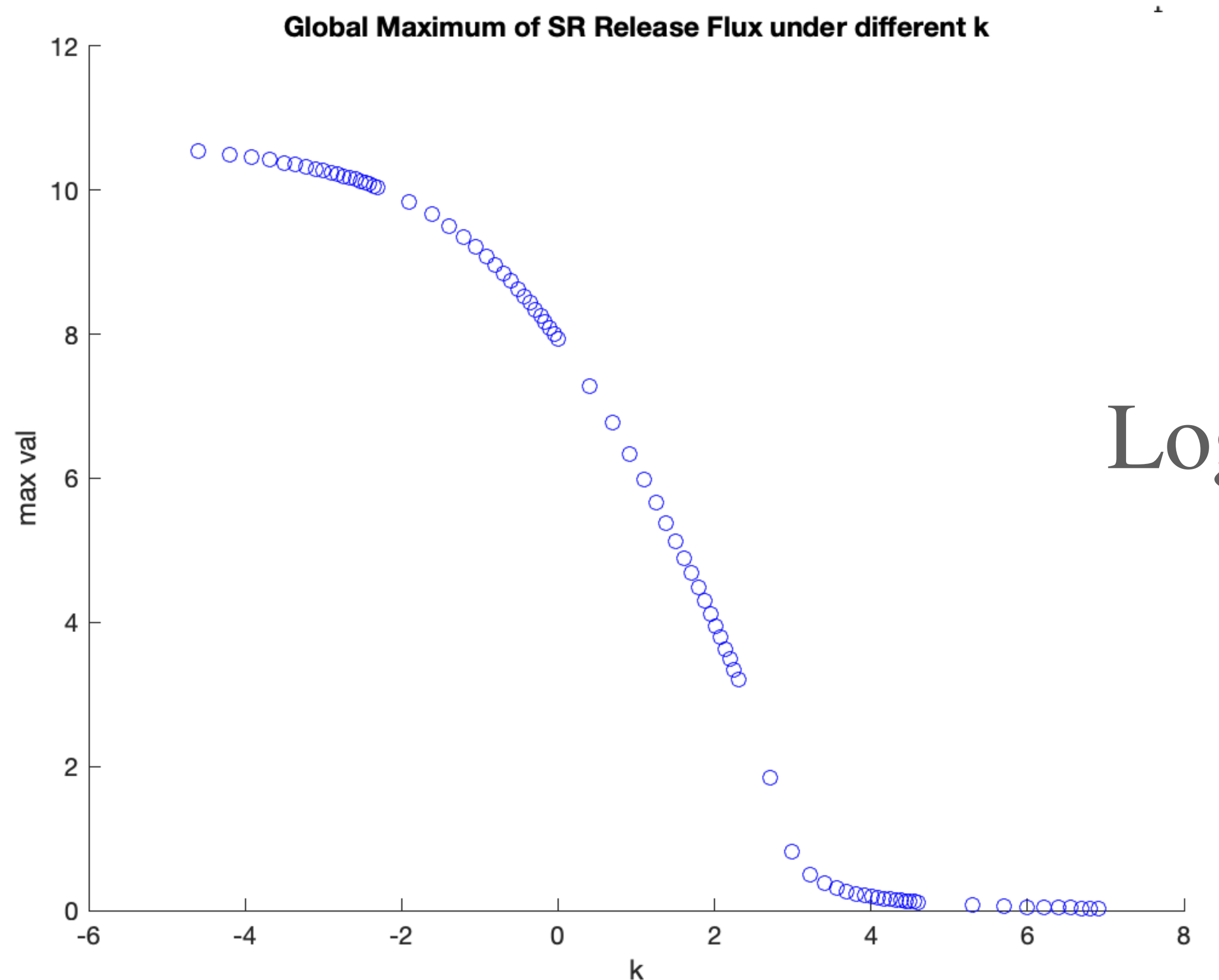


- V_{SS} progresses inversely to V_{JSR}

$$\frac{d[Ca^{2+}]_{JSR}}{dt} = \beta_{JSR}(-J_{RyR}\frac{V_{SS}}{V_{JSR}} + J_{refill})$$



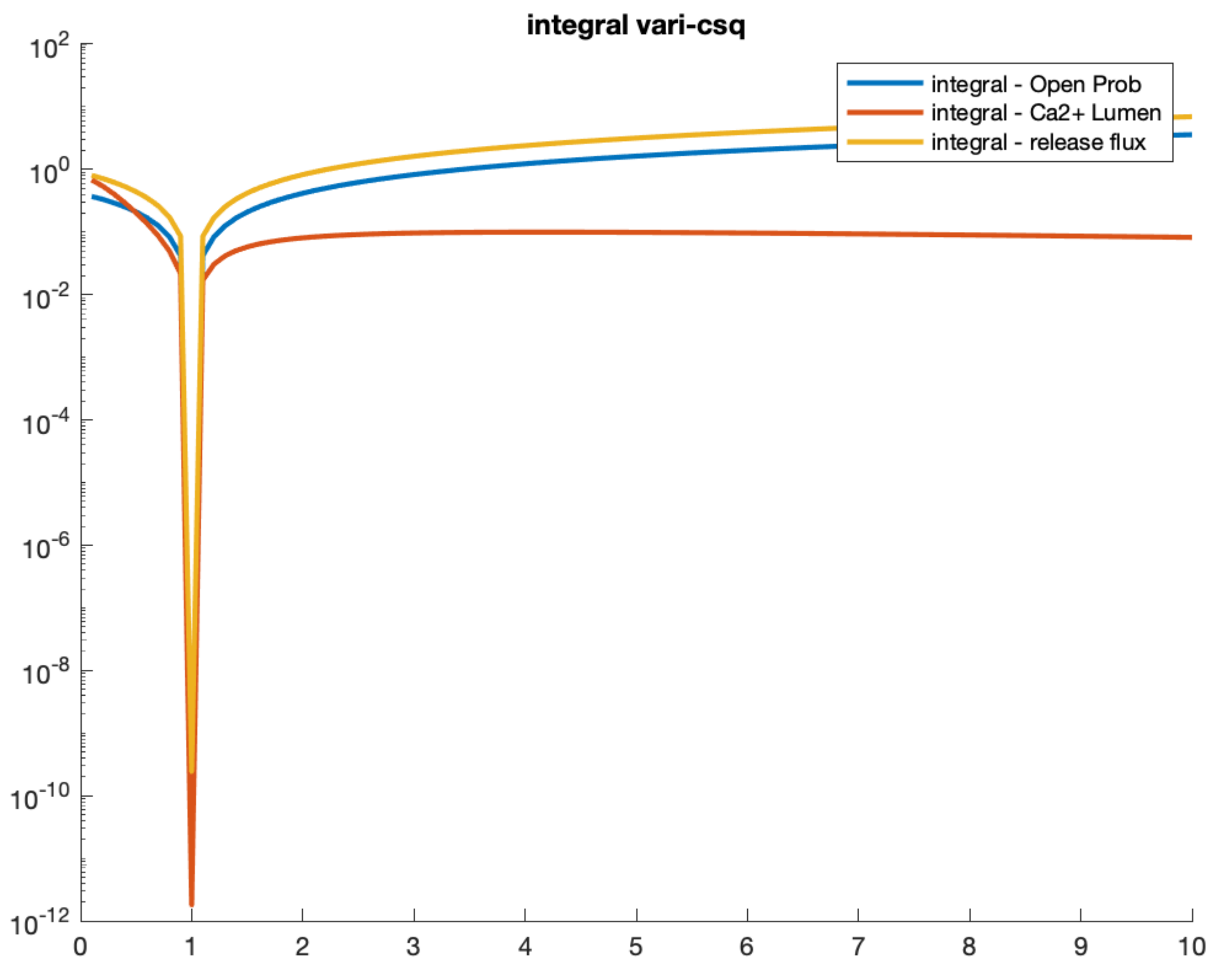


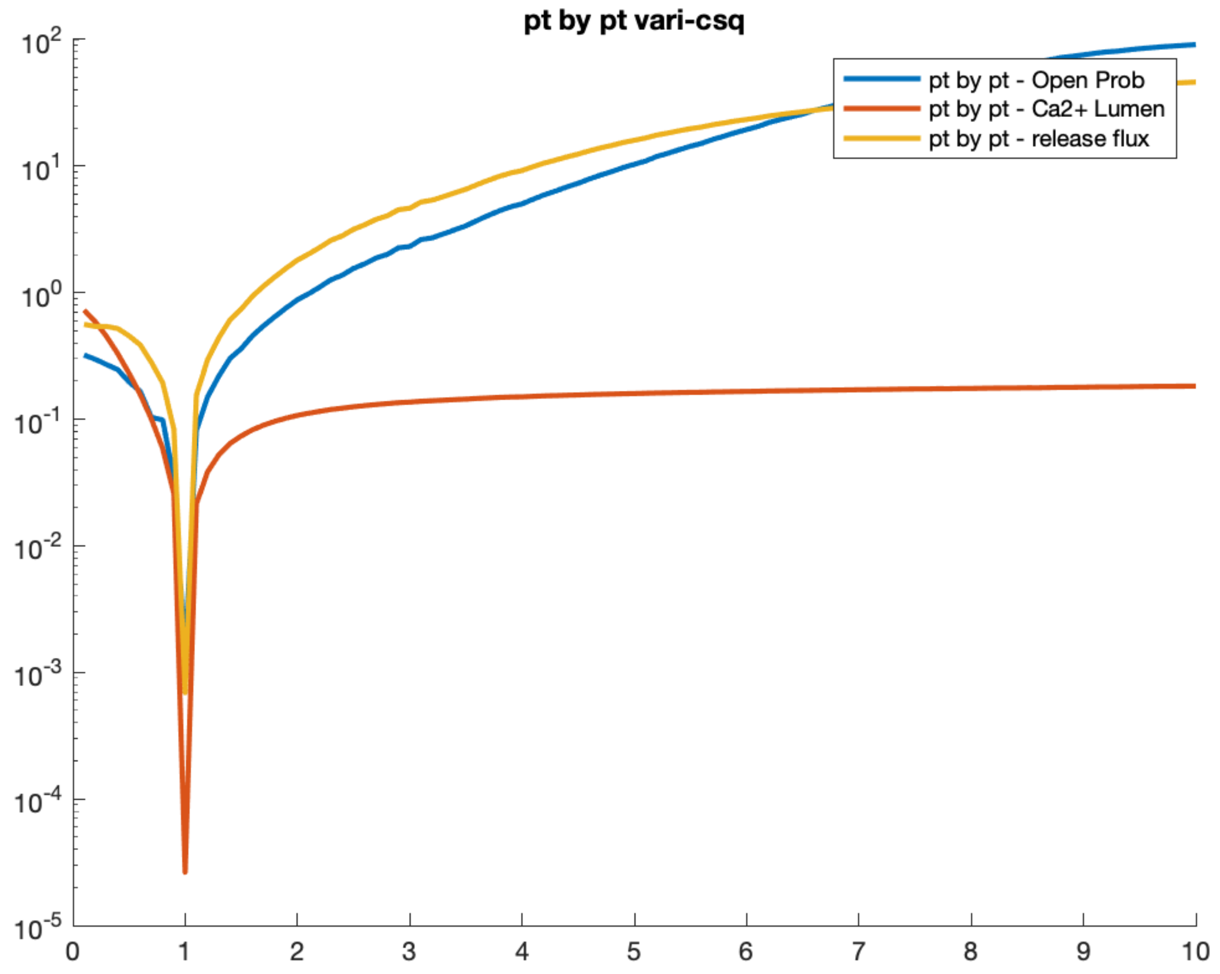


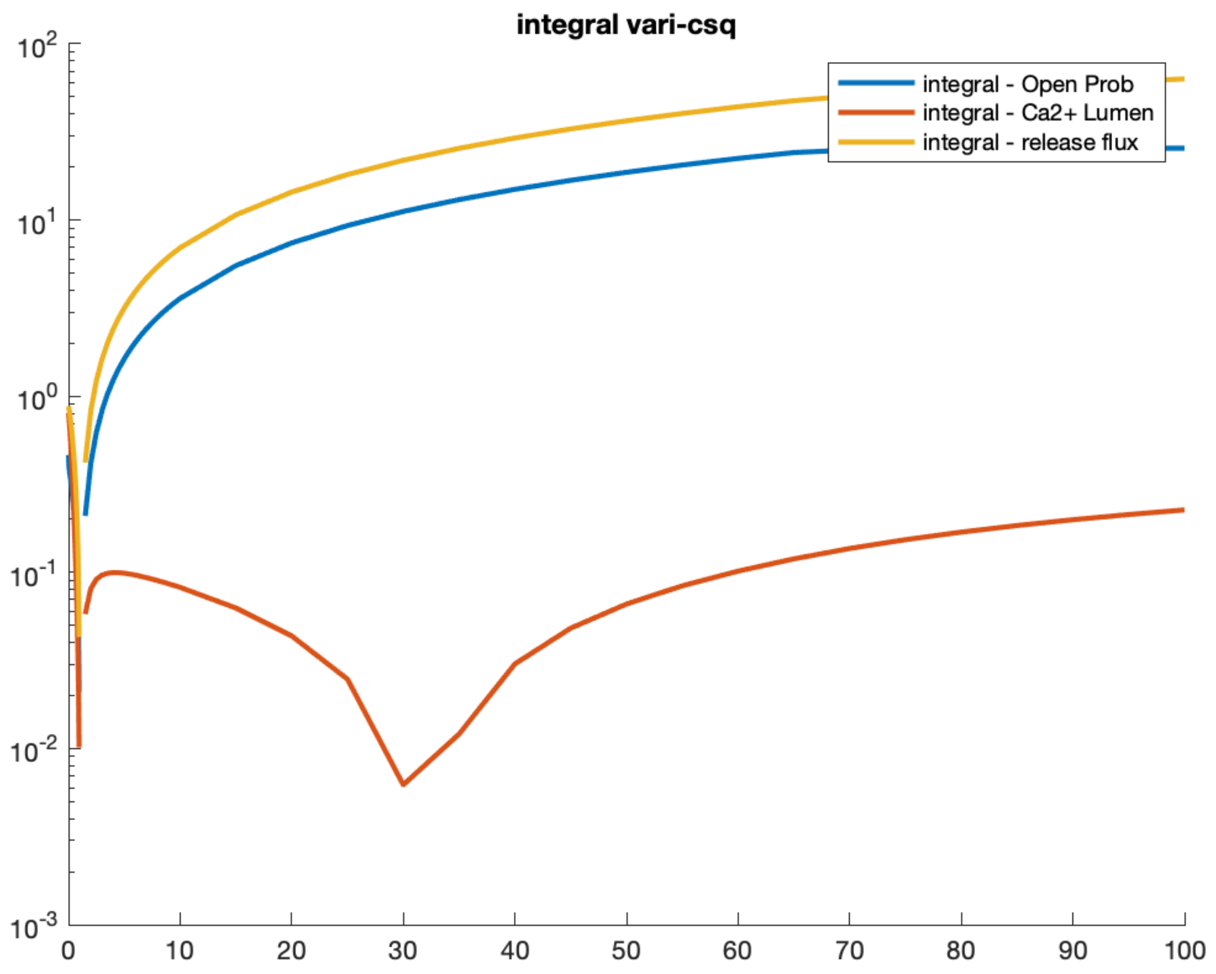
Log scale for x

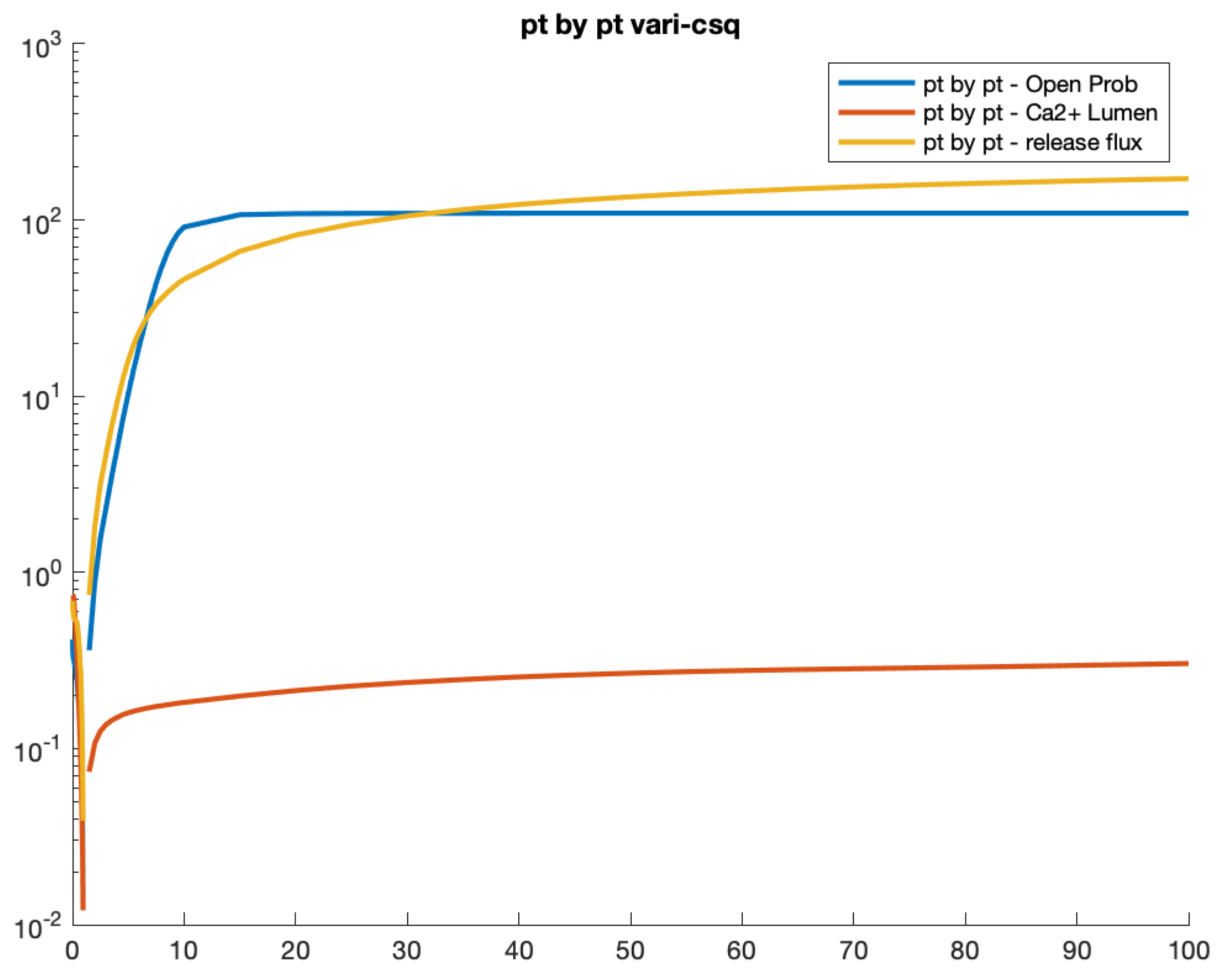
$[CSQ]$

α_1 α_2



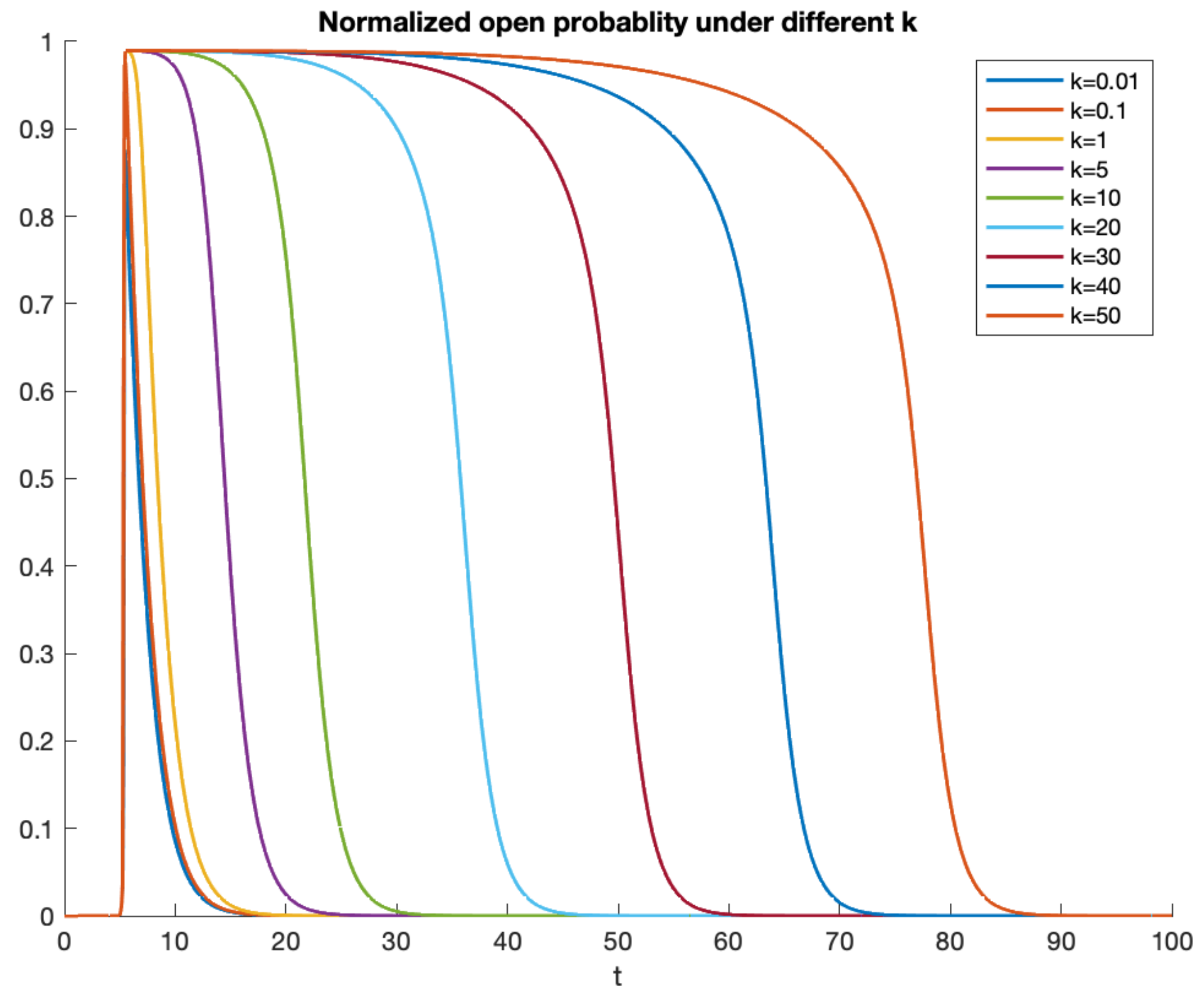


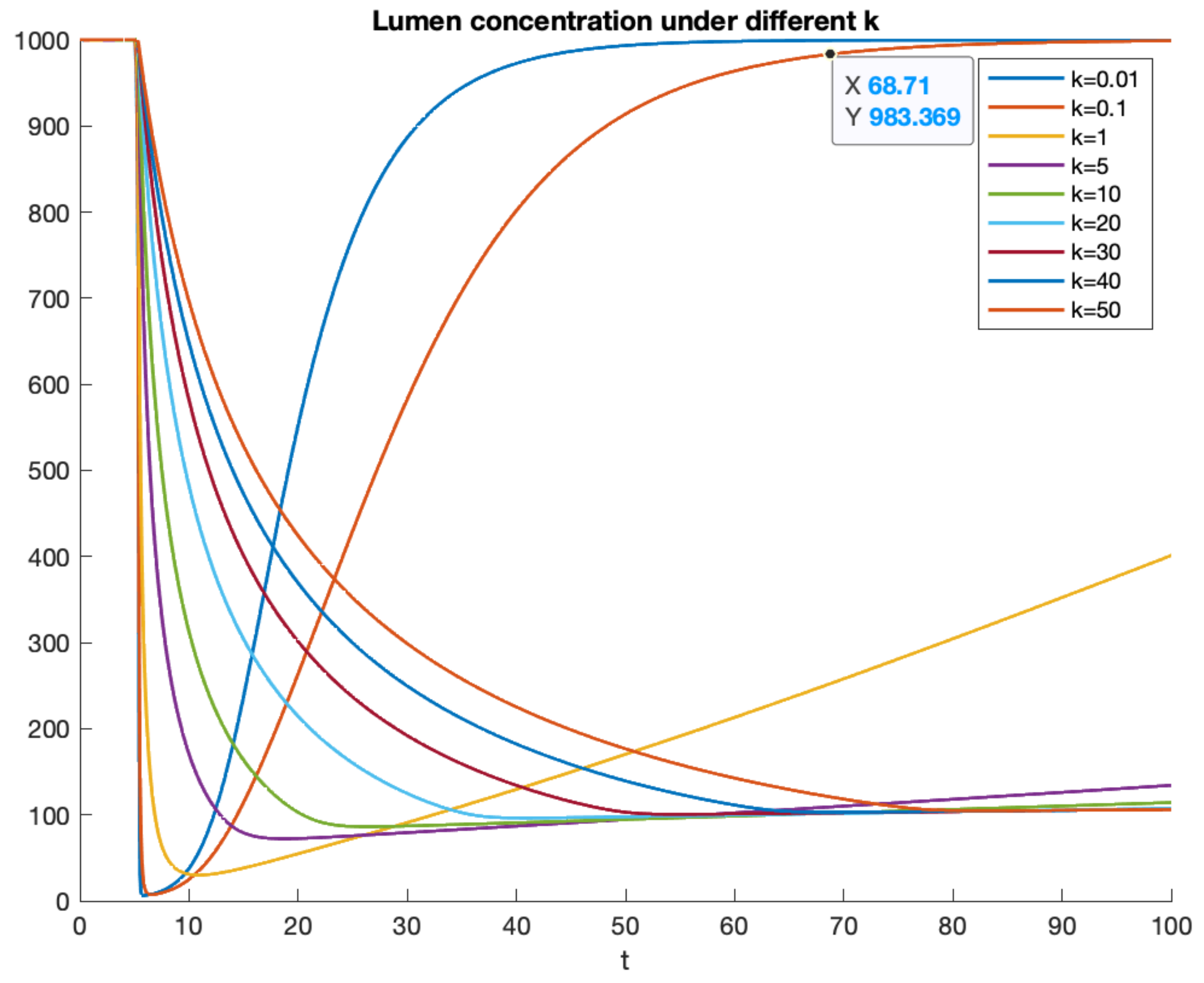


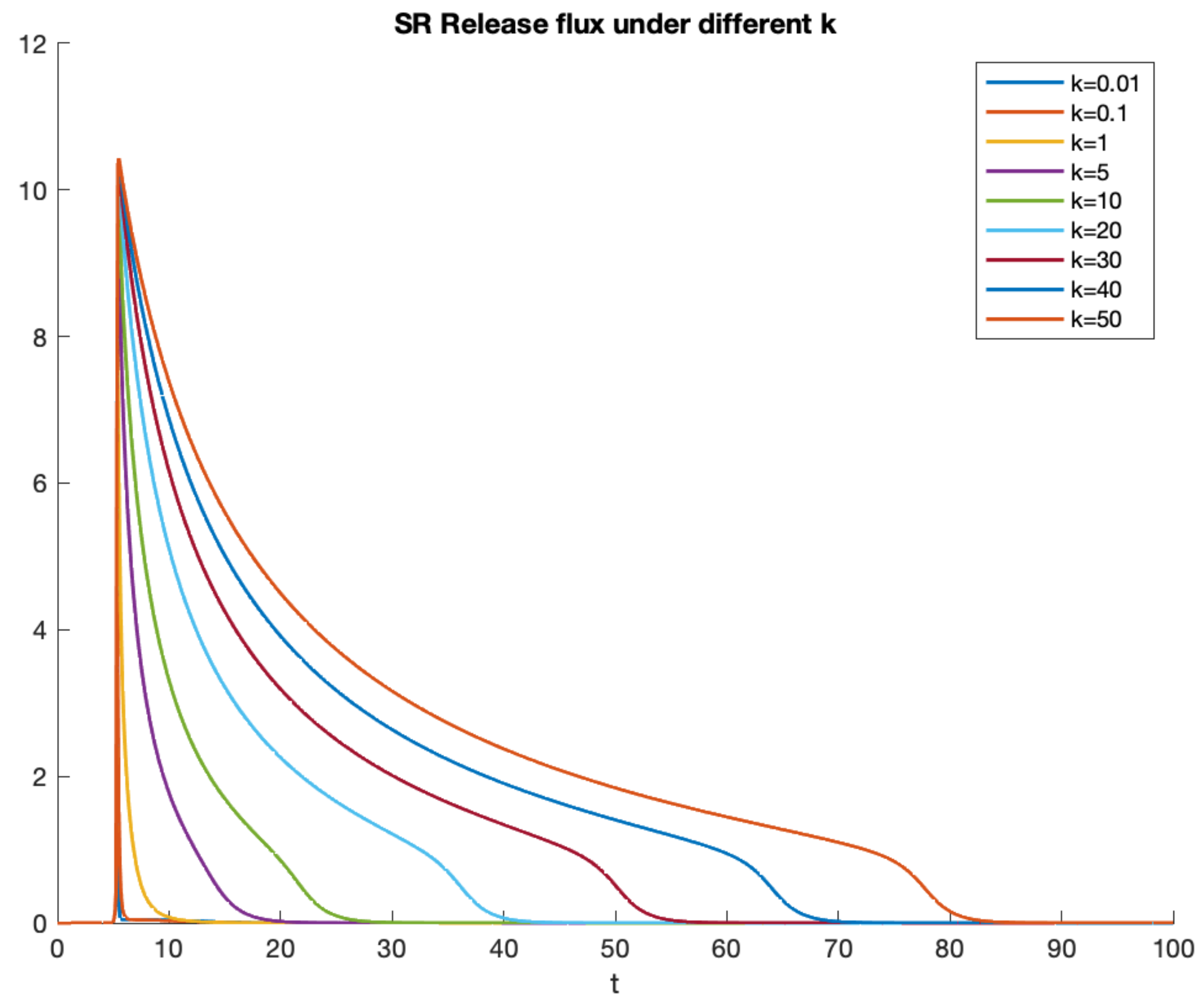


- Also monotonically expansion of curve when k grows.

$[CSQ]$







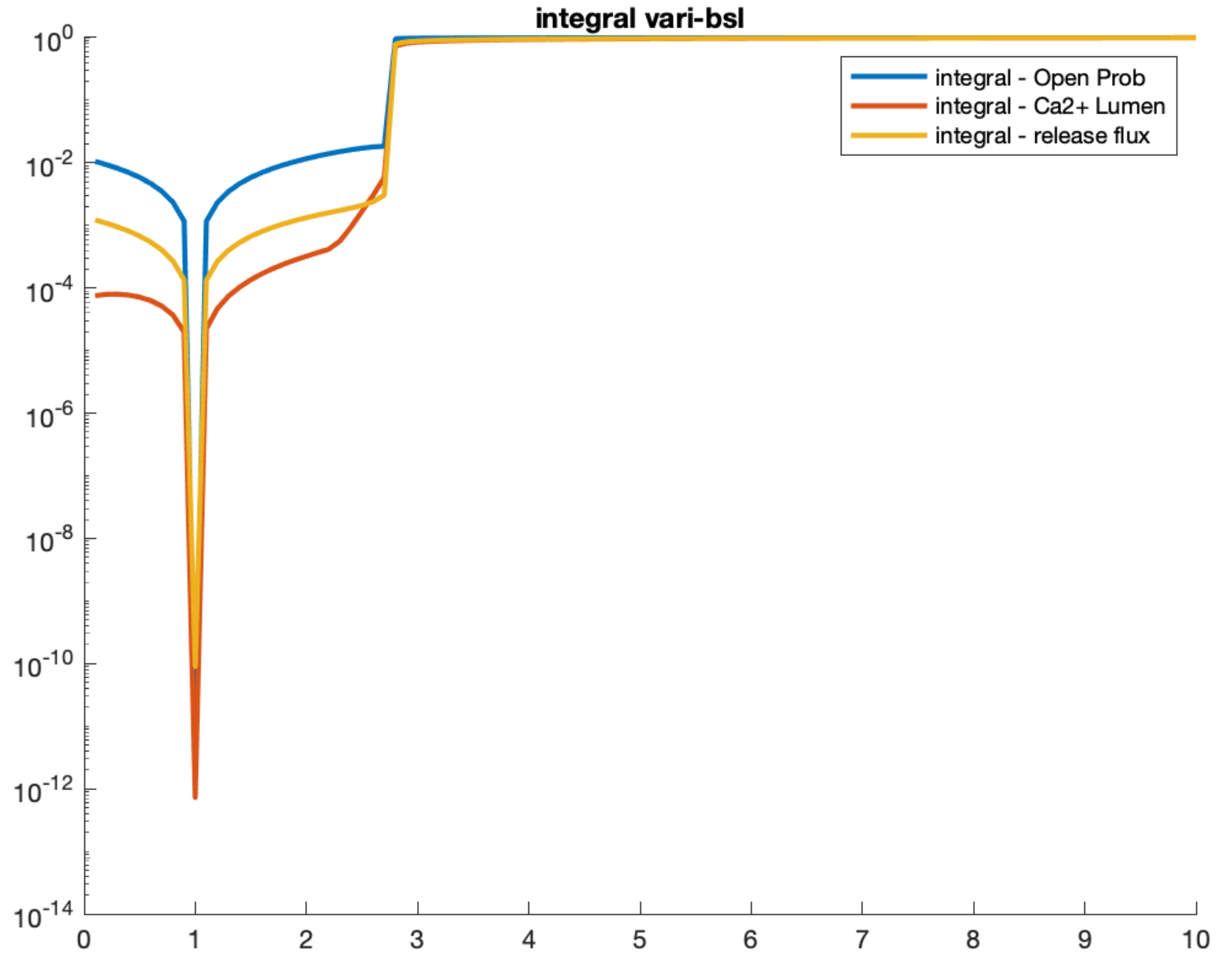
- For instance, when k≈30, $\alpha_1 \to 0$ for the lumenal concentration, but the curves significant differ, which reveals the necessity to examine both α_1 and α_2 simultaneously.

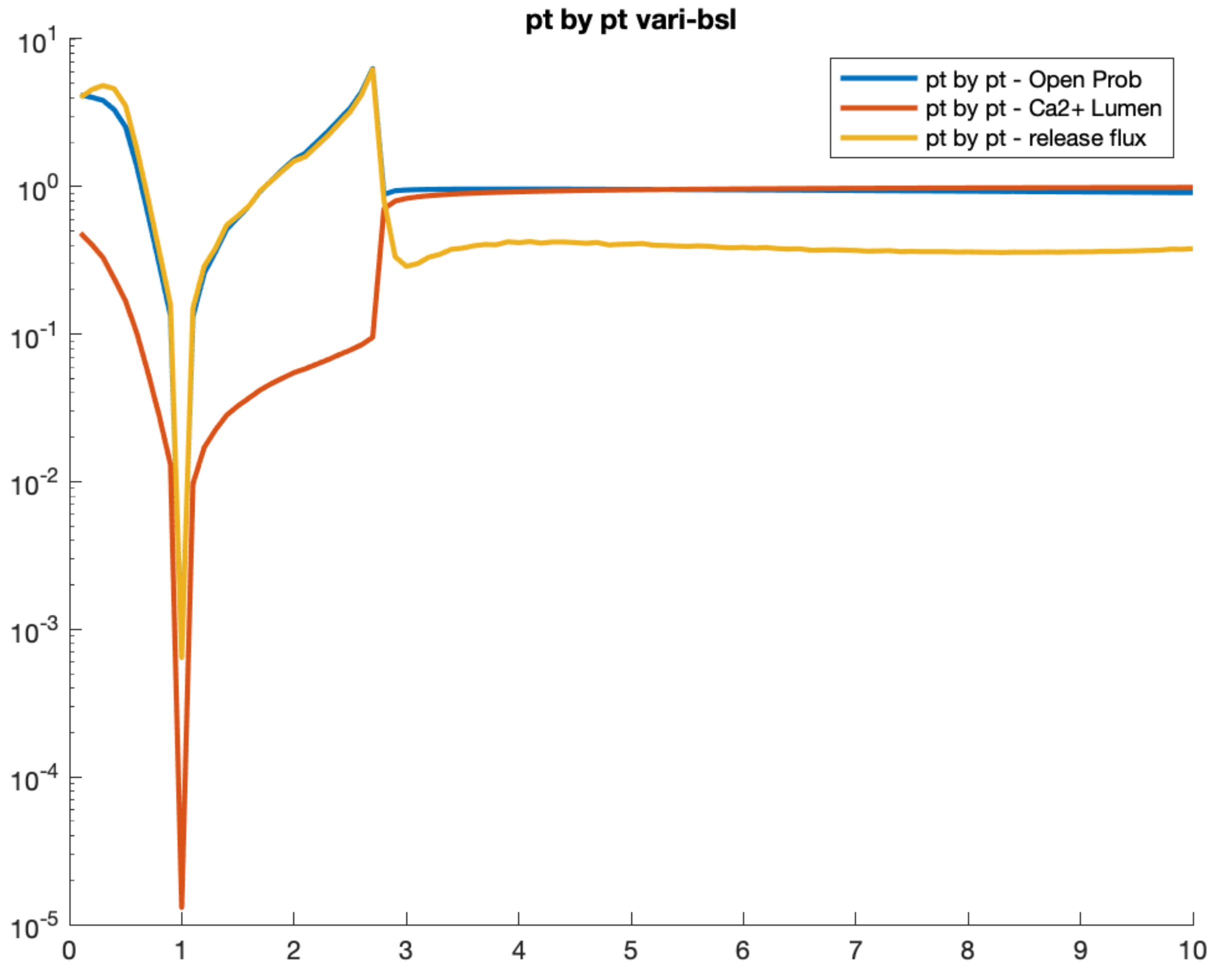
$[B_{SL}]_{total}$

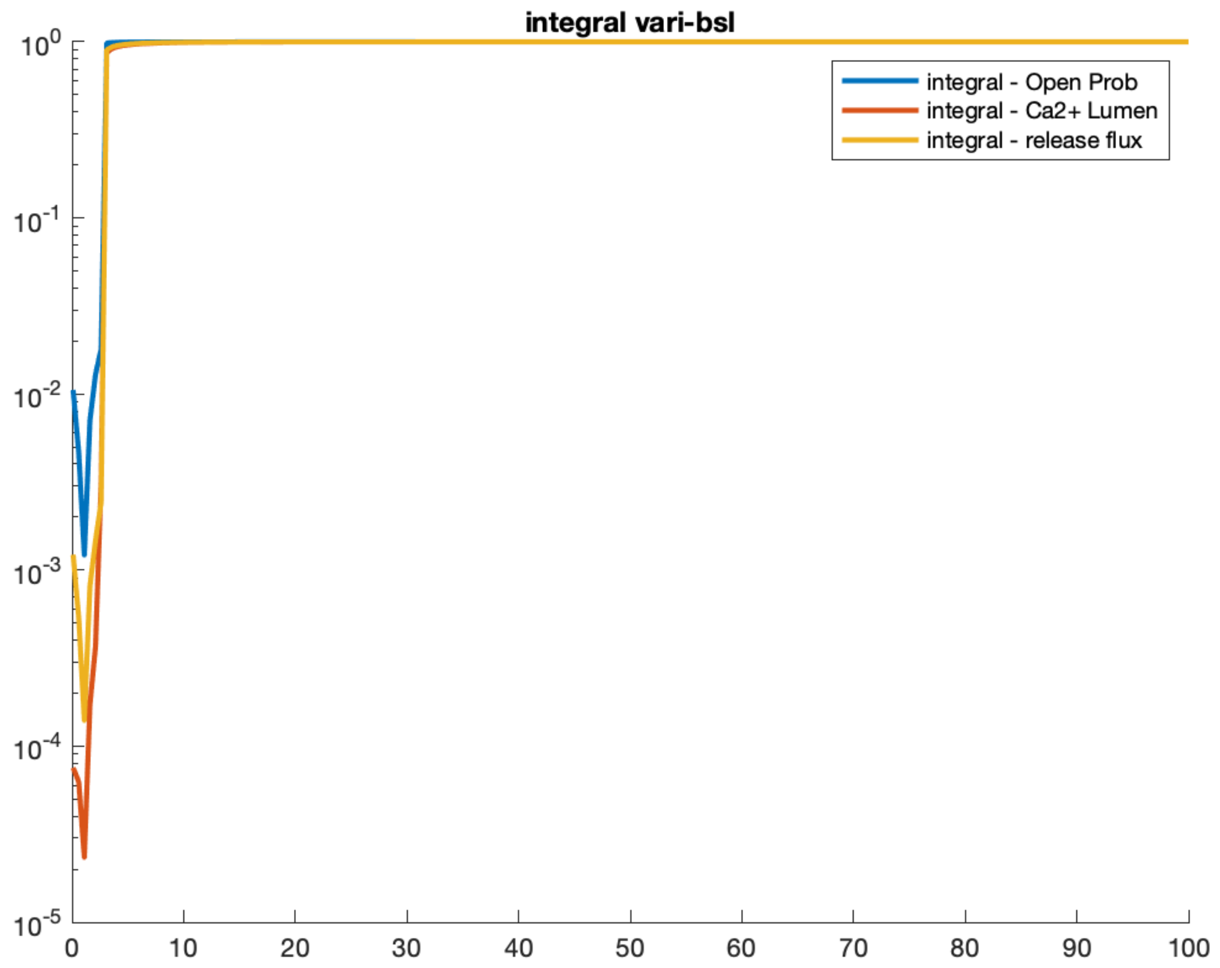
- Stable when k is small (0.01~3), but shrinks to 0 when k>3.

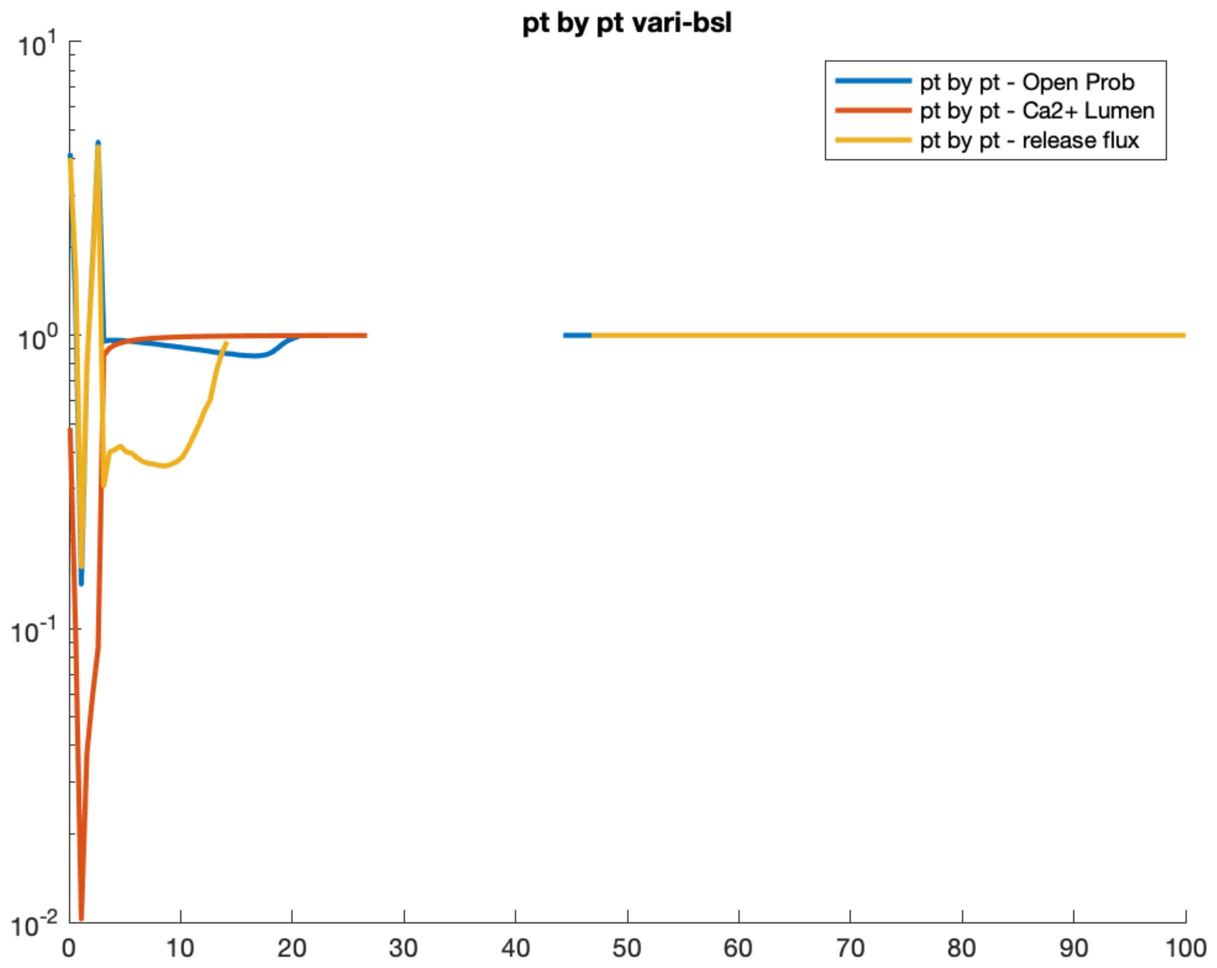
α_1

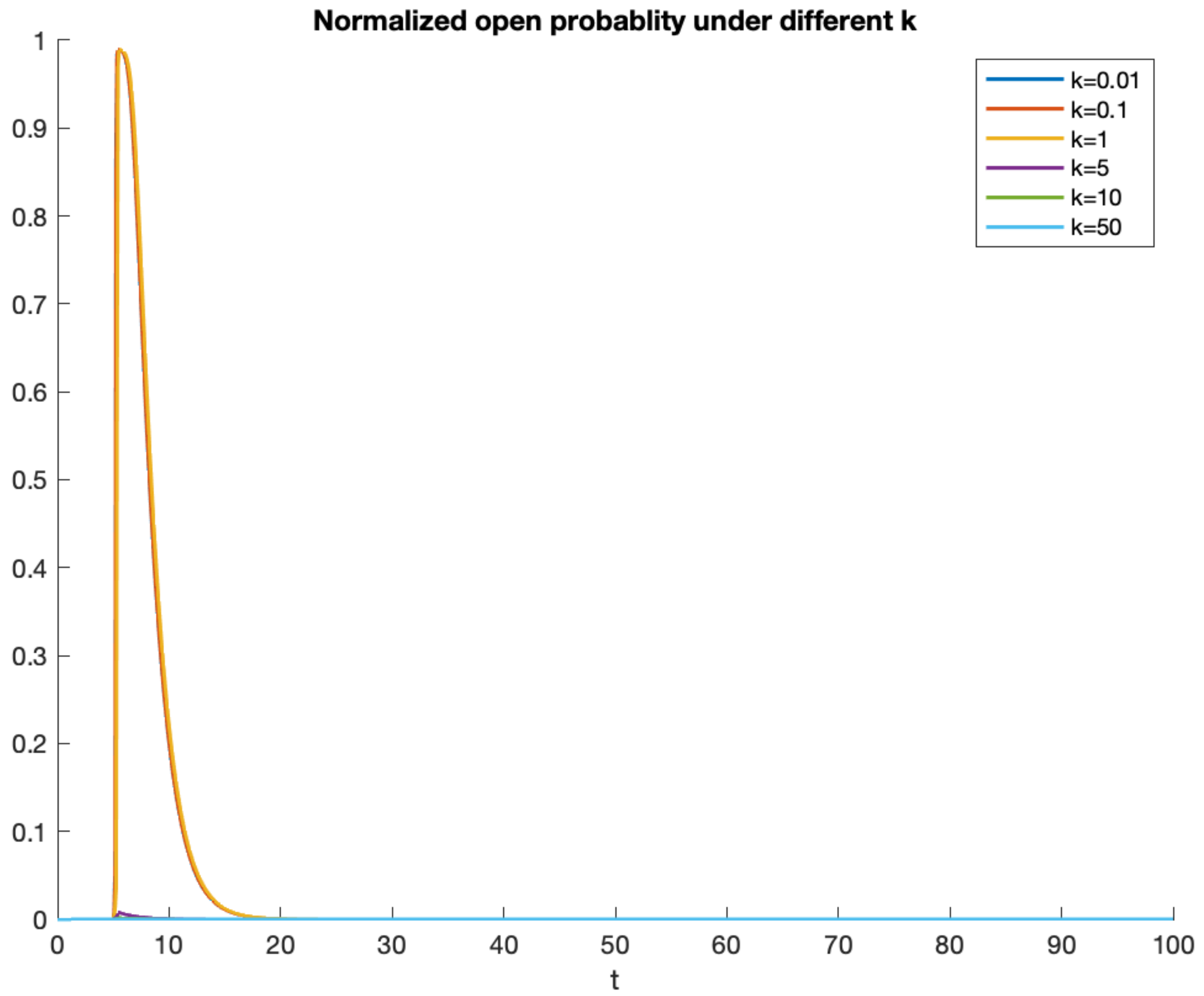
α_2

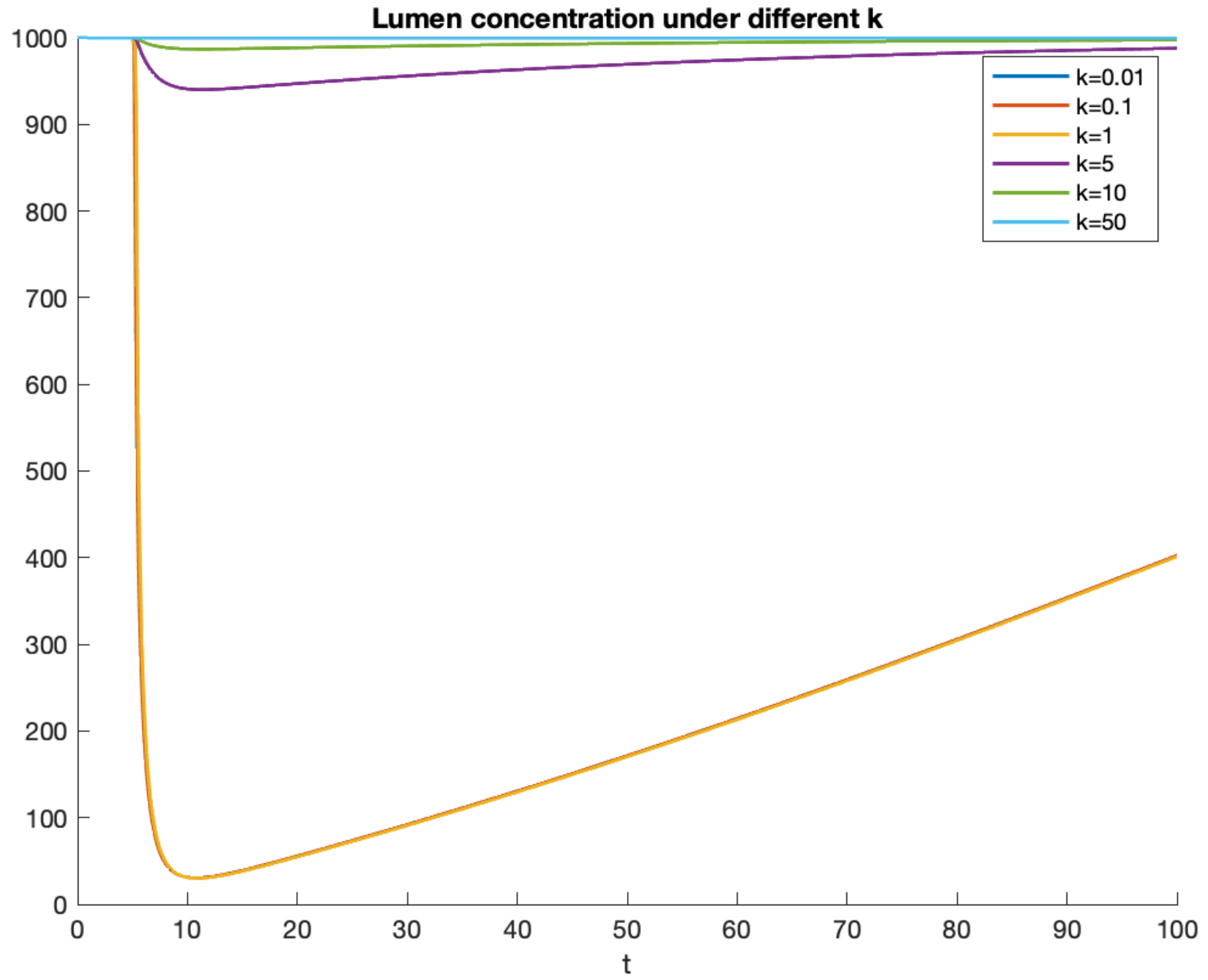












Systematic Approaches

- Direct Method (Dickinson, 1975)
- Adjoint Method (Cao, 2003)
- I have consulted some experts in numerical simulations, like Professor Greengard and Professor Overton, who suggested these methods but also told me that our models might be too complicated to use these systematic approaches.