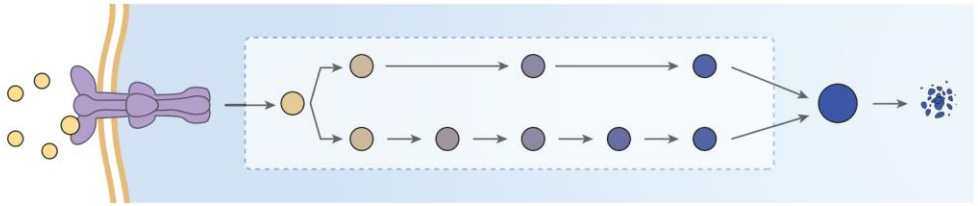
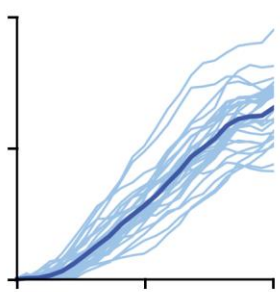
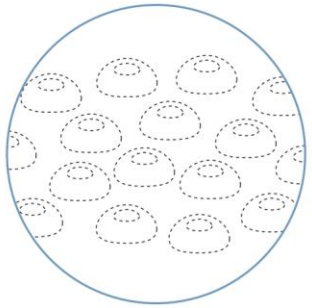
Multiple-timescale pathways reduce the cell-to-cell heterogeneity in response to external stress.

Multiple-timescale pathways



Small cell-to-cell heterogeneity





Multiple-timescale pathways reduce the cell-to-cell heterogeneity in response to external stress.

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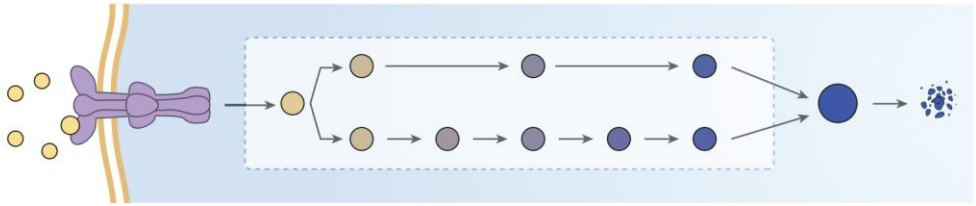
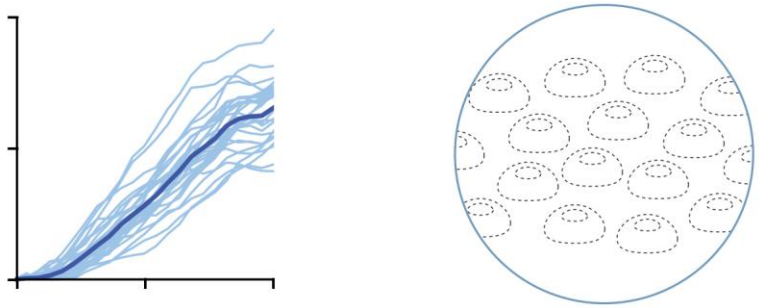
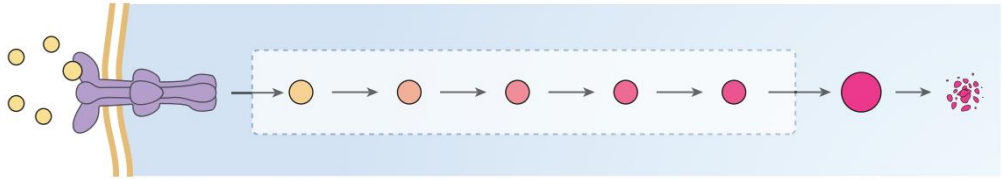


Small cell-to-cell heterogeneity

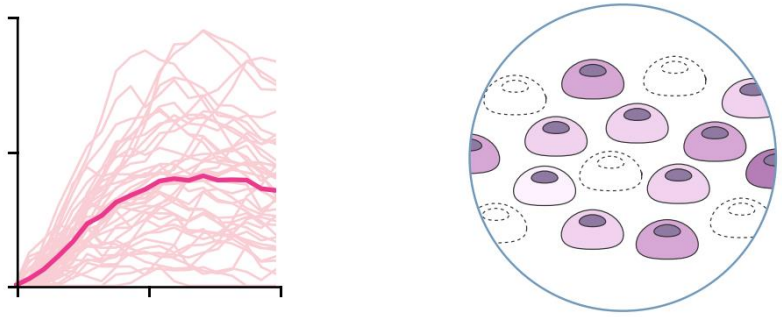


VS

Single-timescale pathways



Large cell-to-cell heterogeneity



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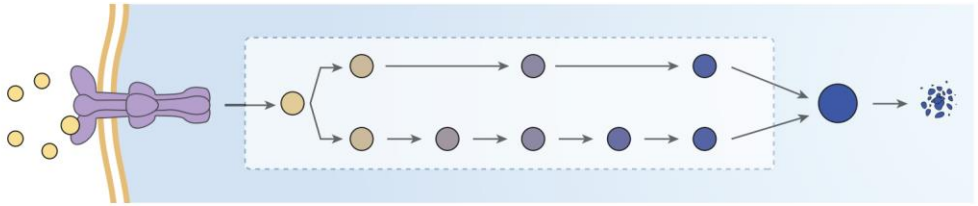
Multiple-timescale pathways



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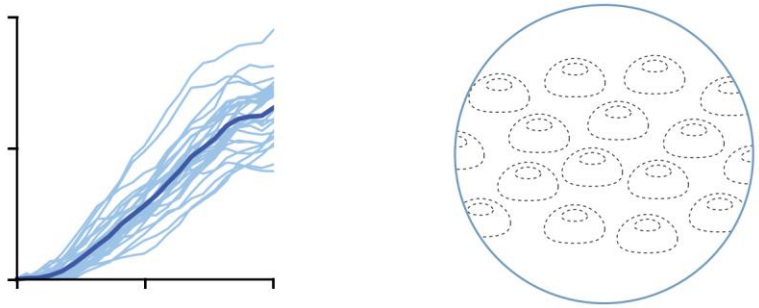

VS

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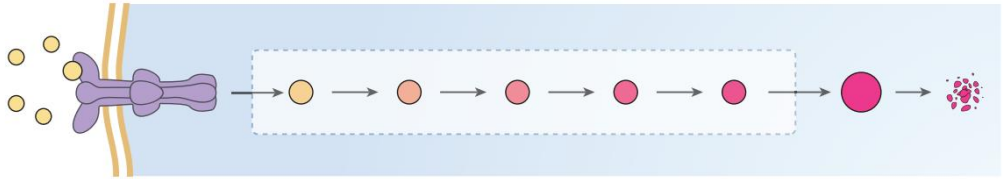

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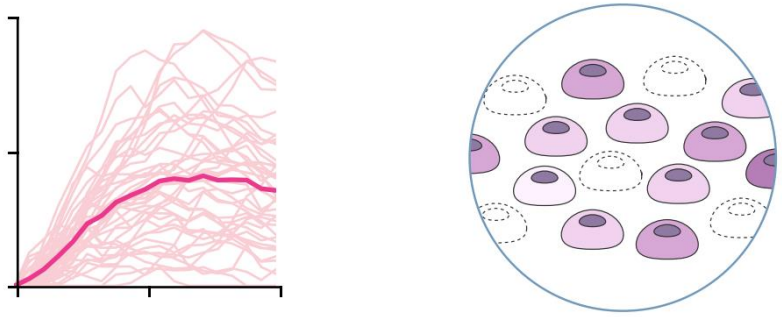
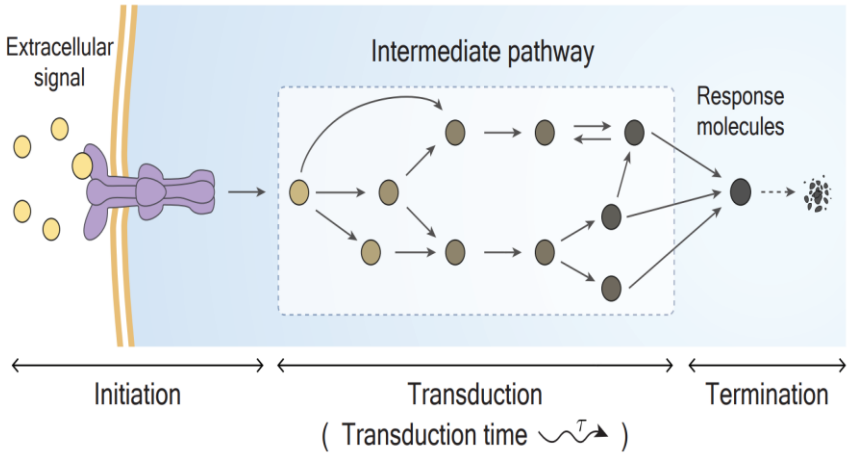


Goal: Find <u>why</u> multiple-timescale pathways reduce the cell-to-cell heterogeneity.

Signal transduction pathways with hidden reactions can be described with a stochastic delayed birth-death process with a single random time delay.



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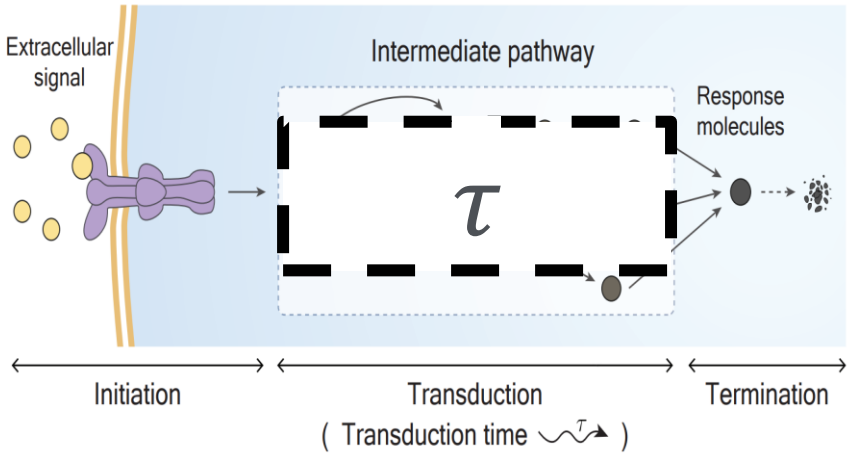

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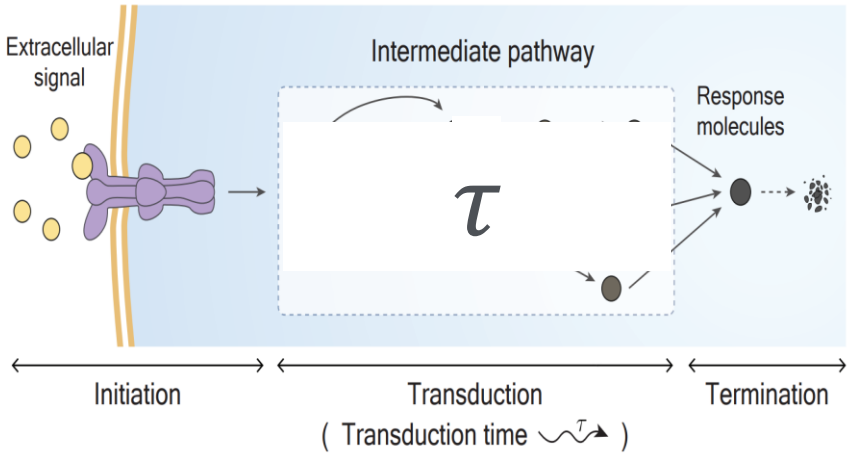
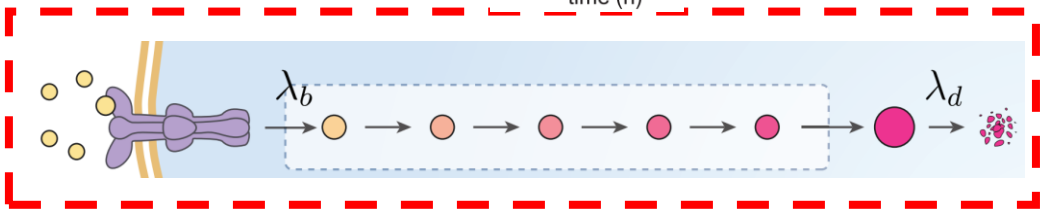


$\tau \sim g(t)$



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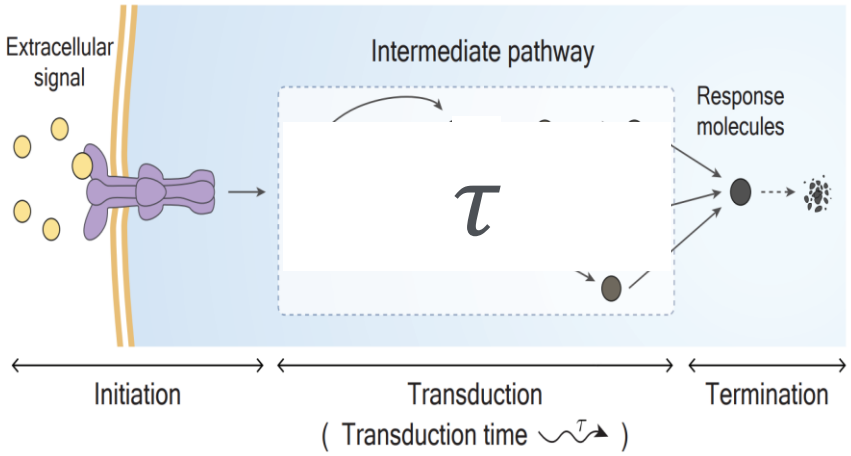

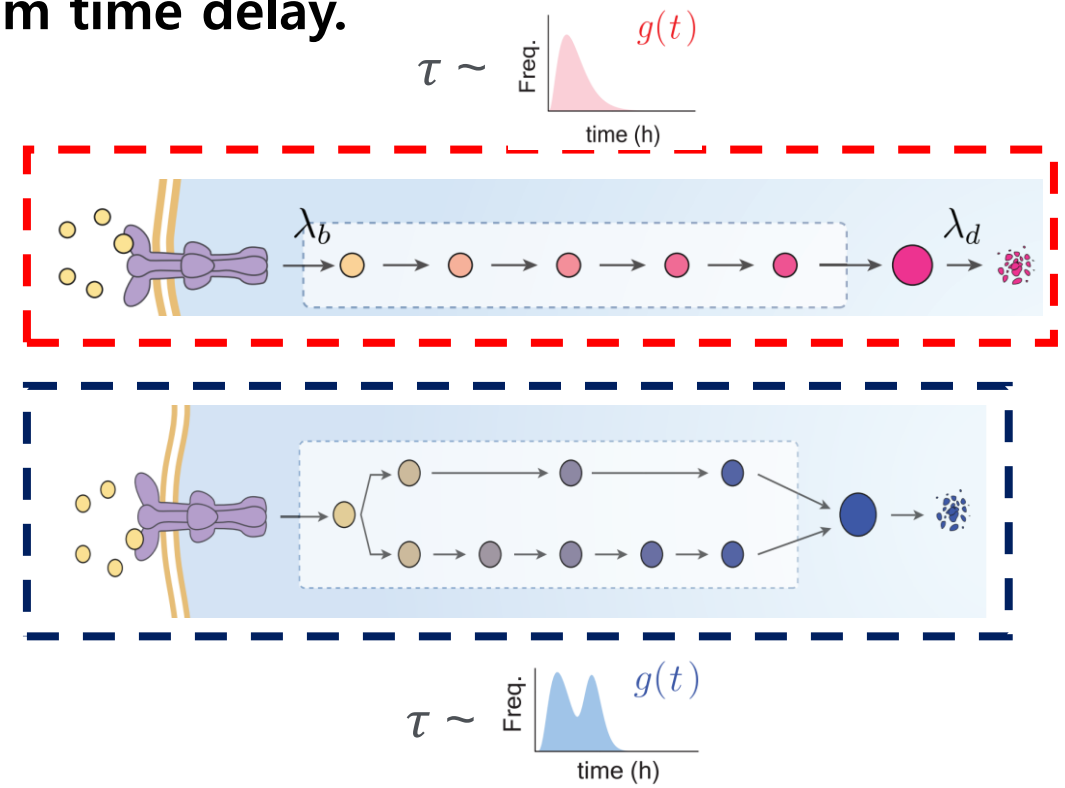

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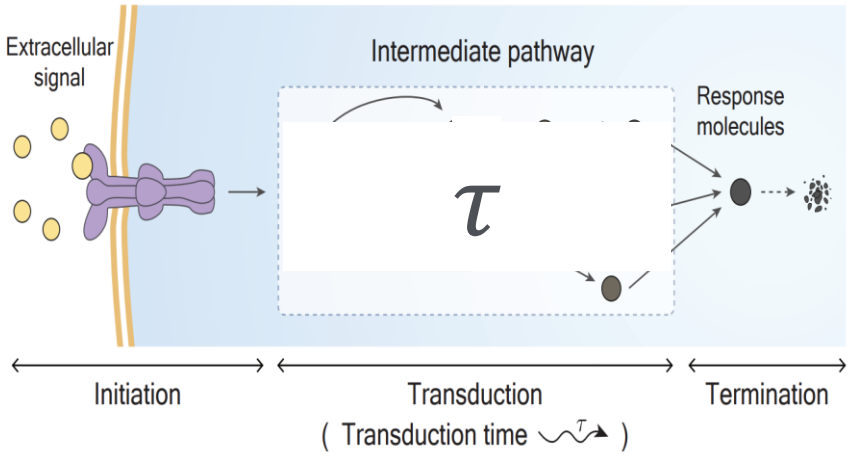

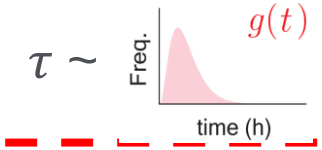

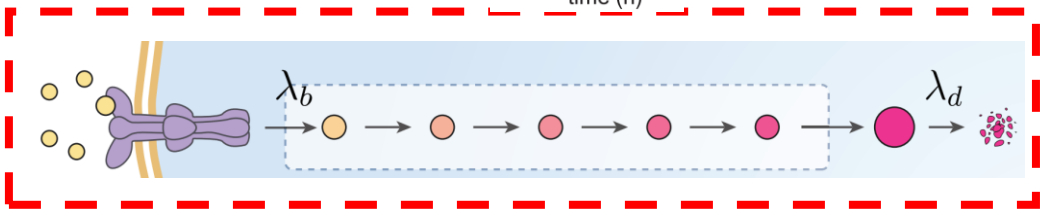

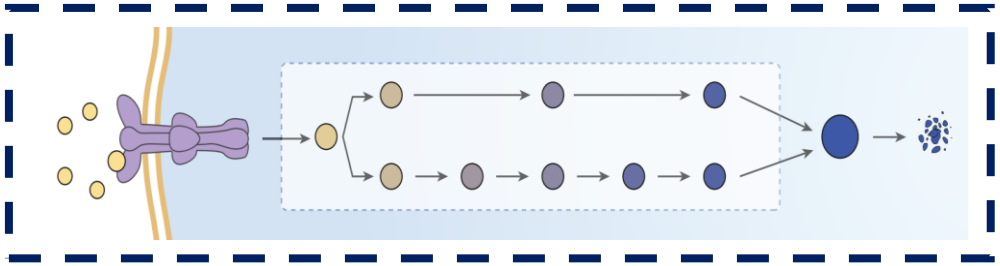

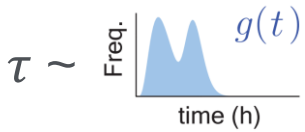

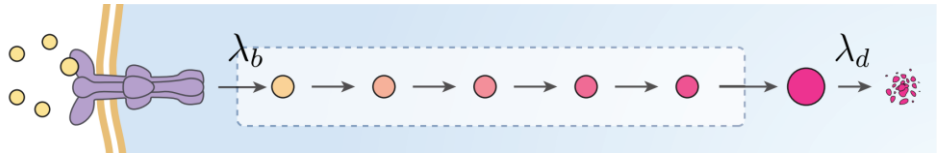

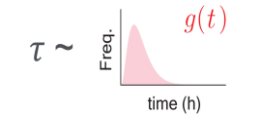

Delayed Gillespie with unimodal delay

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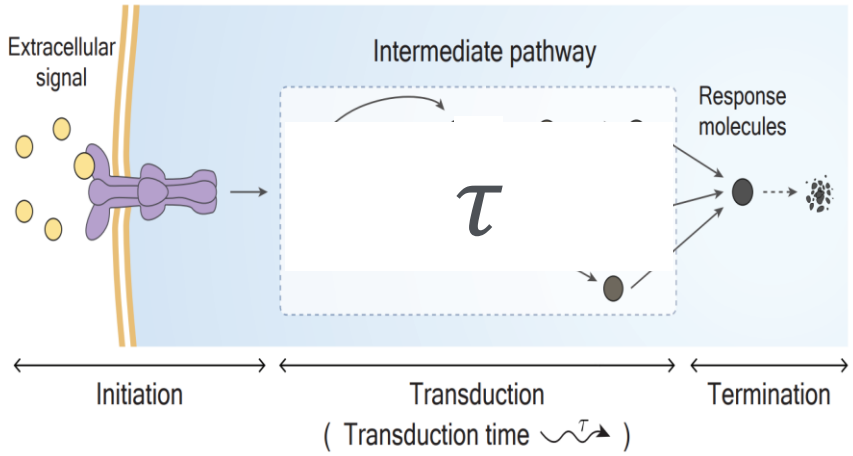

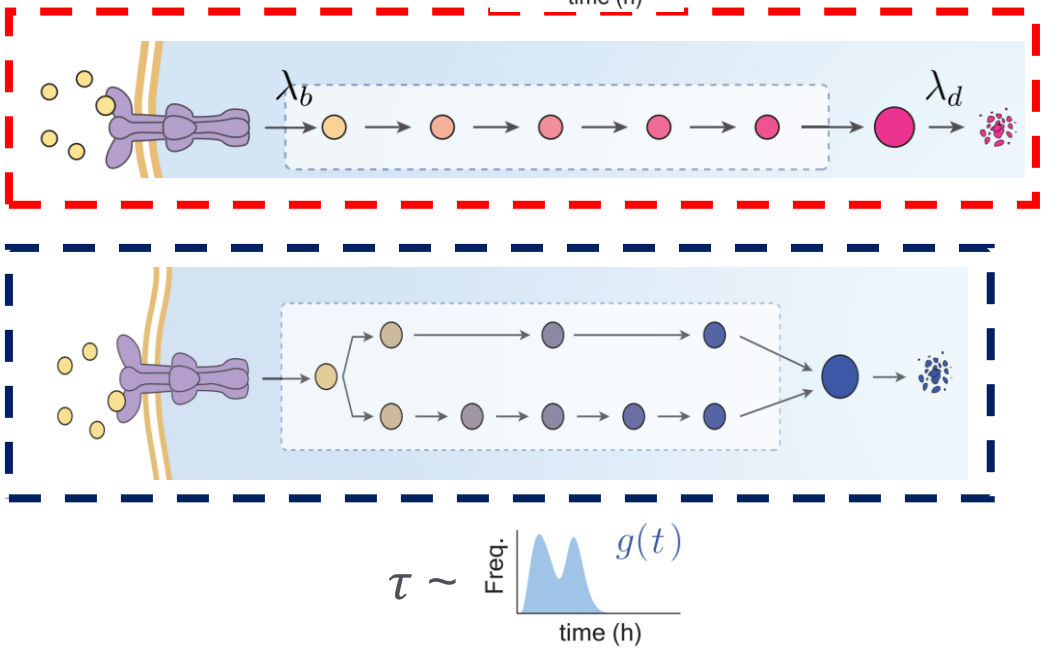

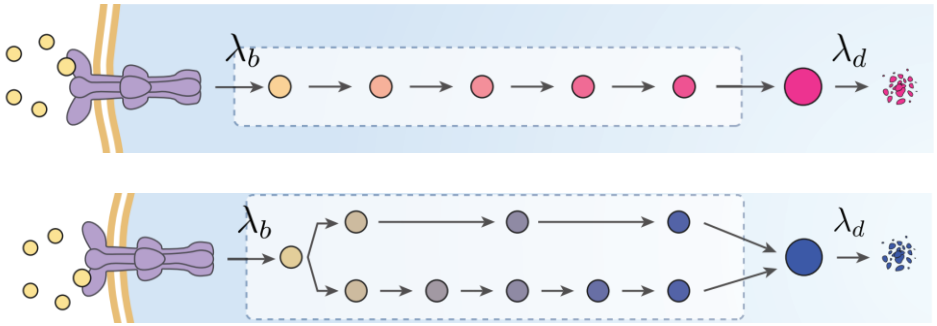

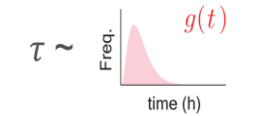

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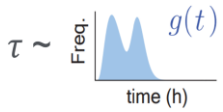
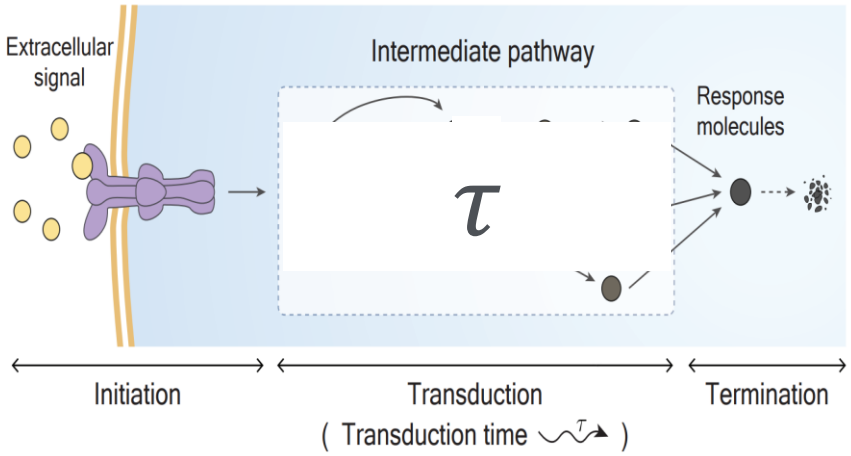
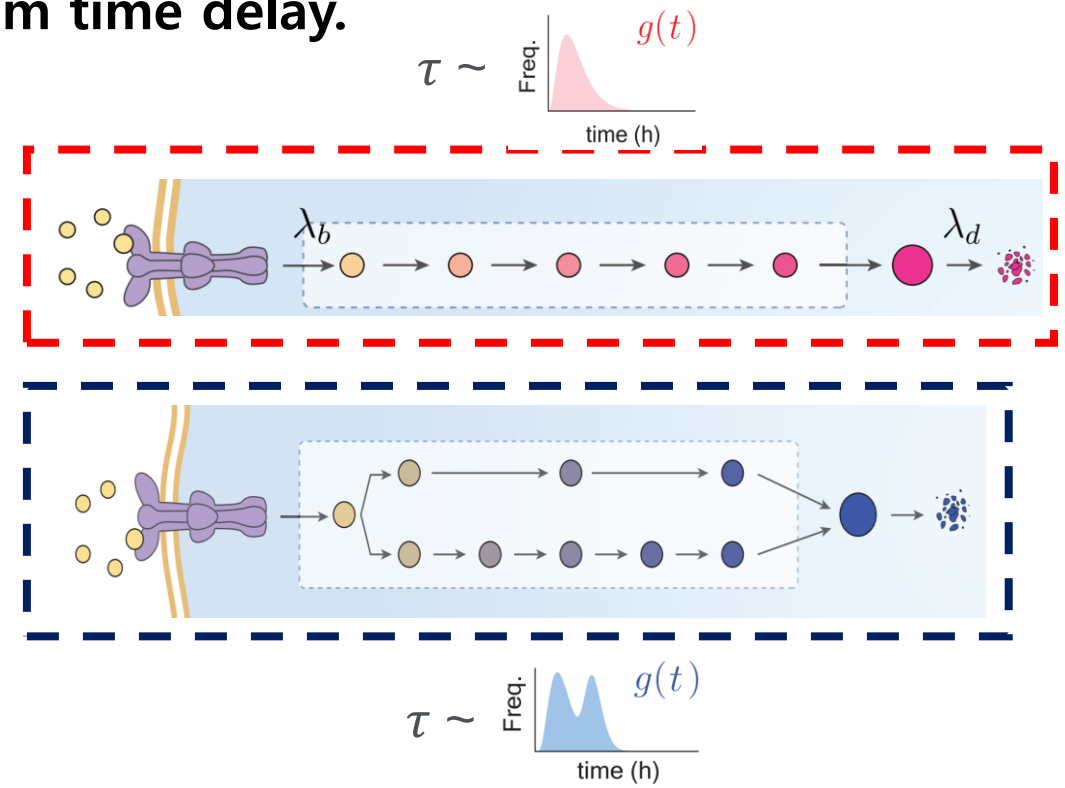
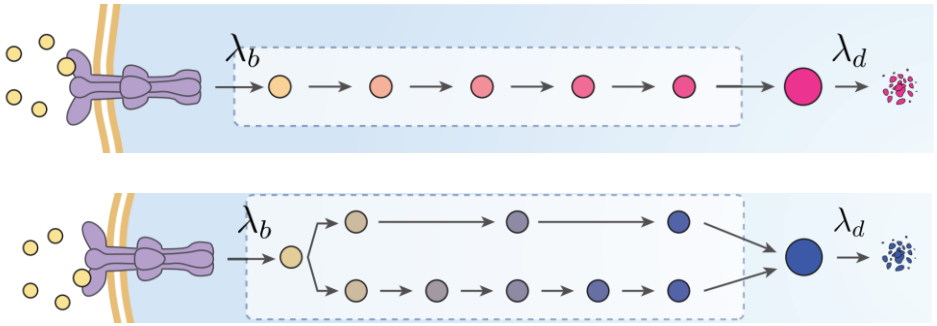


Delayed Gillespie with bimodal delay

Signal transduction pathways with hidden reactions can be described with a stochastic delayed birth-death process with a single random time delay.







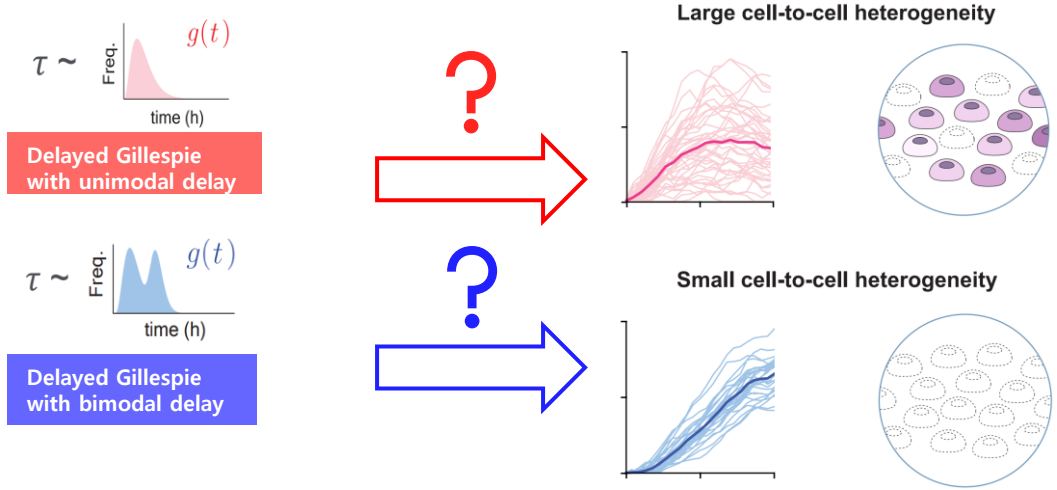
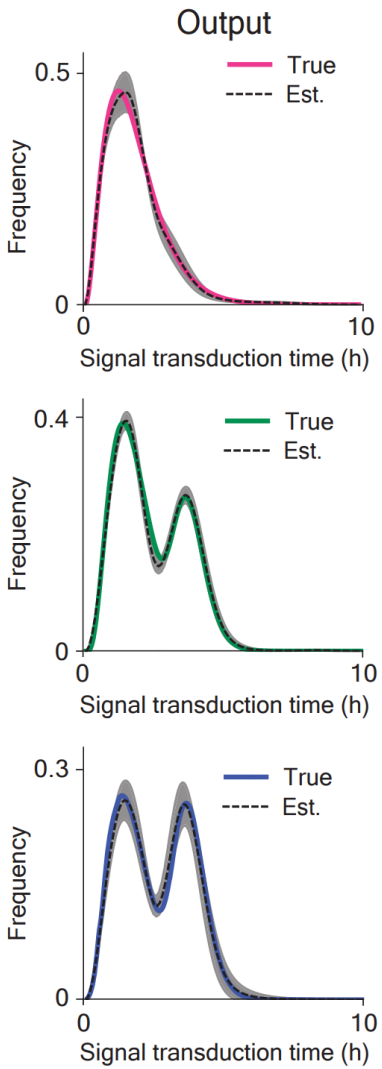


Fig.3.B time traces show no significant differences between unimodal and bimodal (weak/strong) delay distributions.



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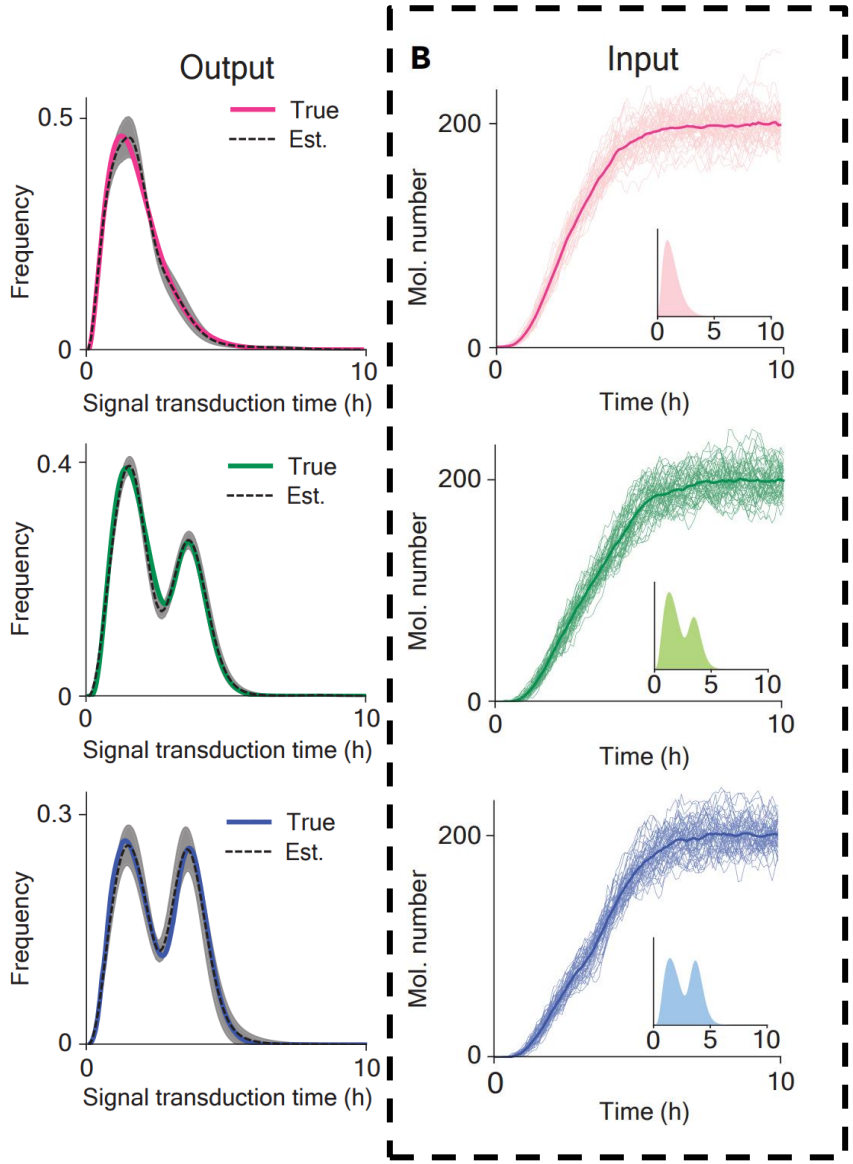

No visible difference.

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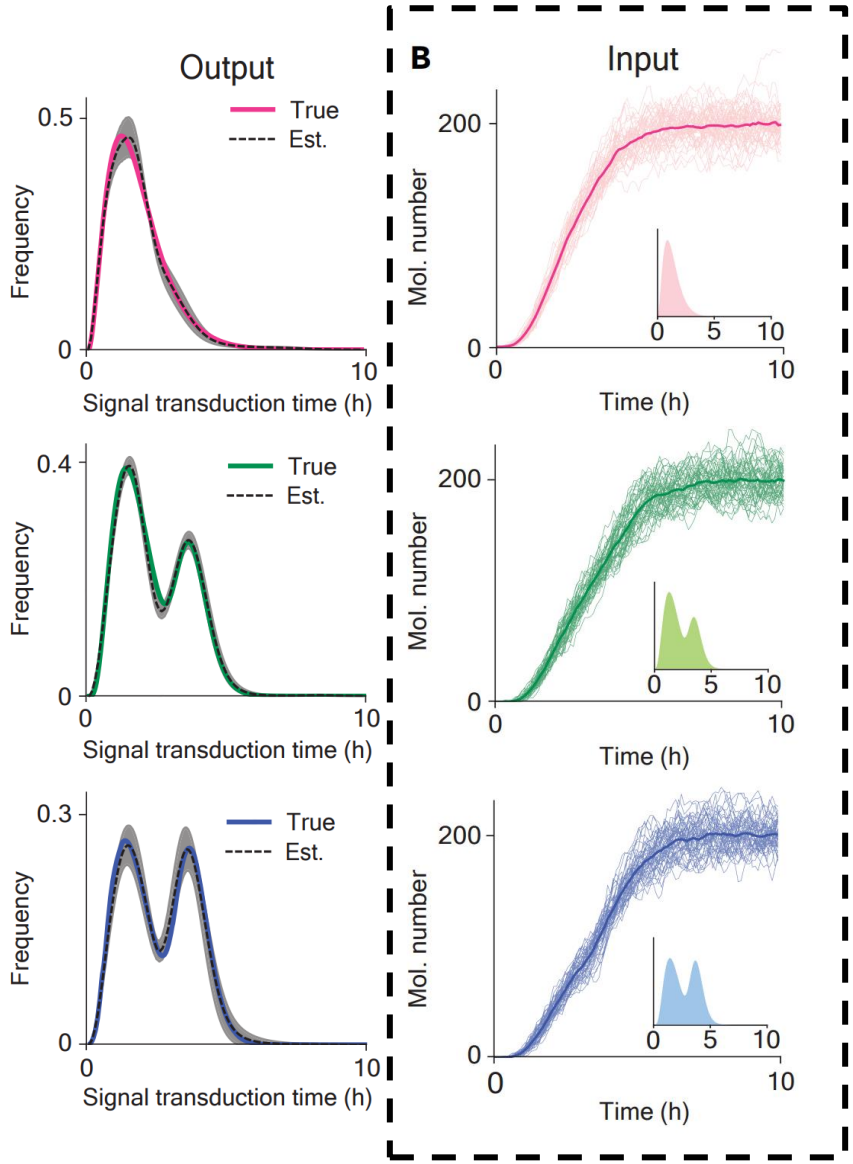
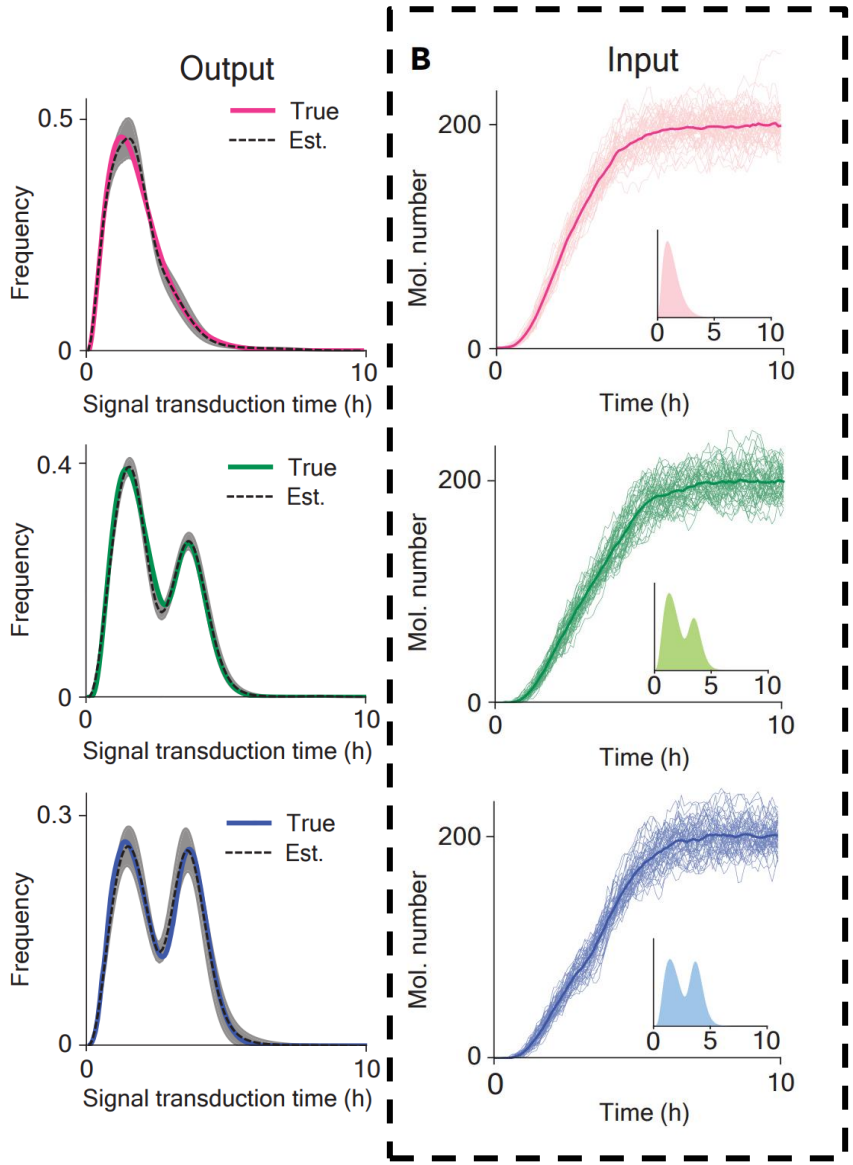


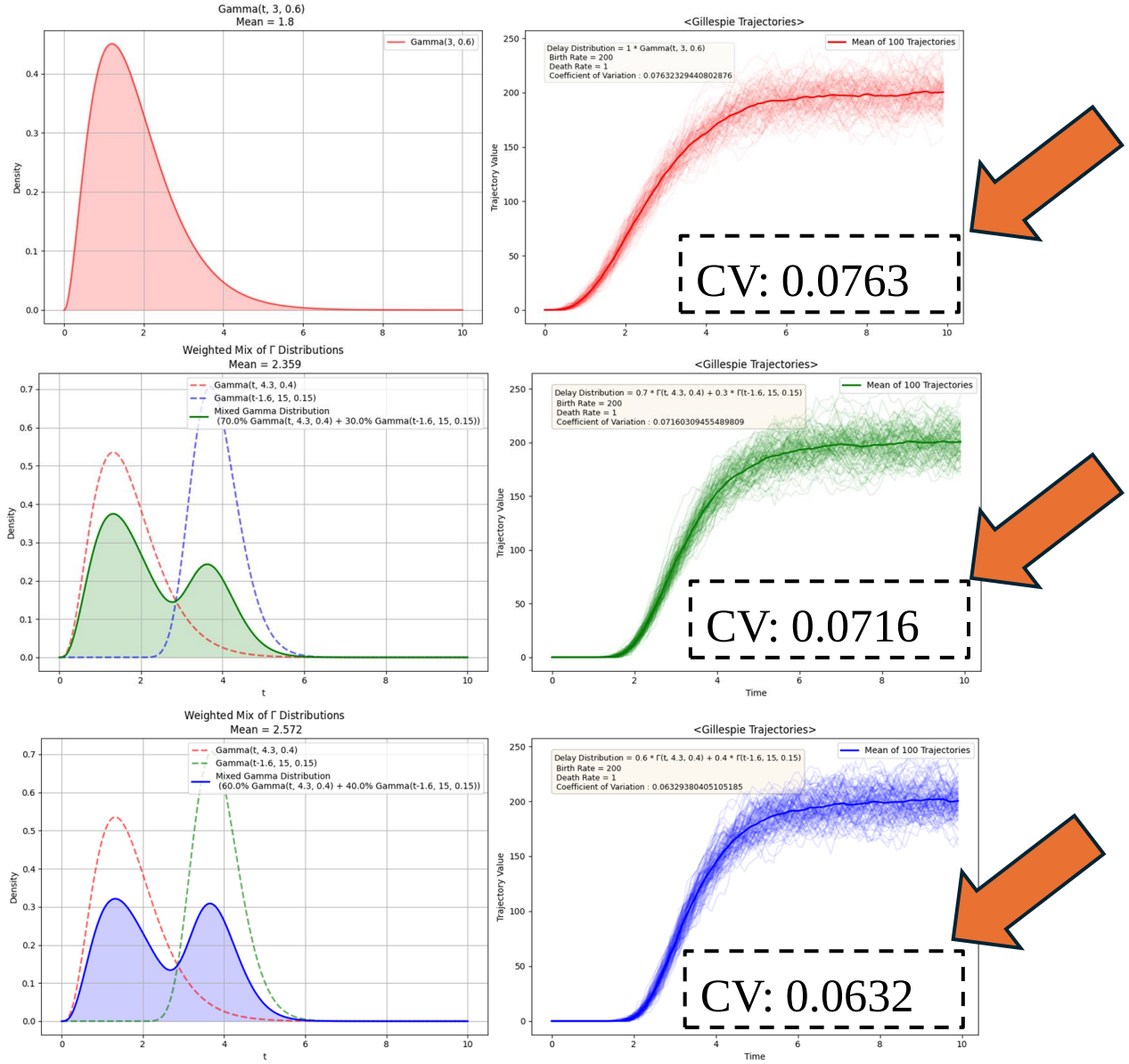
No visible difference.

But Exact CV..??

$$CV = \left(\frac{\sigma}{\mu}\right) \times 100\%$$

Fig.3.B time traces show no significant differences between unimodal and bimodal (weak/strong) delay distributions.





Exact Coefficient of Variation (CV)? $CV = \left(\frac{\sigma}{\mu}\right) \times 100\%$

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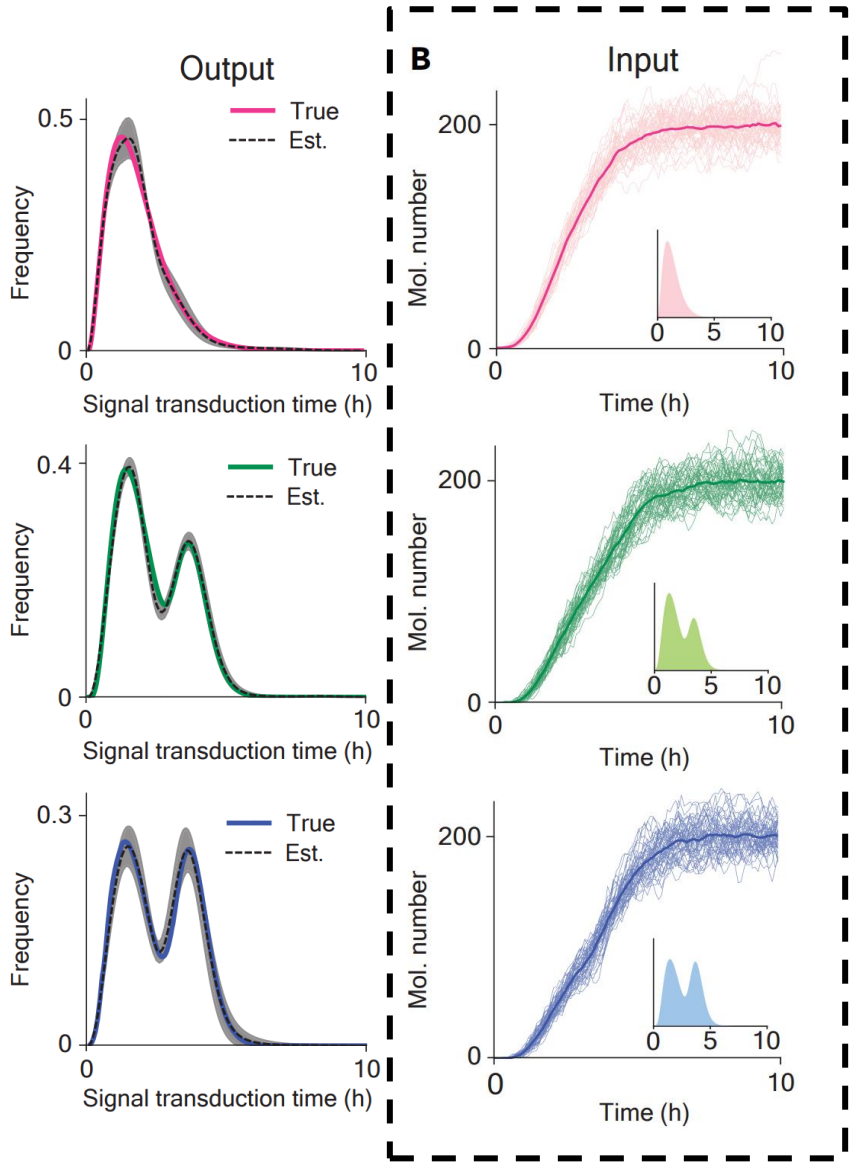

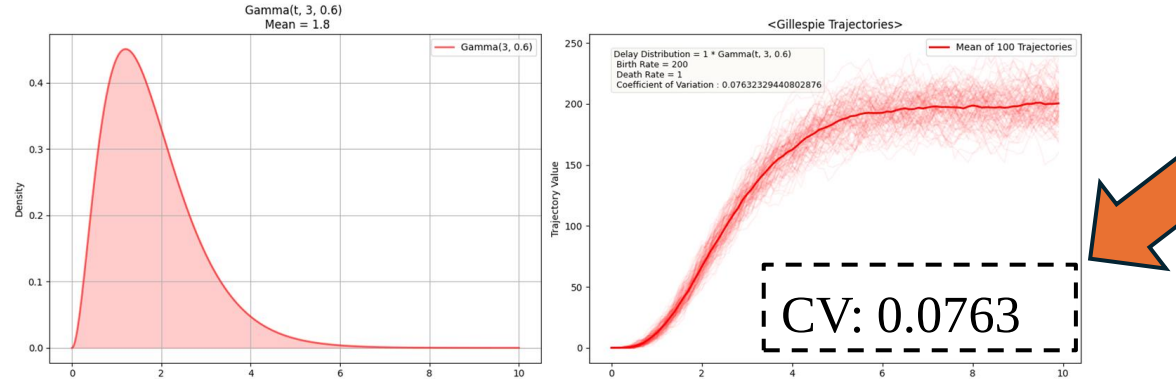

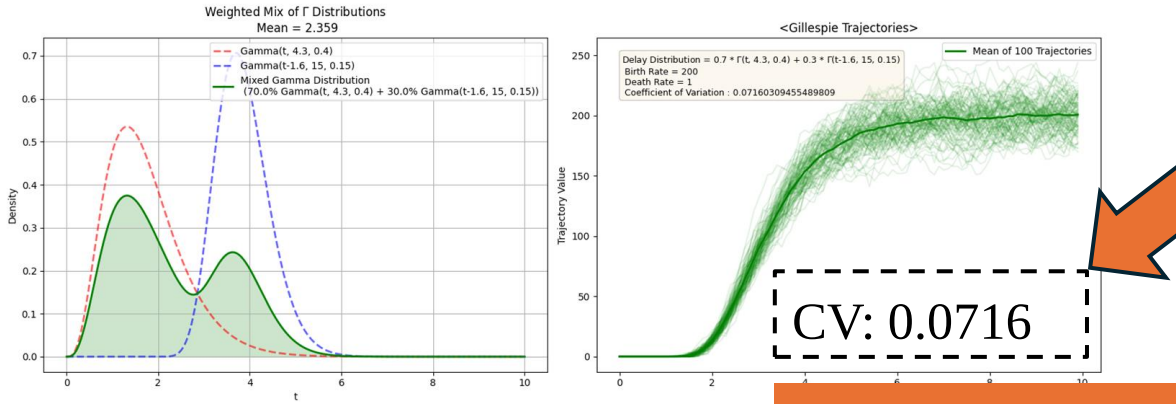

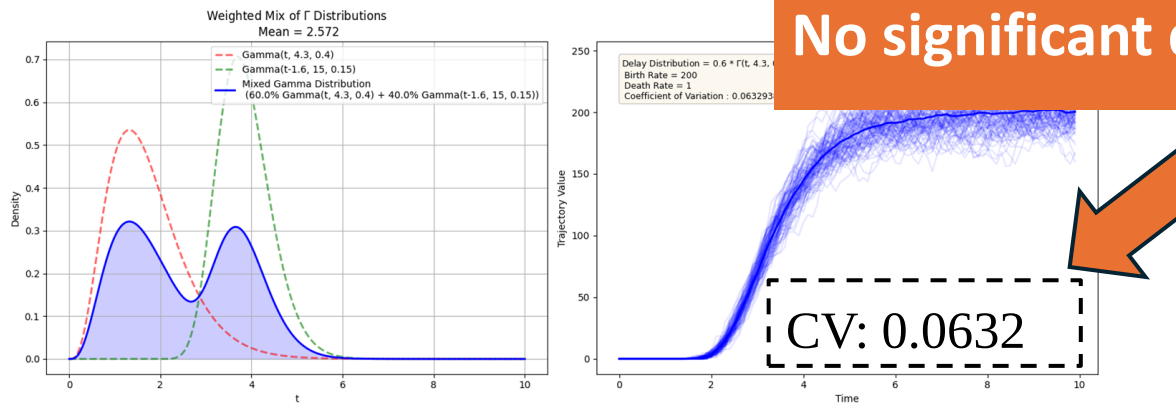

No significant difference

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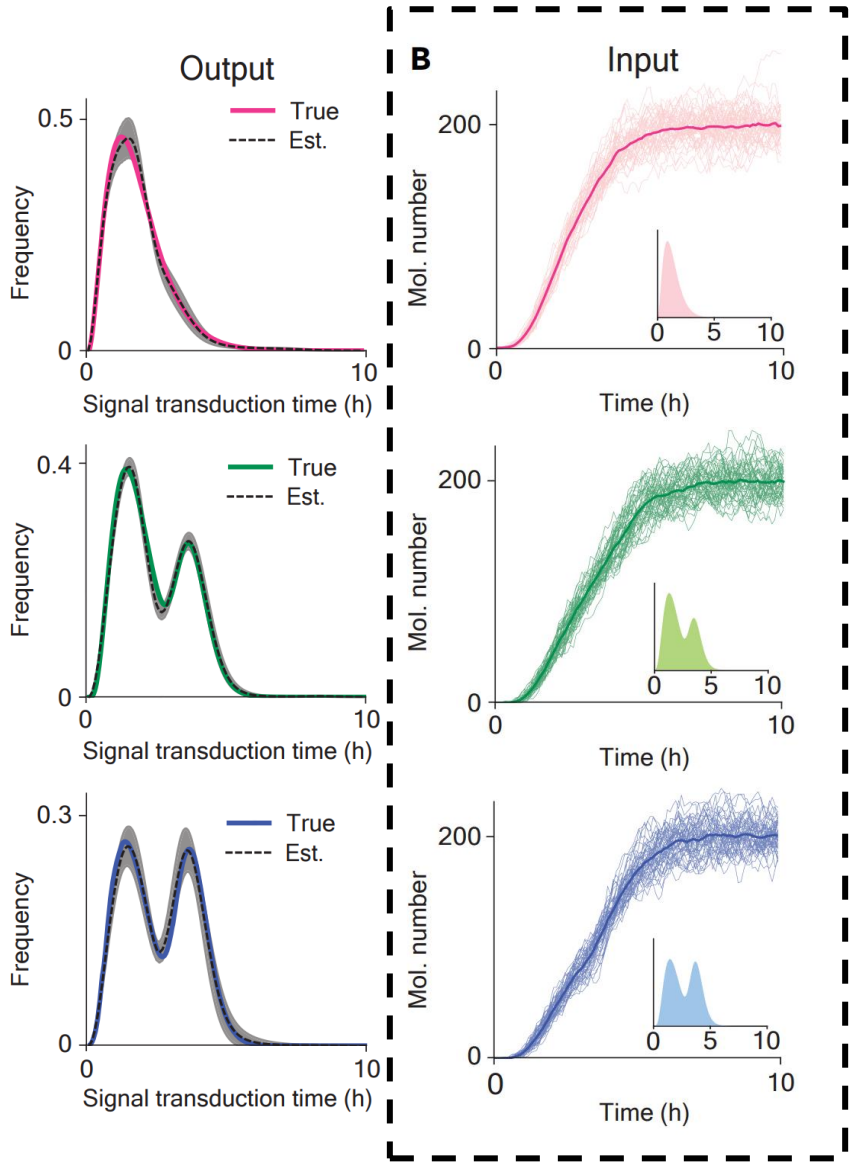

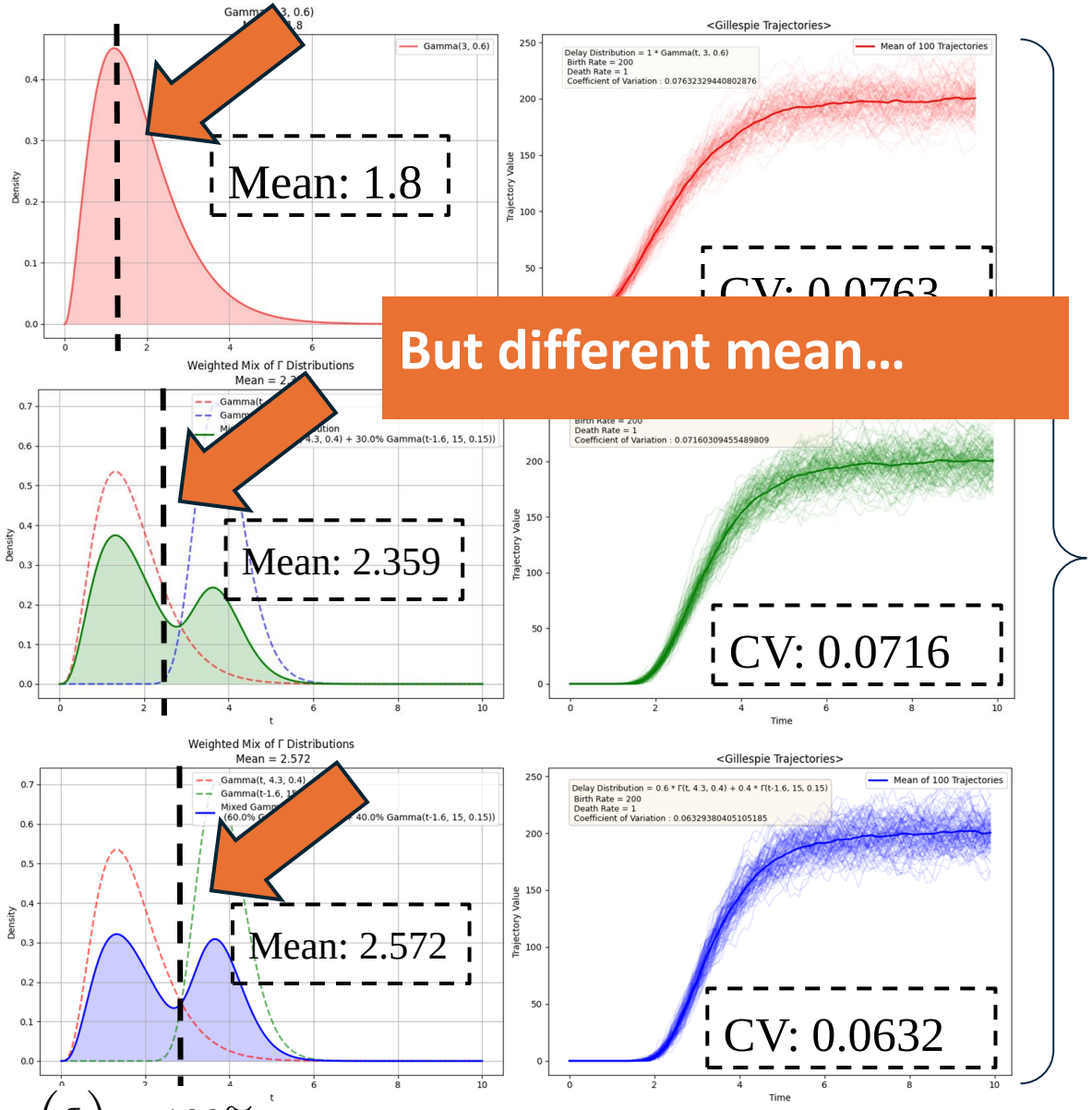

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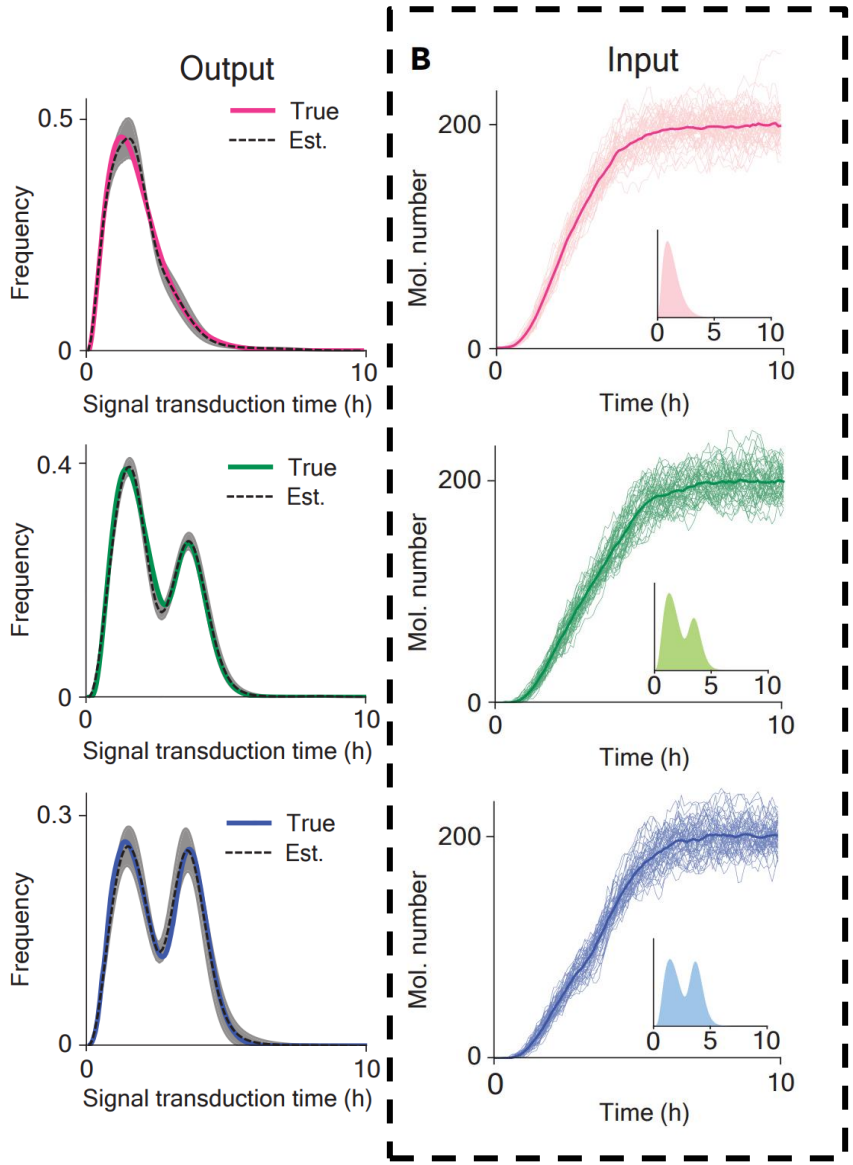
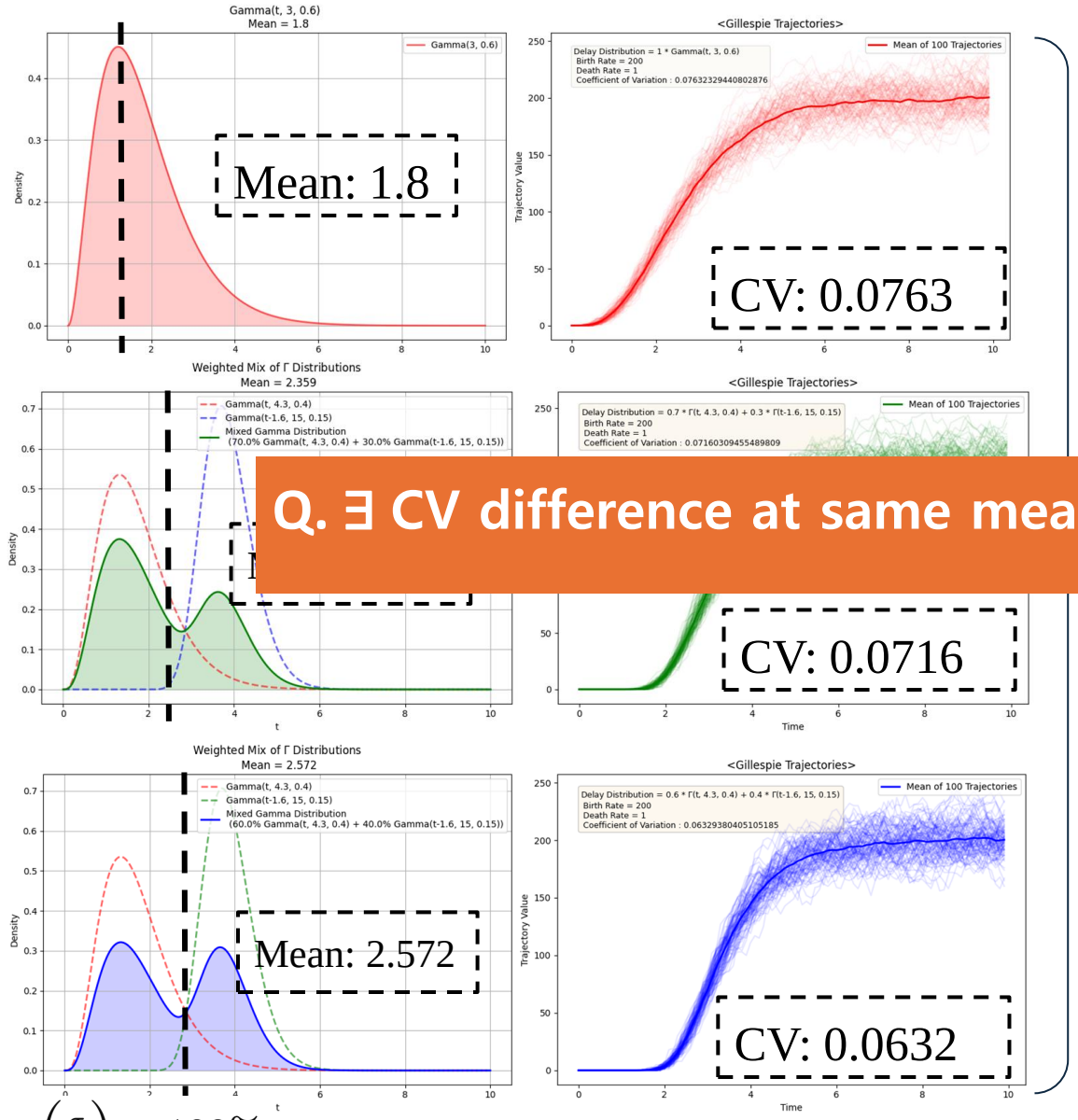
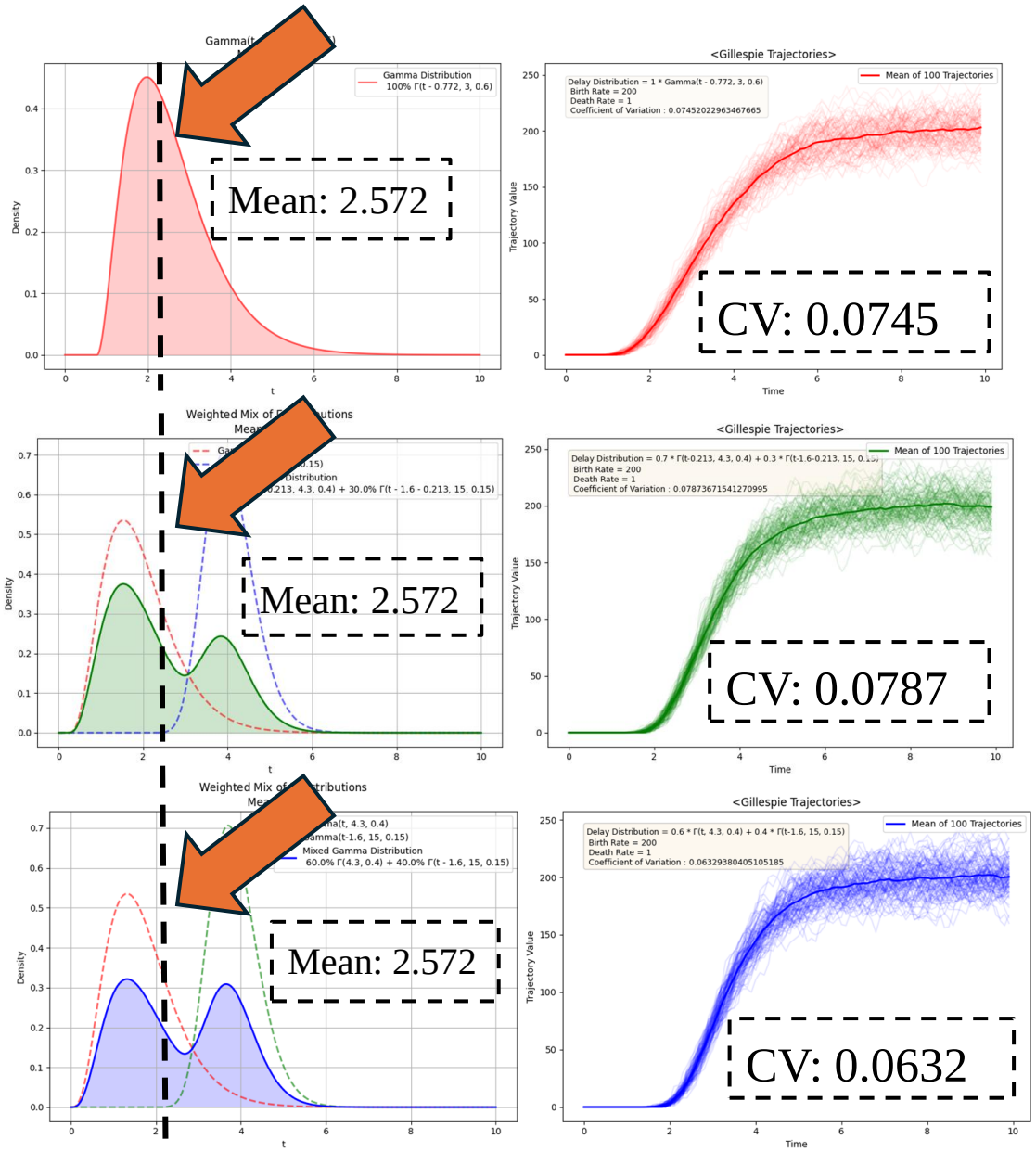




Q. ∃ CV difference at same mean?

Exact Coefficient of Variation (CV)? $CV = \left(\frac{\sigma}{\mu}\right) \times 100\%$

Unimodal and bimodal (weak/strong) delay distributions with the same mean show no significant differences in final time trace heterogeneity.



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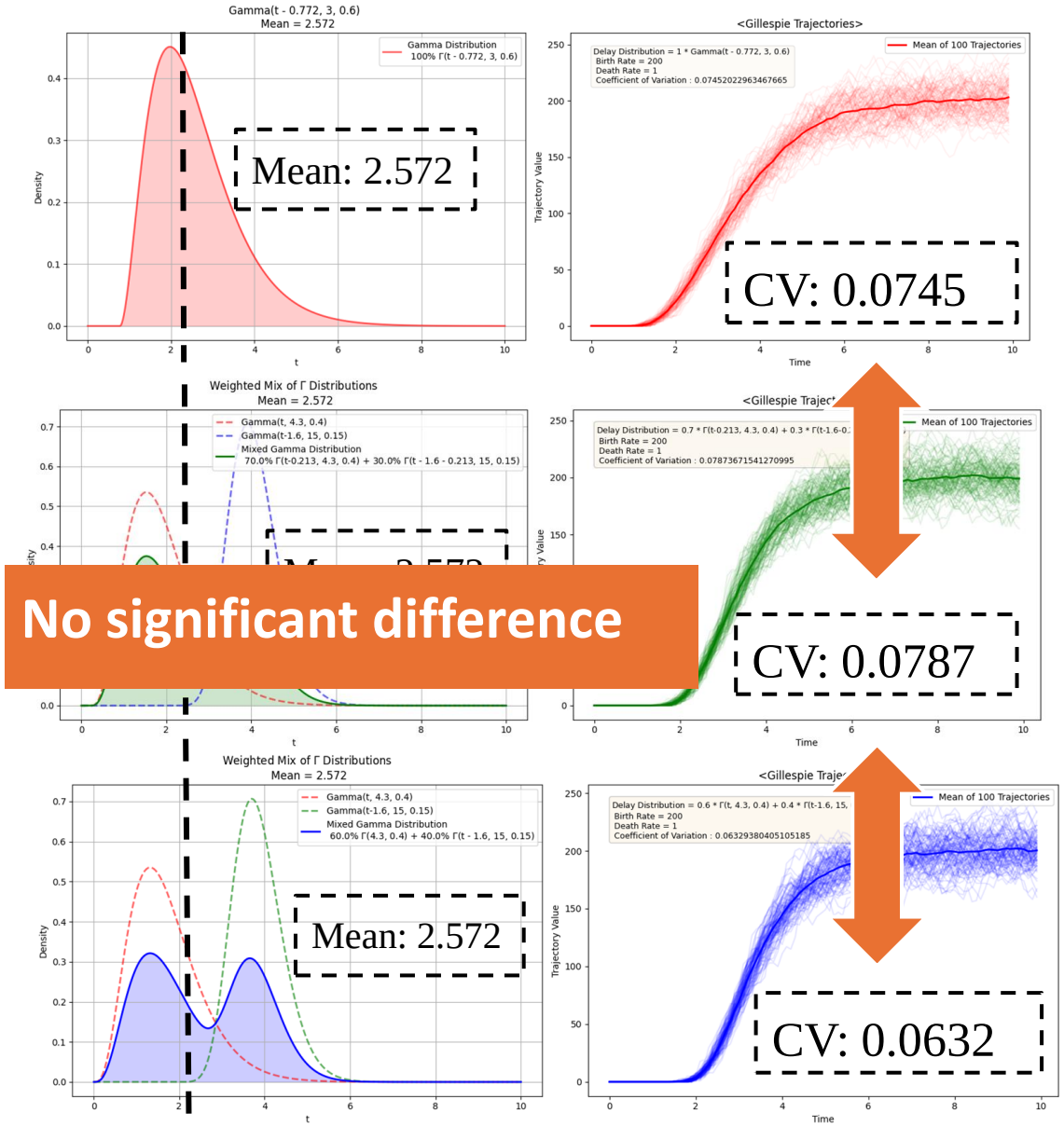

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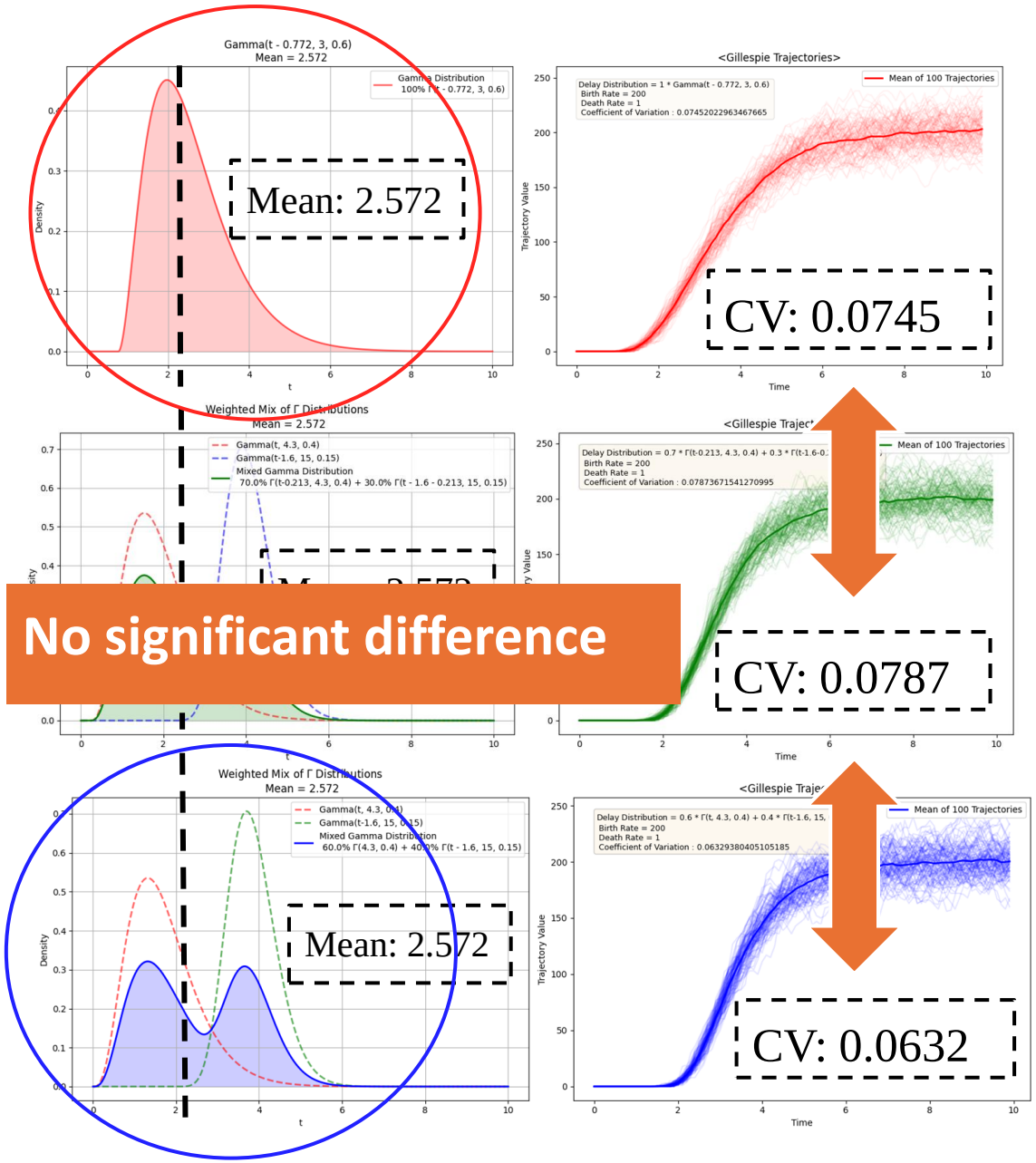
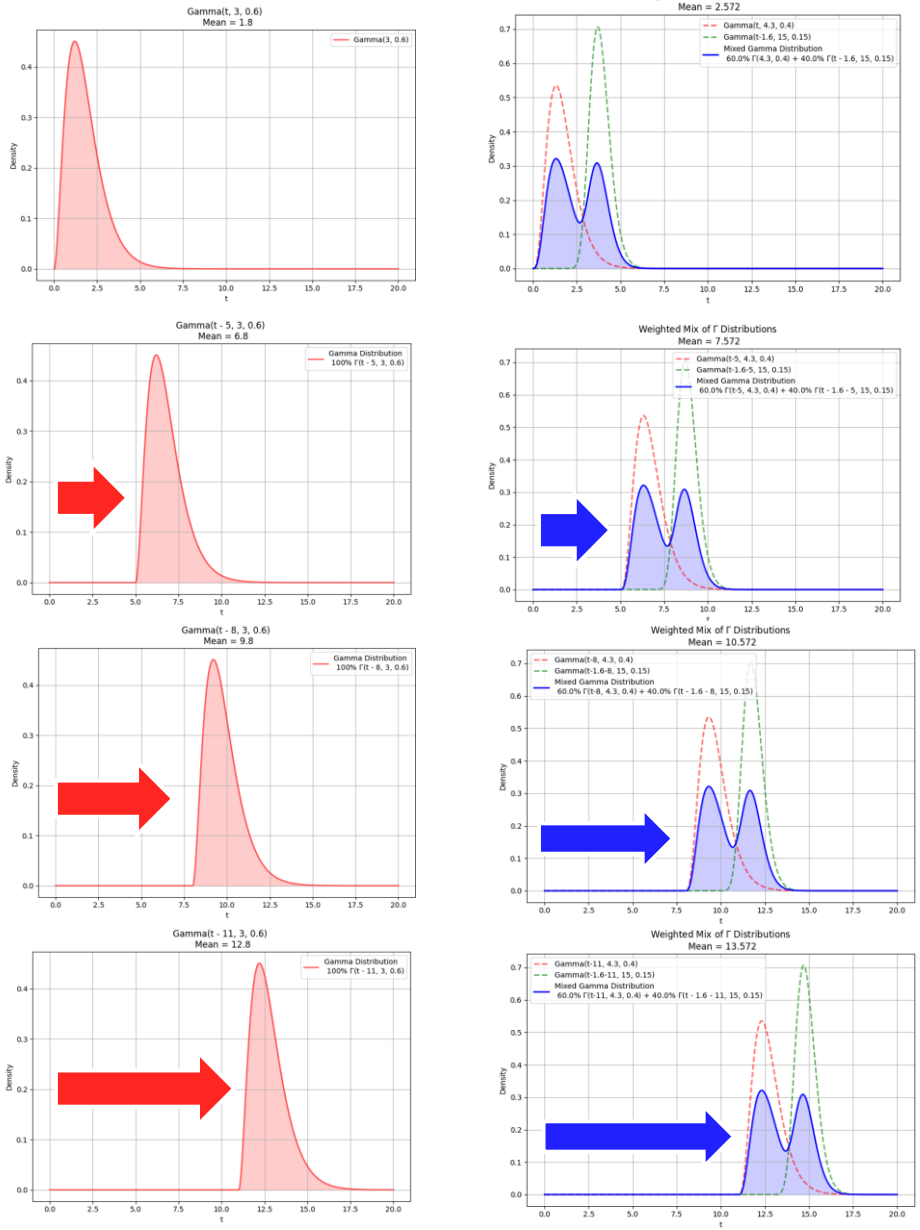


No significant difference



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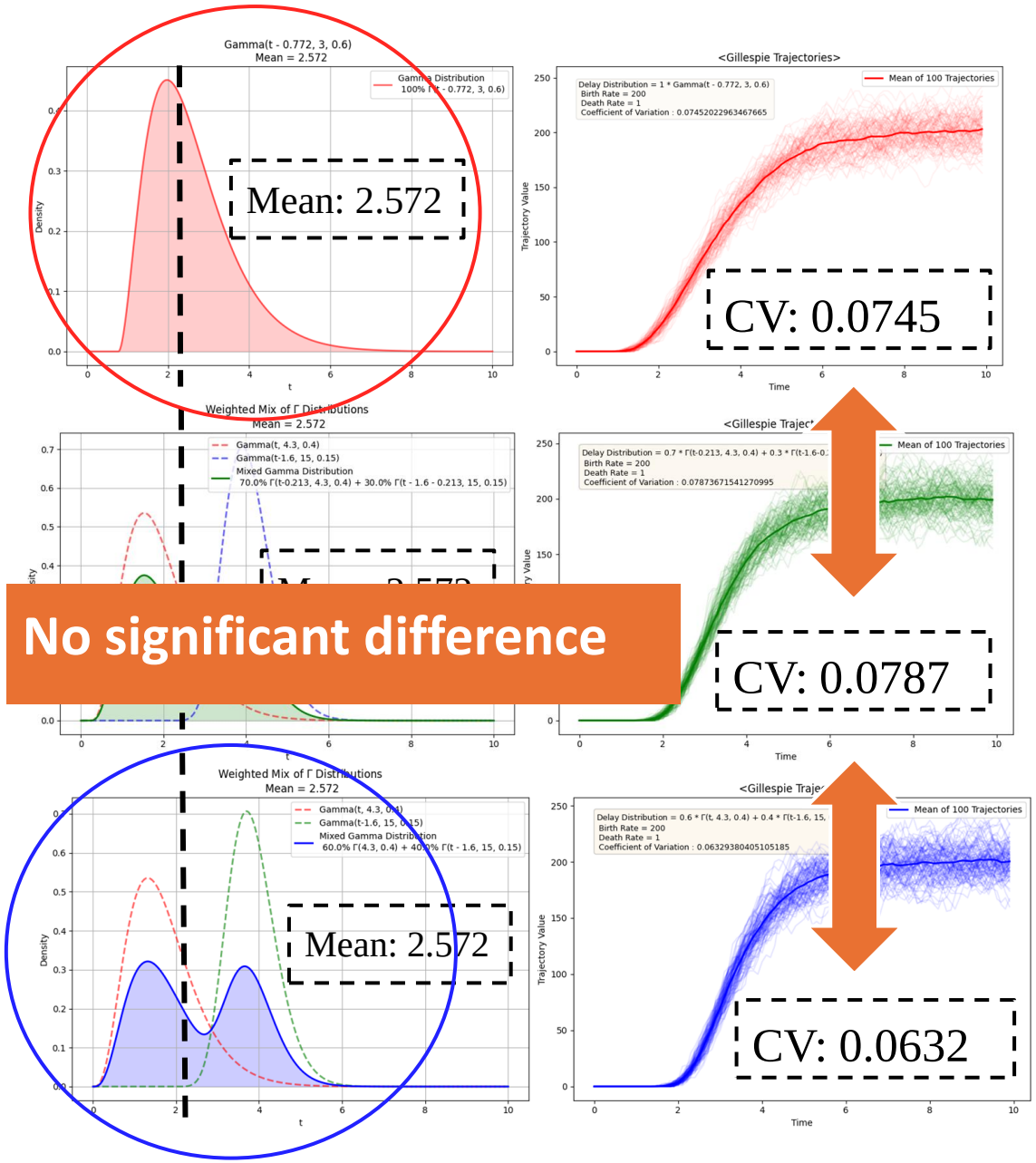
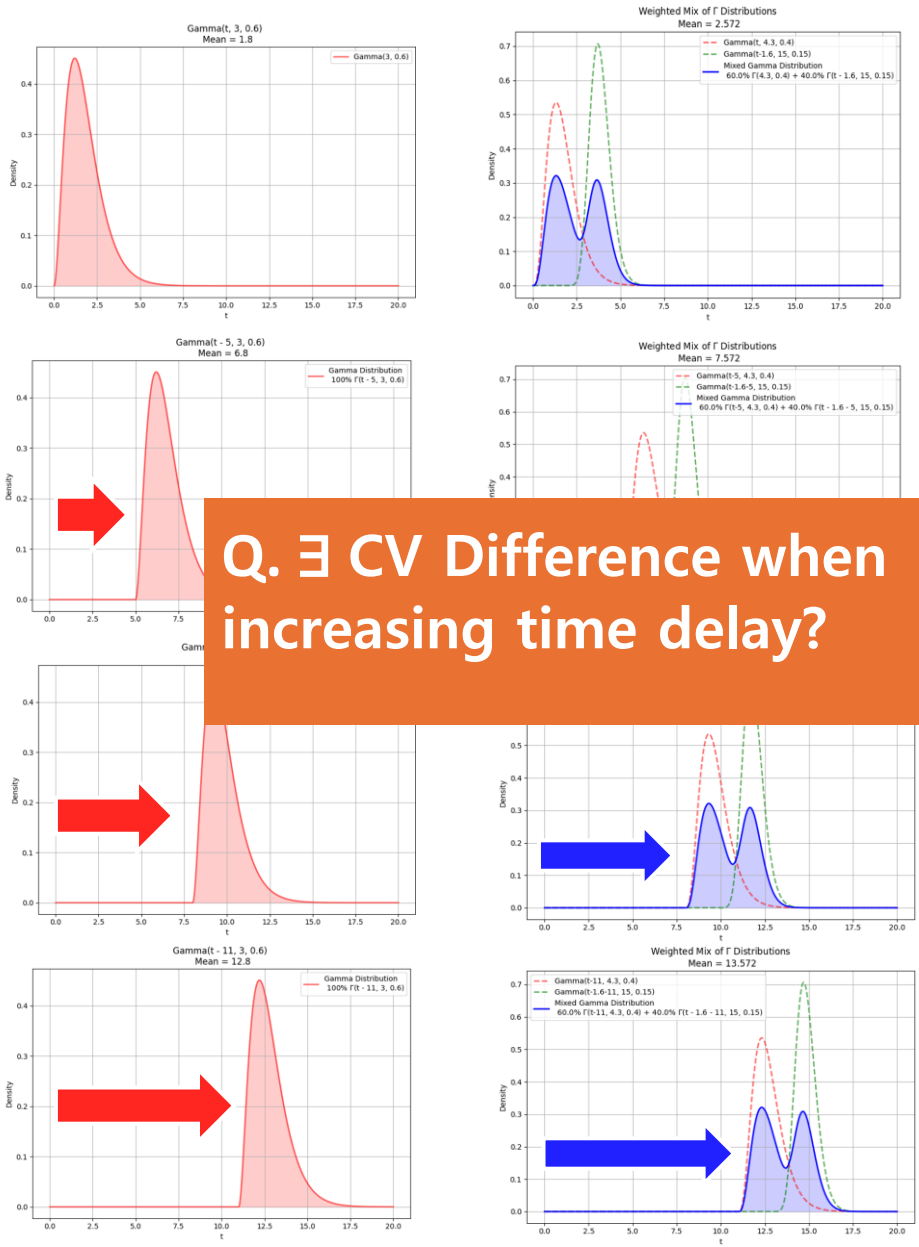
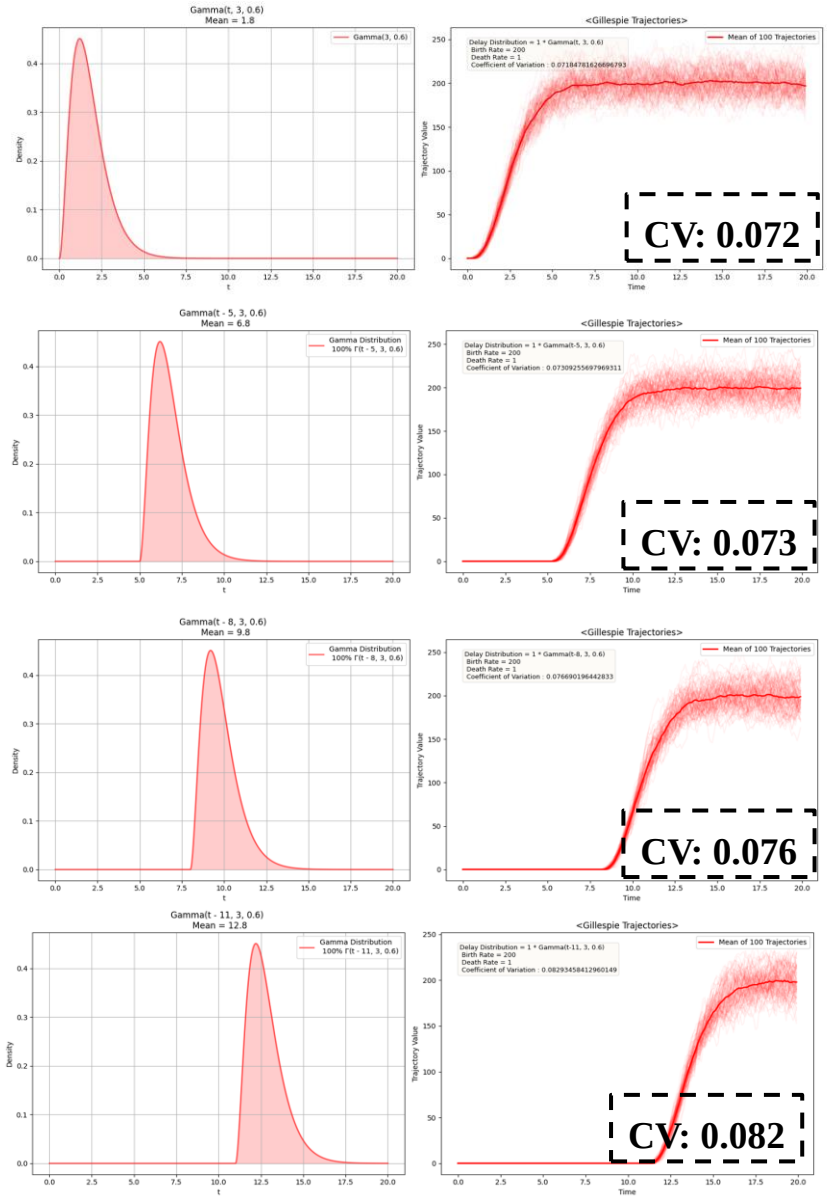


No significant difference



Q. ∃ CV Difference when increasing time delay?

Increasing time delay by horizontal shift slightly increases unimodal heterogeneity and slightly decreases bimodal heterogeneity, but no significant differences in final time trace heterogeneity.



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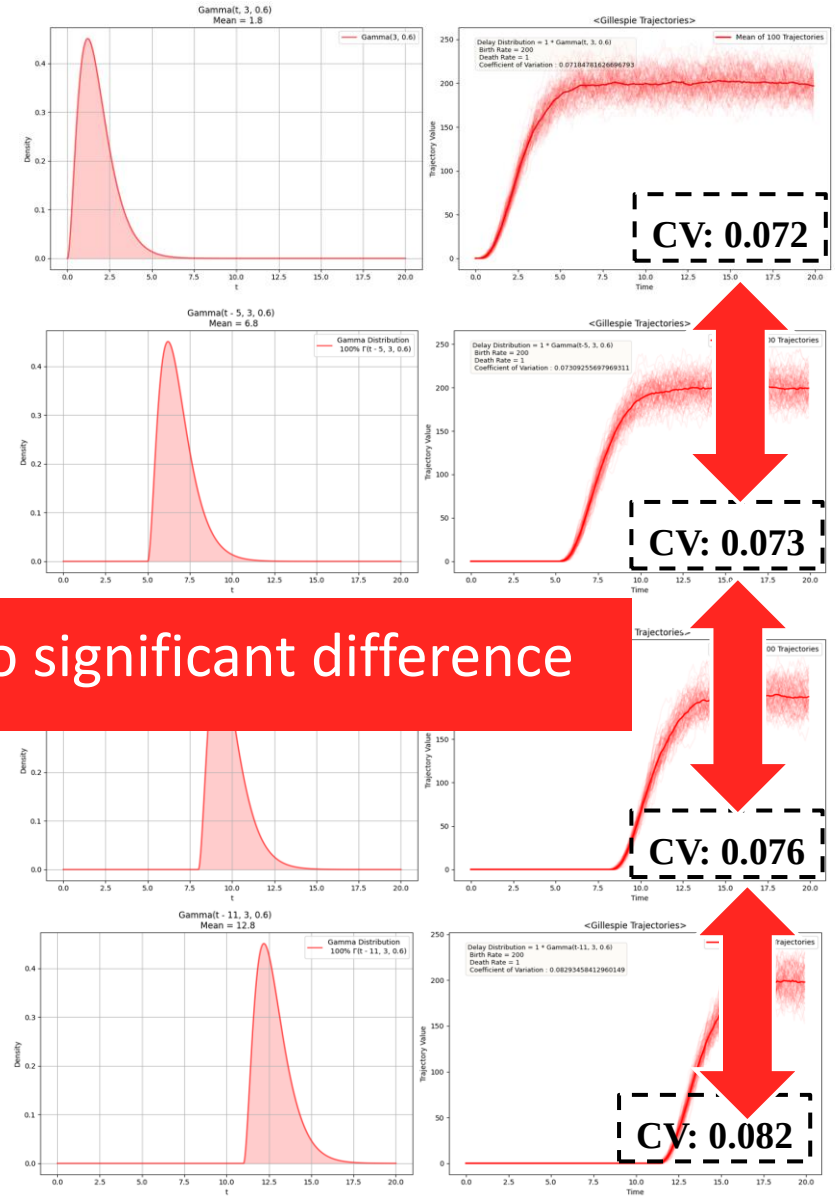

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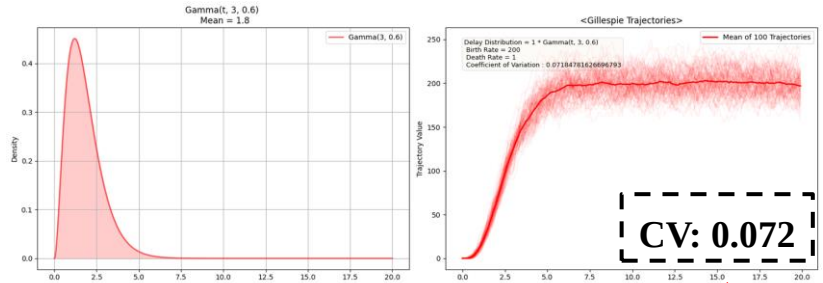
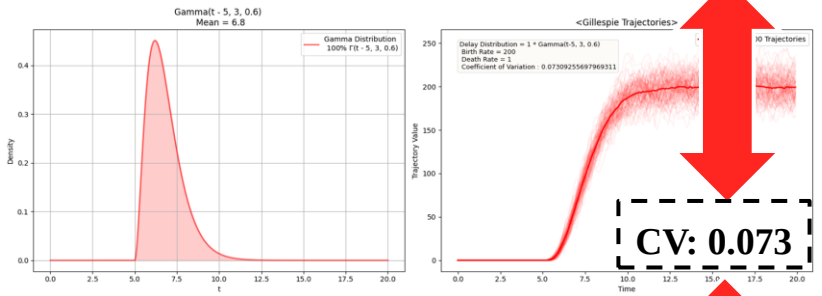
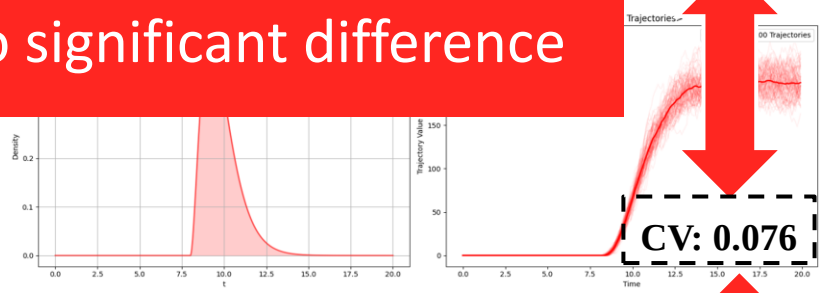
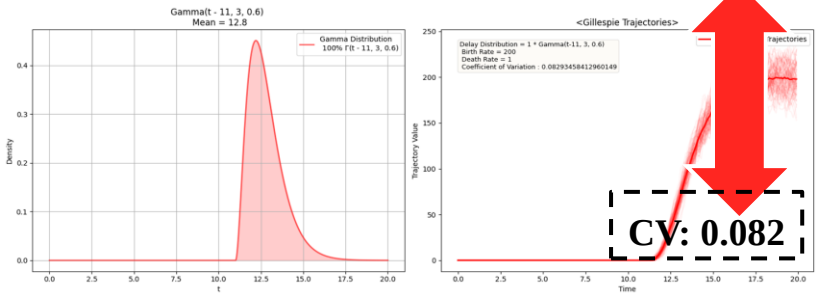
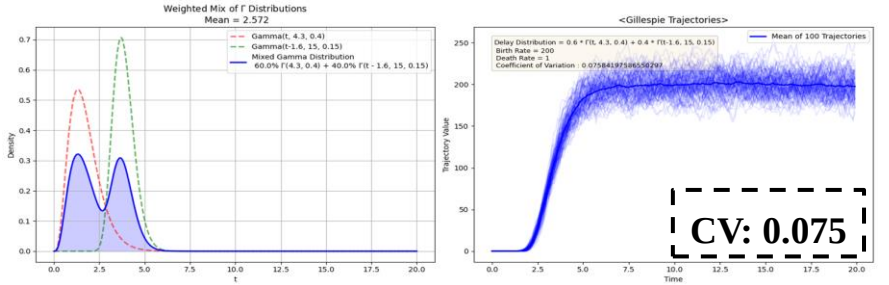


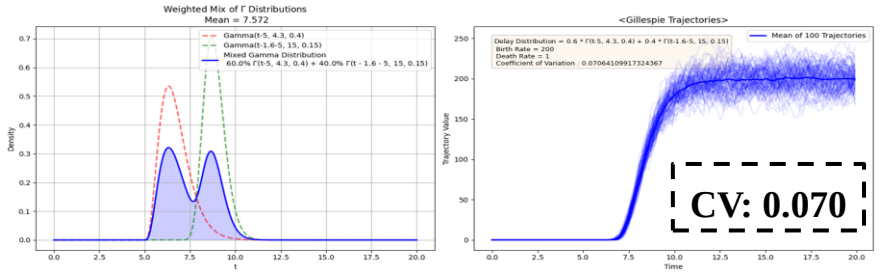


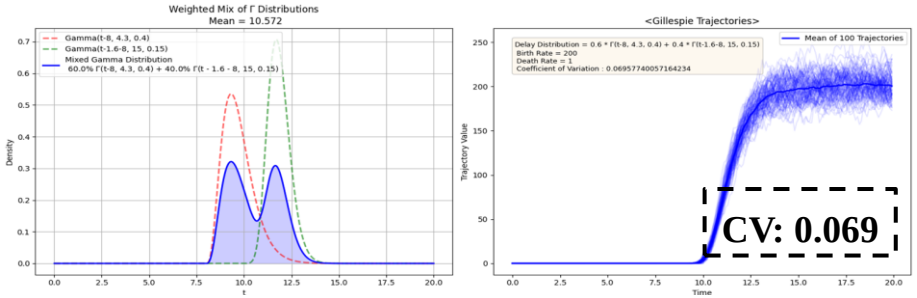
No significant difference

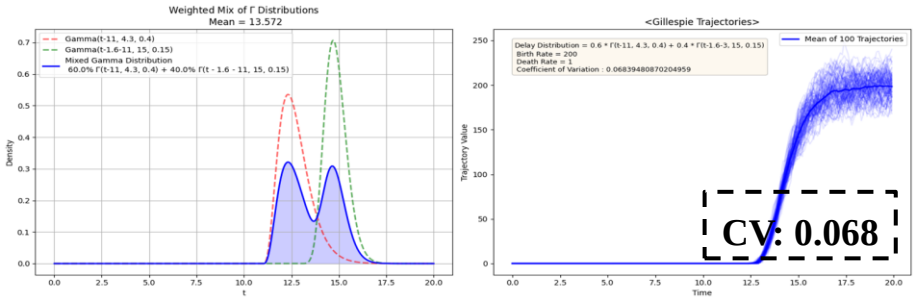












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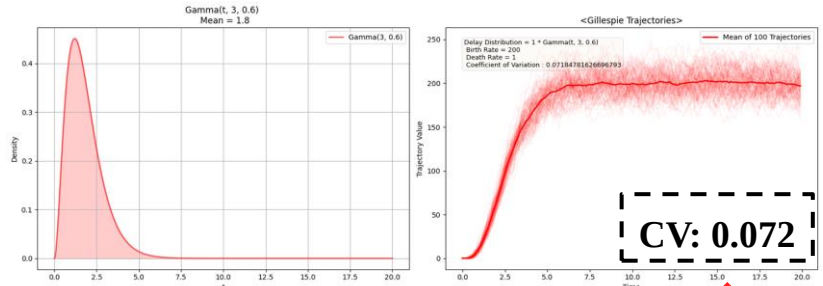
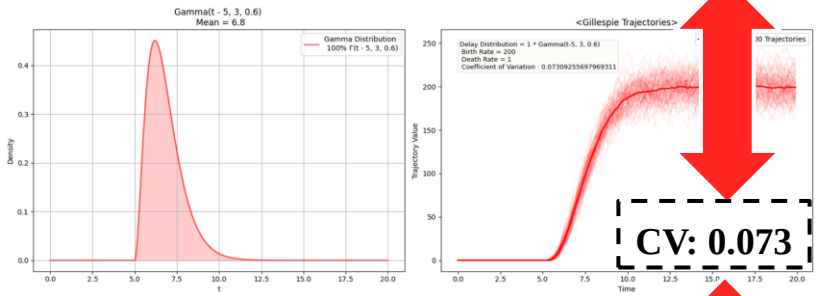
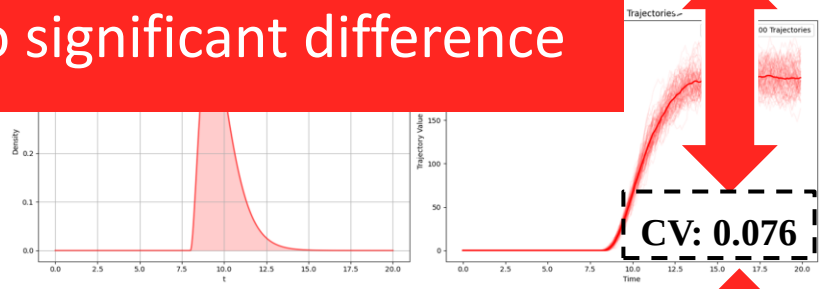
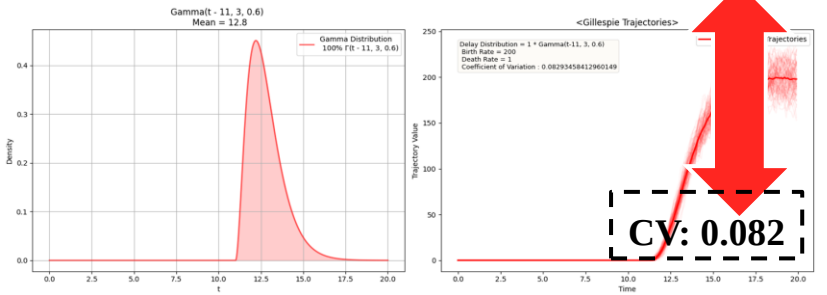




No significant difference





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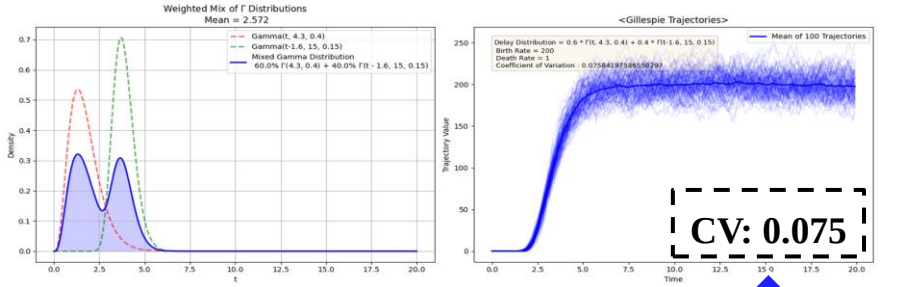
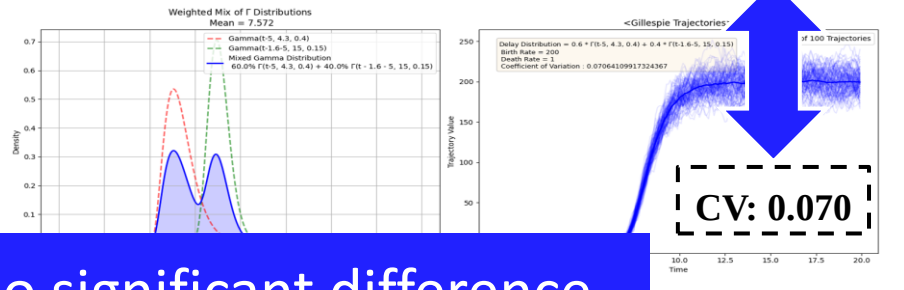
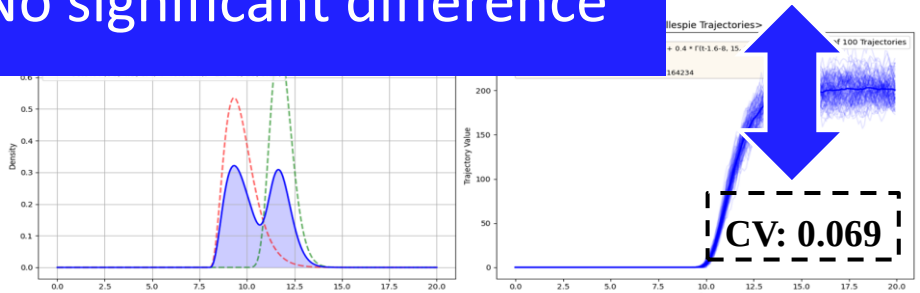
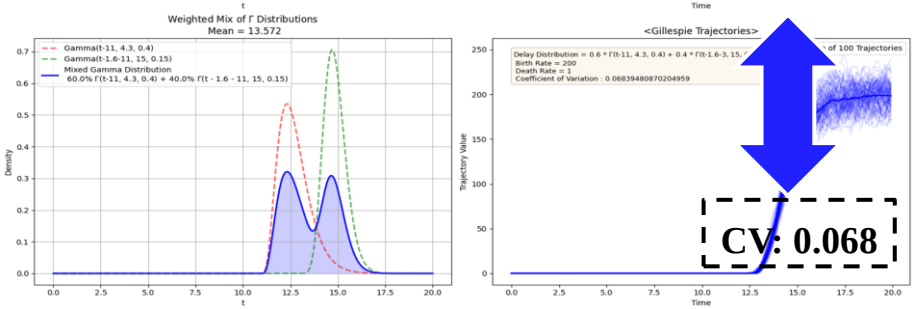




No significant difference





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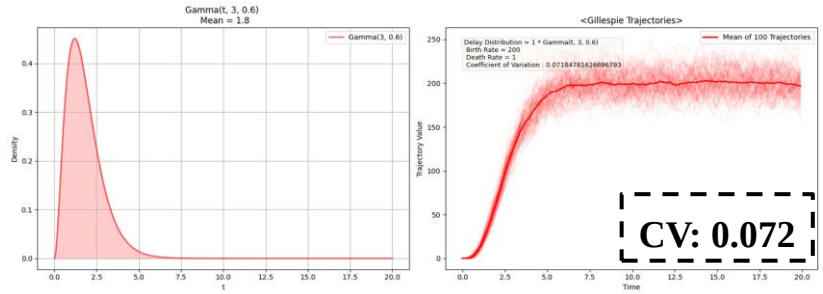

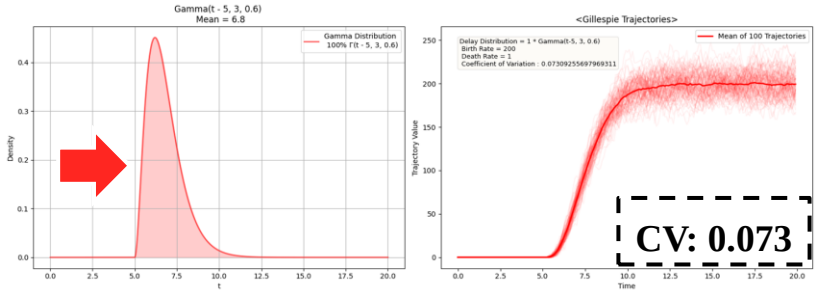

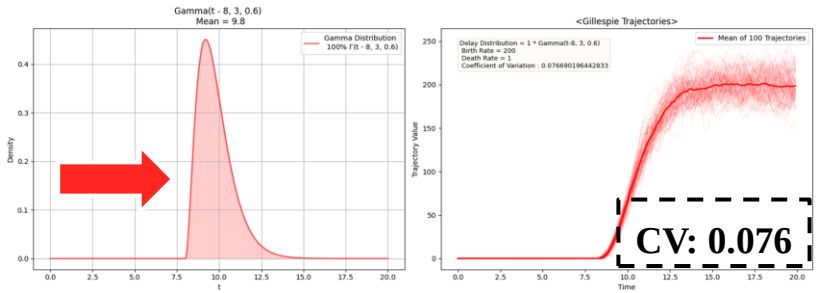

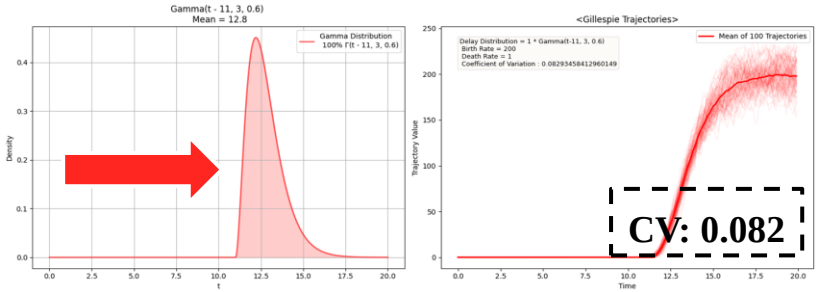

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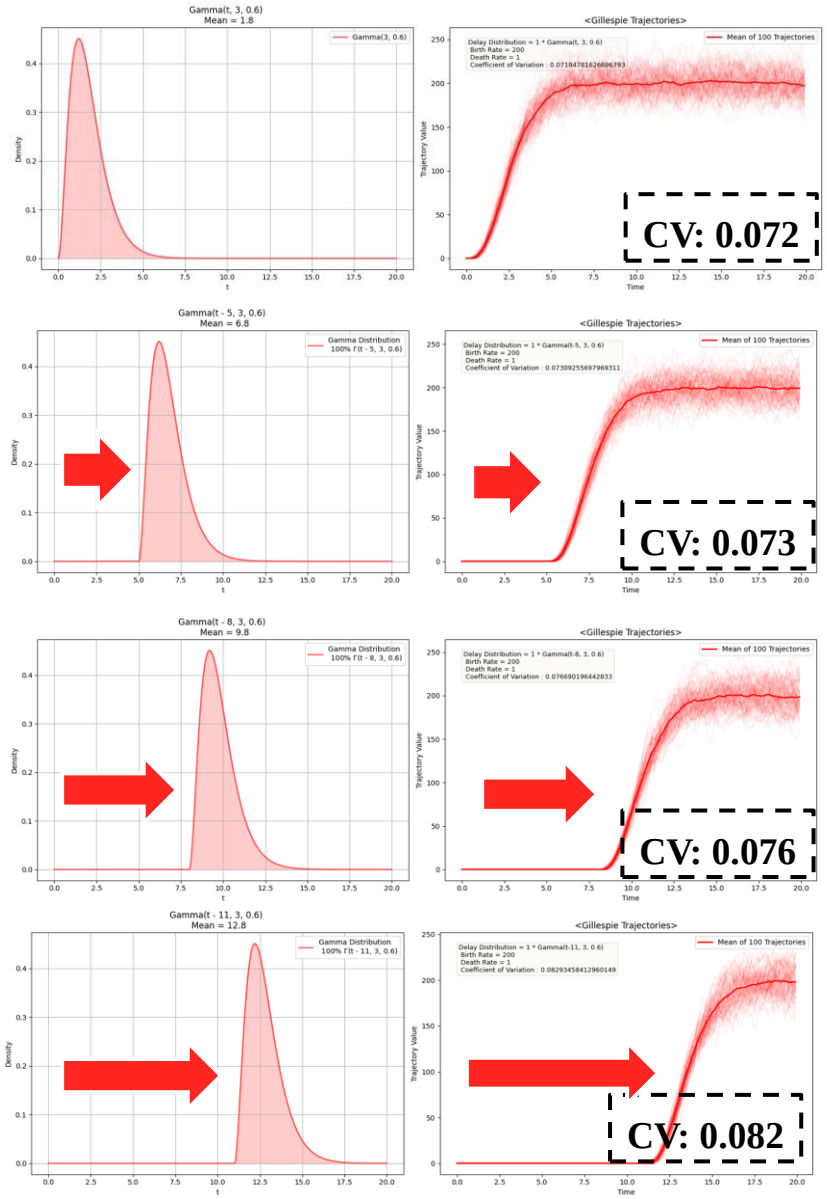

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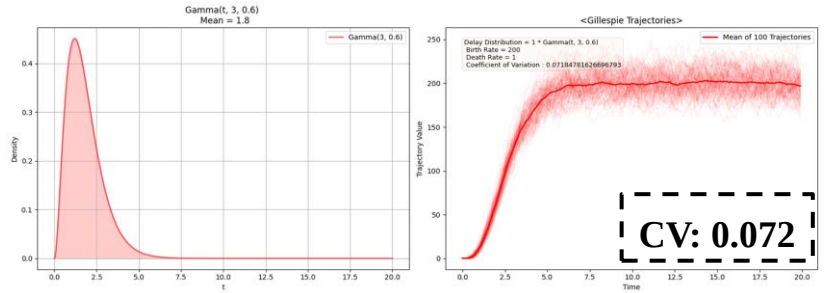
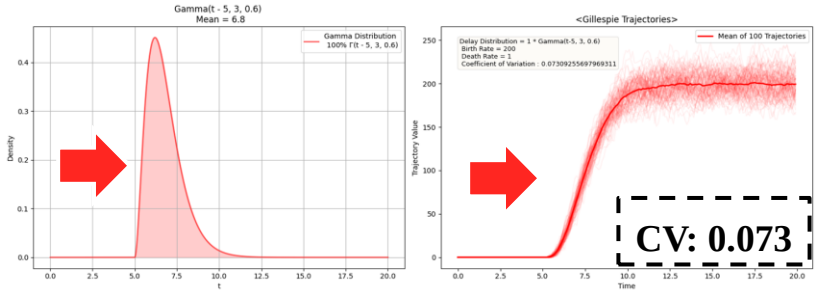
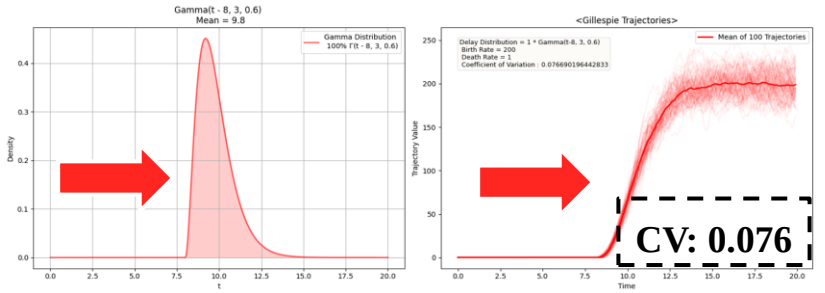
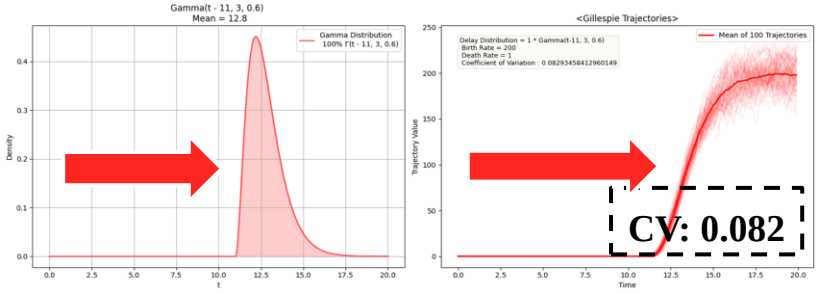




Size Change X

Intuitively, Shift → **Change in Variance**





Size Change X

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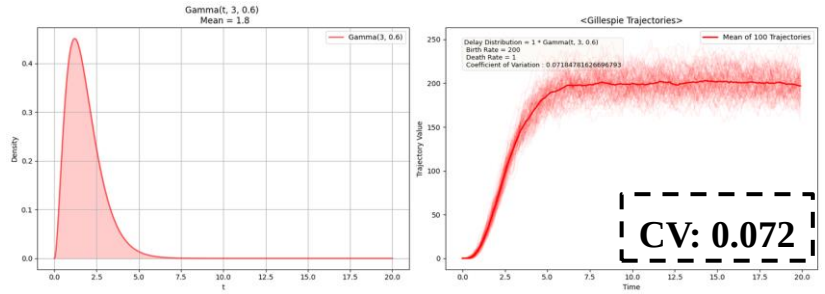

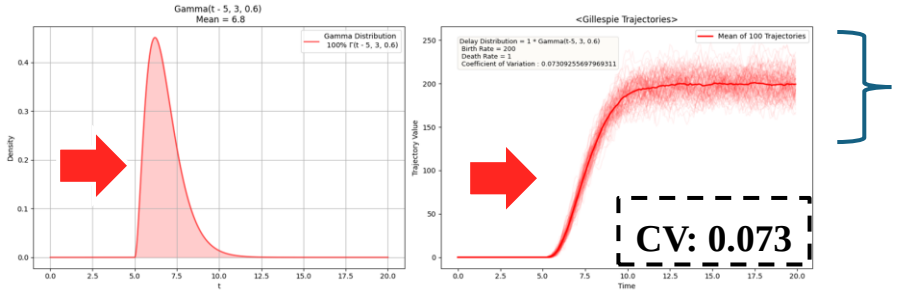

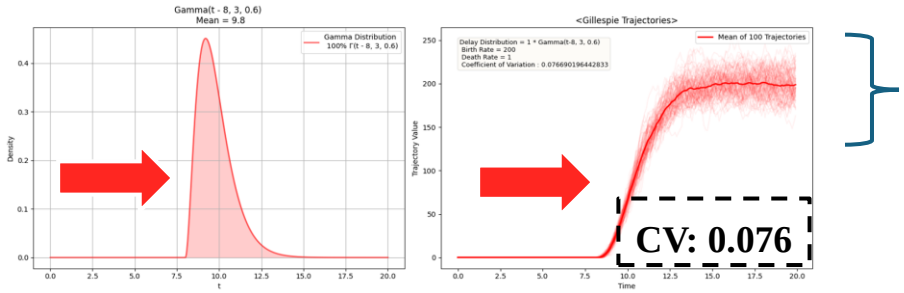

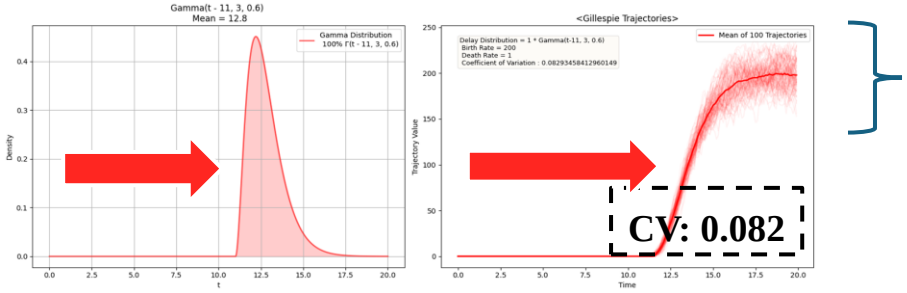

Intuitively, Shift → Change in Variance

Q. What about changing birth/death rate??
∃ CV Difference??

At lower birth/death ratio, there is no significant difference in the final time trace heterogeneity, (although the CV value increases with fixed distribution).

$$\lambda_b = 200, \quad \lambda_d = 1$$

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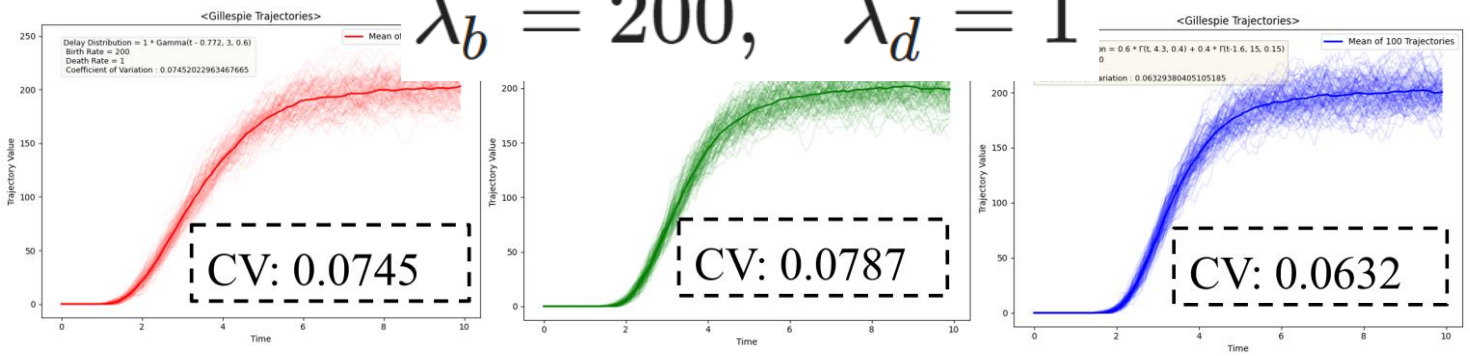
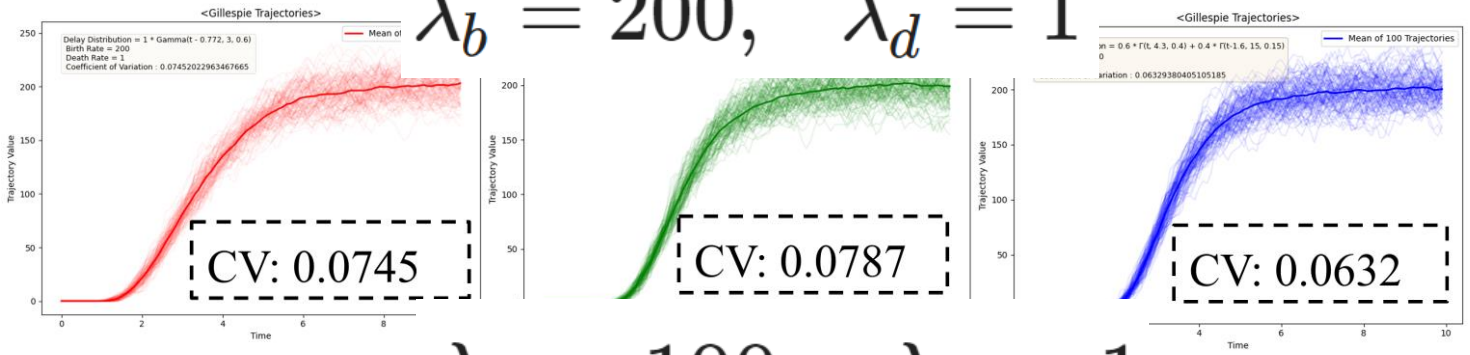
$\lambda_b = 200, \quad \lambda_d = 1$



Little CV difference (200:1)

At lower birth/death ratio, there is no significant difference in the final time trace heterogeneity, (although the CV value increases with fixed distribution).

$\lambda_b = 200, \quad \lambda_d = 1$



$\lambda_b = 200, \quad \lambda_d = 1$

$\lambda_b = 100, \quad \lambda_d = 1$

Little CV difference (200:1)

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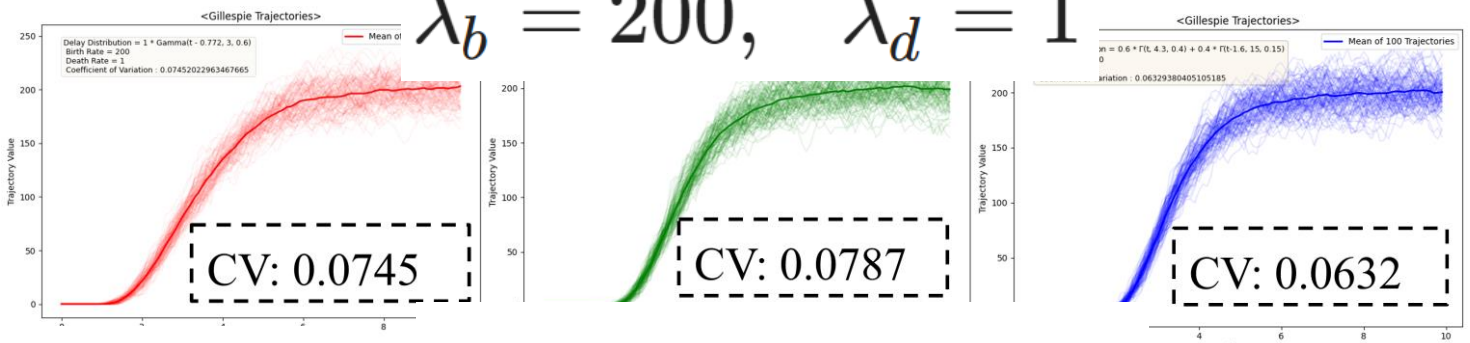
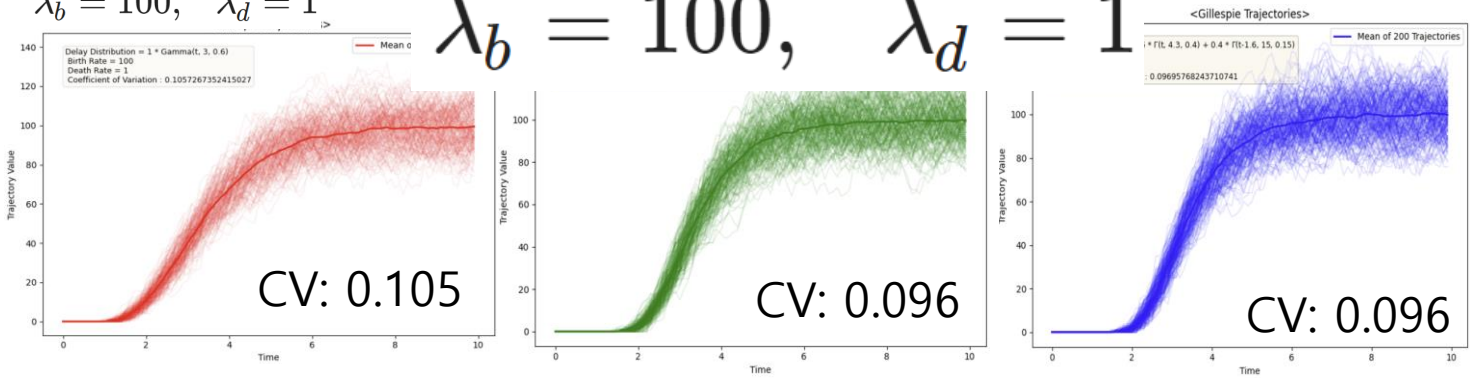
$\lambda_b = 200, \quad \lambda_d = 1$



Little CV difference (200:1)

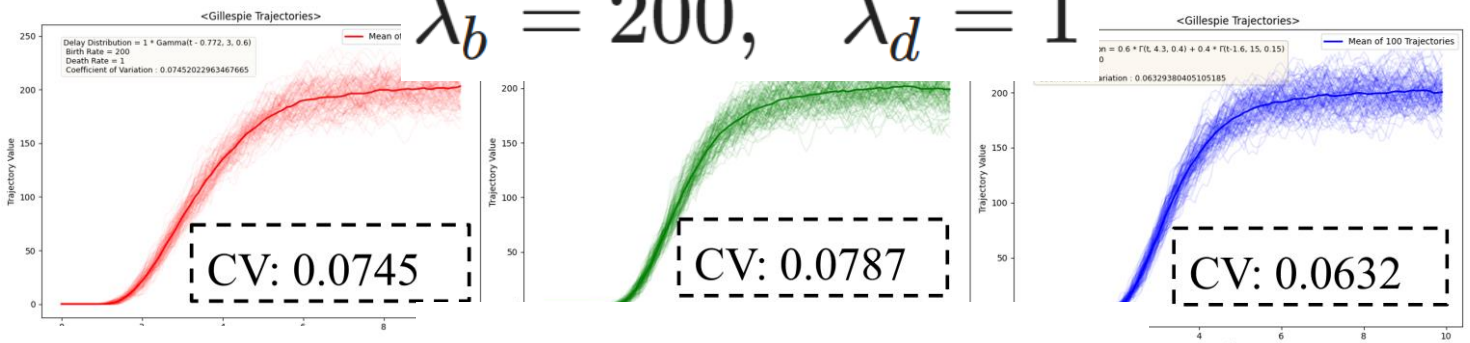
$\lambda_b = 100, \quad \lambda_d = 1$



Still little CV difference (100:1)

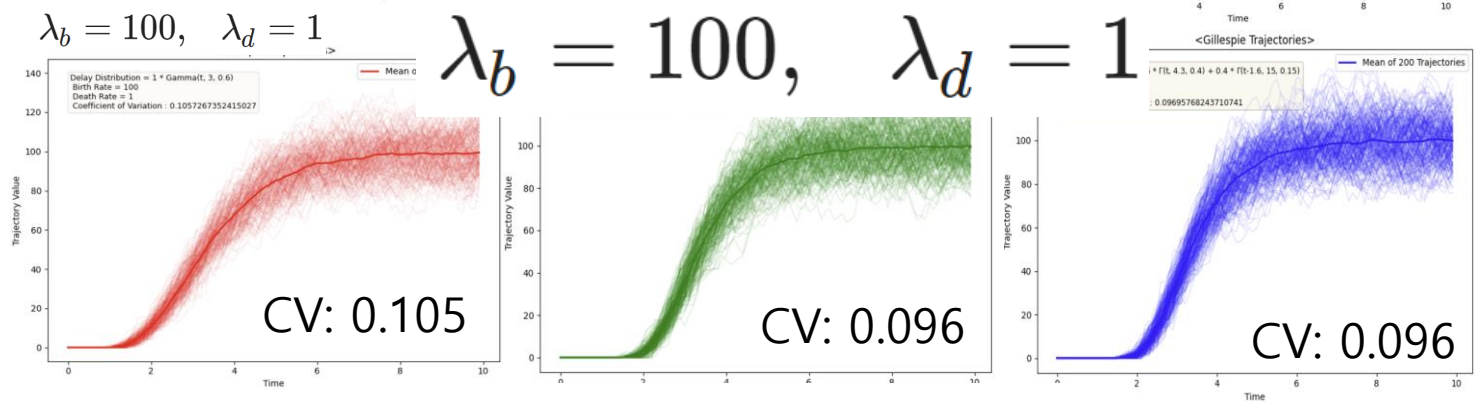
At lower birth/death ratio, there is no significant difference in the final time trace heterogeneity, (although the CV value increases with fixed distribution).

$\lambda_b = 200, \quad \lambda_d = 1$



Little CV difference (200:1)

$\lambda_b = 100, \quad \lambda_d = 1$

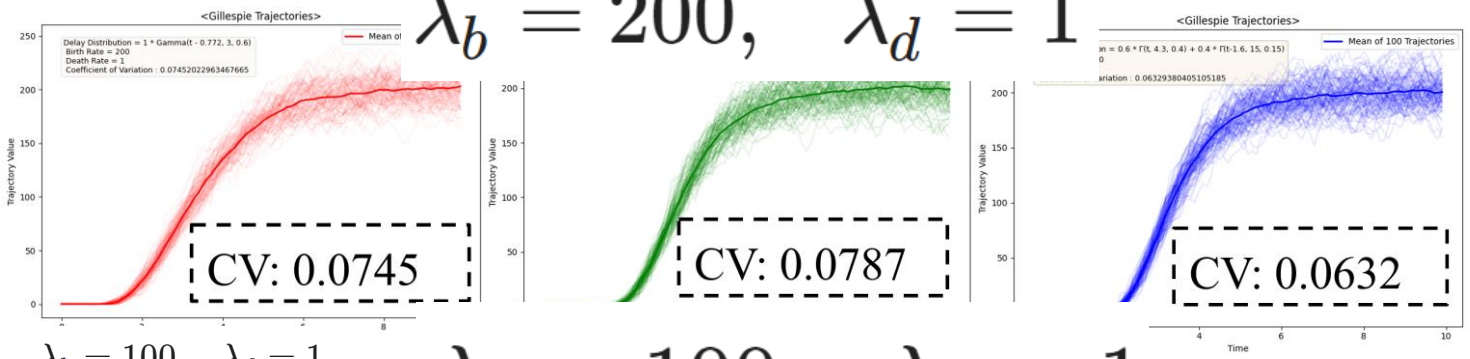


Still little CV difference (100:1)

$\lambda_b = 4, \quad \lambda_d = 1$

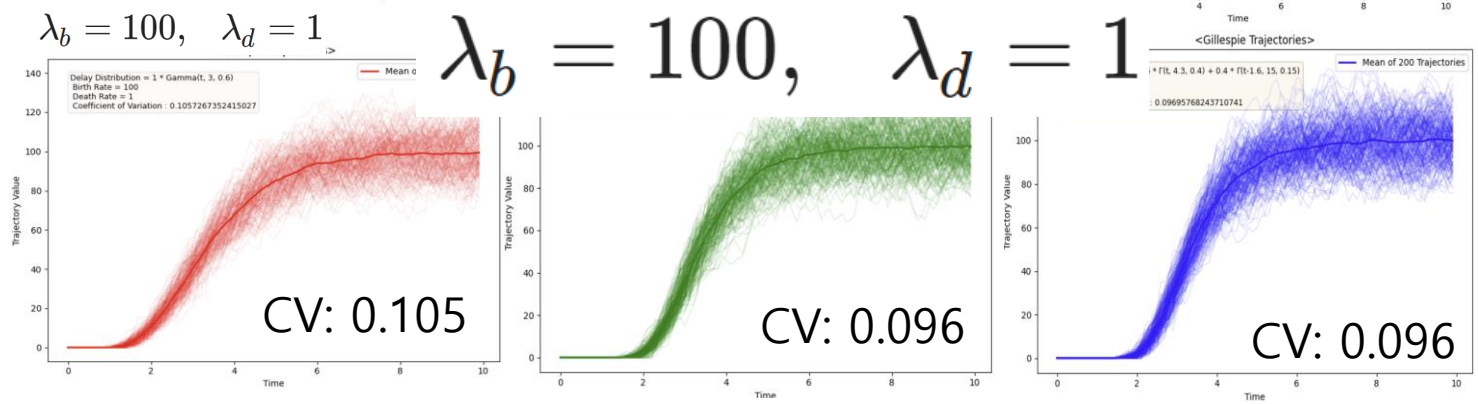
At lower birth/death ratio, there is no significant difference in the final time trace heterogeneity, (although the CV value increases with fixed distribution).

$\lambda_b = 200, \quad \lambda_d = 1$



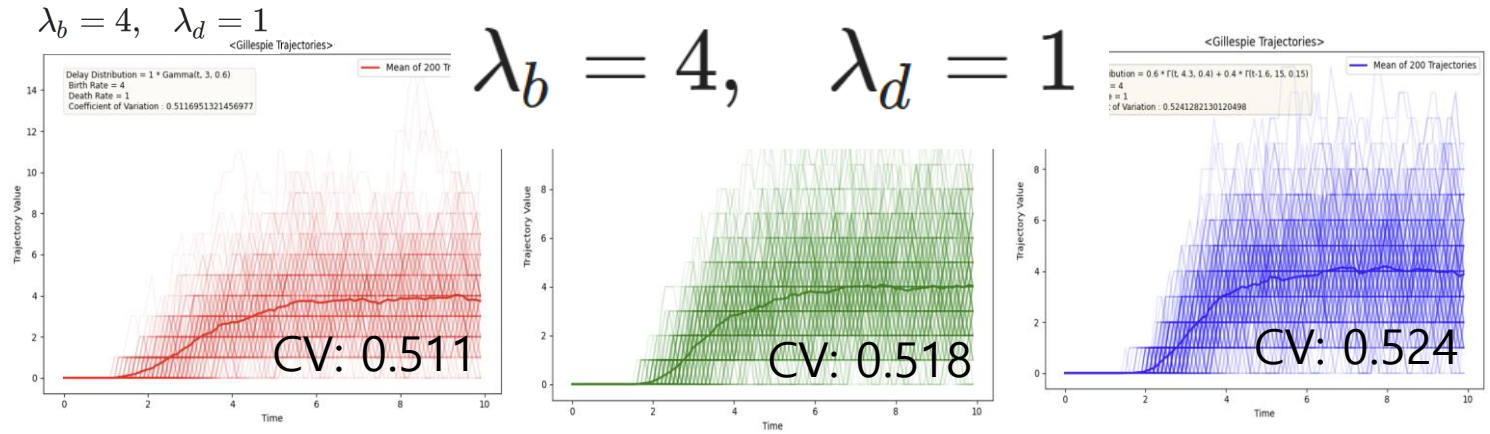
Little CV difference (200:1)

$\lambda_b = 100, \quad \lambda_d = 1$



Still little CV difference (100:1)

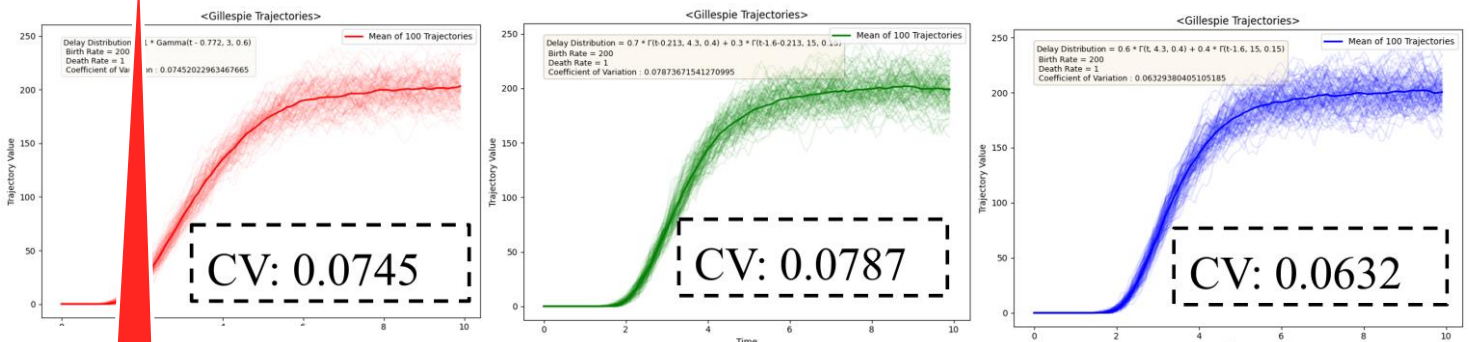
$\lambda_b = 4, \quad \lambda_d = 1$



Still very little CV difference (4:1)

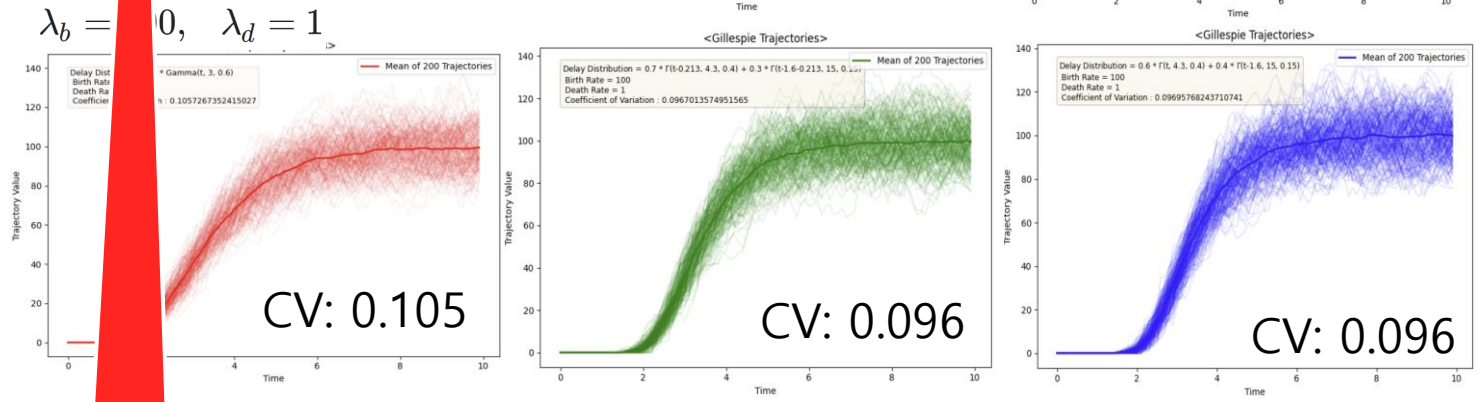
At lower birth/death ratio, there is no significant difference in the final time trace heterogeneity, (although the CV value increases with fixed distribution).

$\lambda_b = 200, \quad \lambda_d = 1$



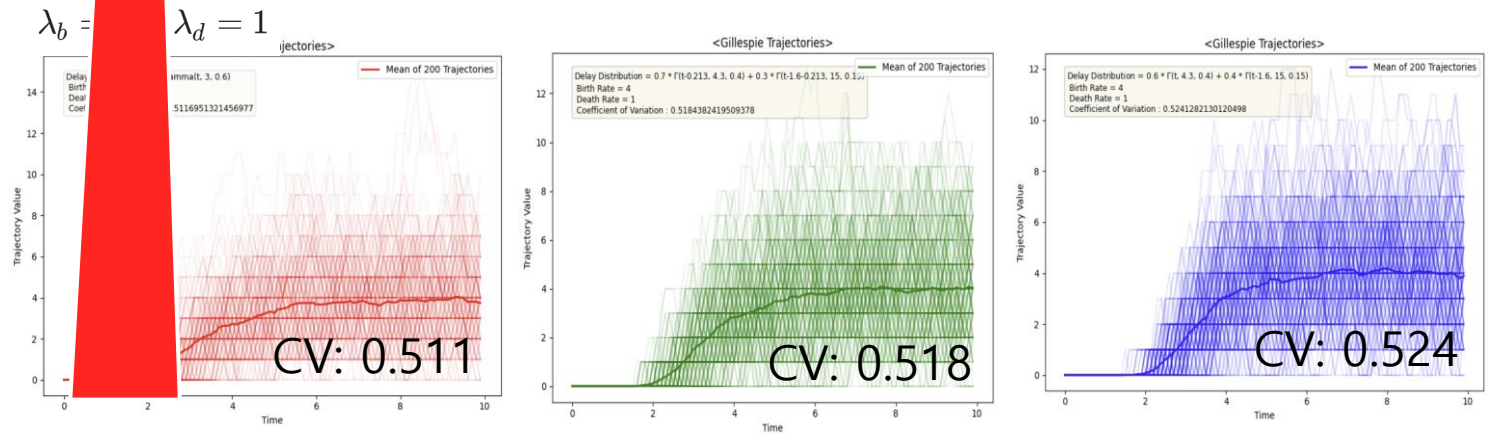
Very little CV difference (200:1)

$\lambda_b = 0, \quad \lambda_d = 1$



Very little CV difference (100:1)

$\lambda_b = \quad \lambda_d = 1$



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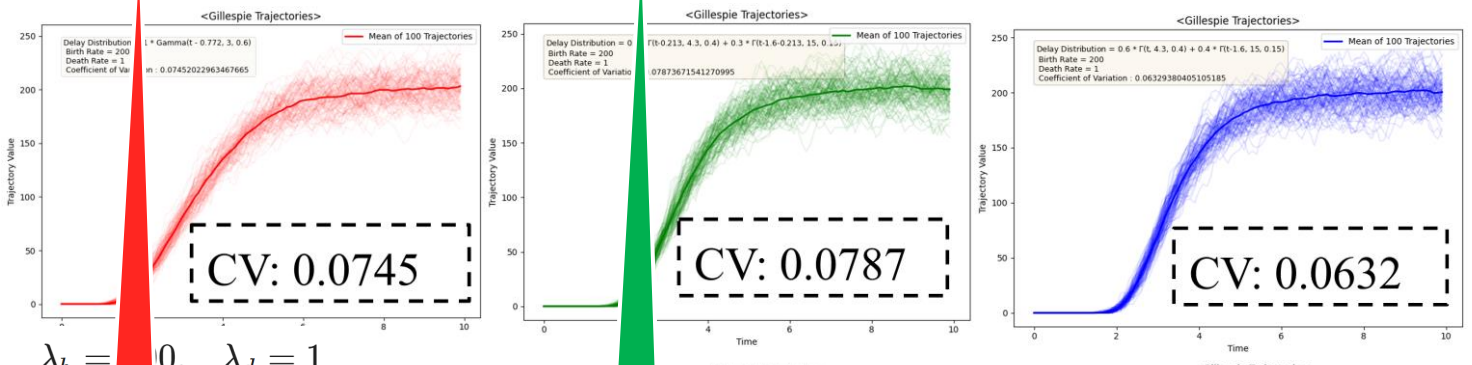

Very little CV difference (200:1)

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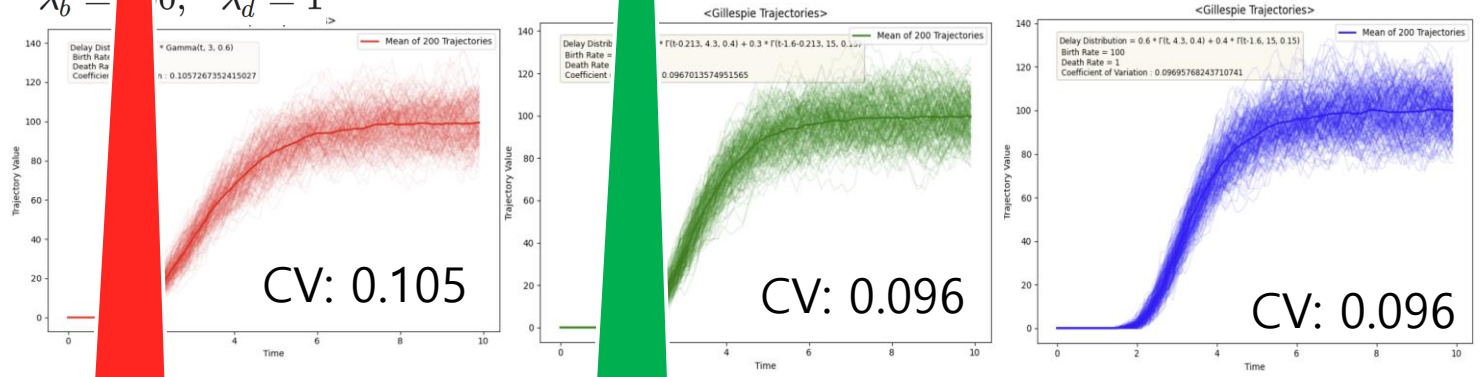
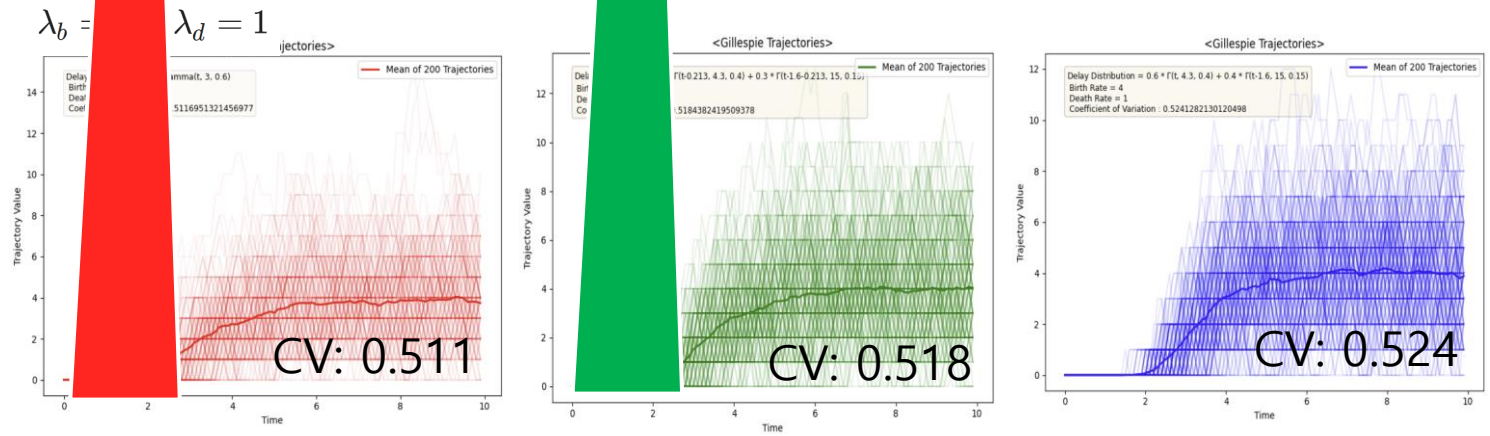


Very little CV difference (100:1)

$\lambda_b = \quad \lambda_d = 1$



Very little CV difference (4:1)

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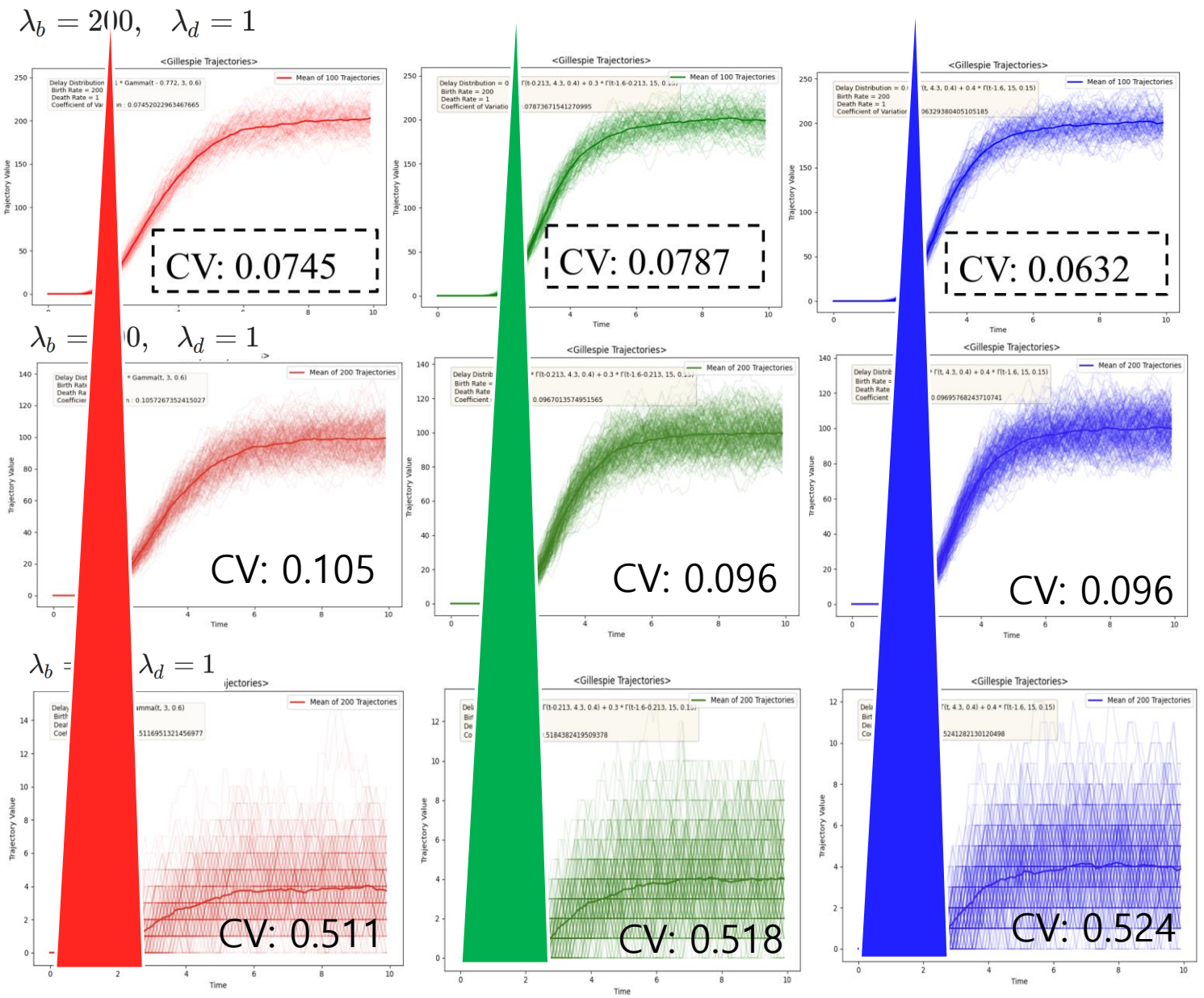

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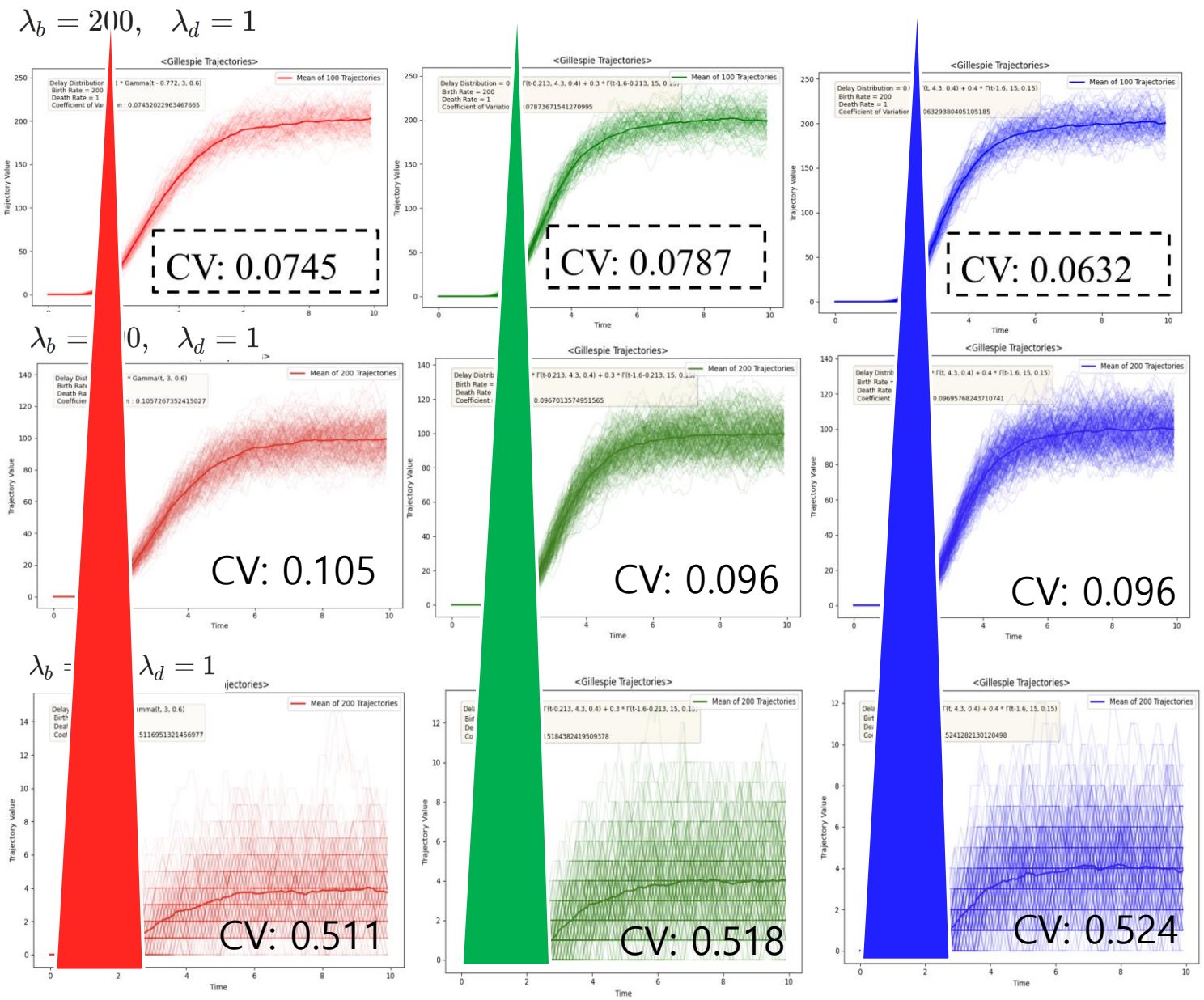
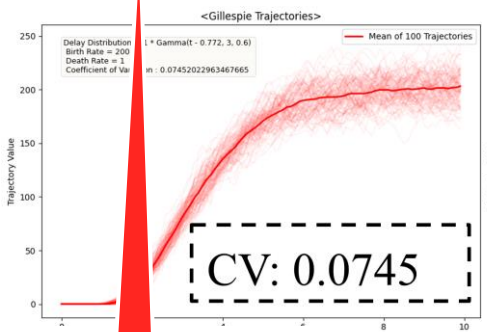


$$CV = \left(\frac{\sigma}{\mu}\right) \times 100\%$$

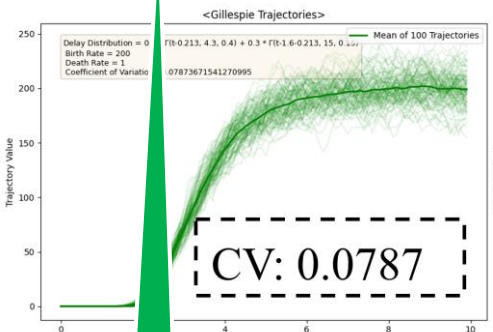
Lower $\mu = \lambda_b / \lambda_d \longrightarrow$ Higher CV

At lower birth/death ratio, there is no significant difference in the final time trace heterogeneity, (although the CV value increases with fixed distribution).

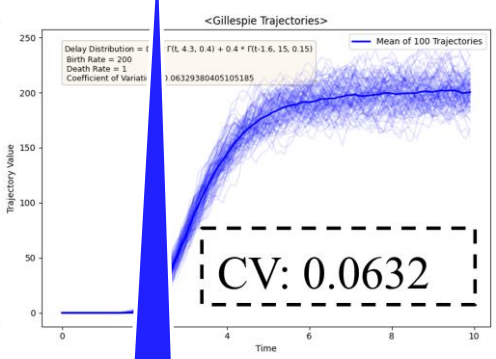
$\lambda_b = 200, \quad \lambda_d = 1$



CV: 0.0745



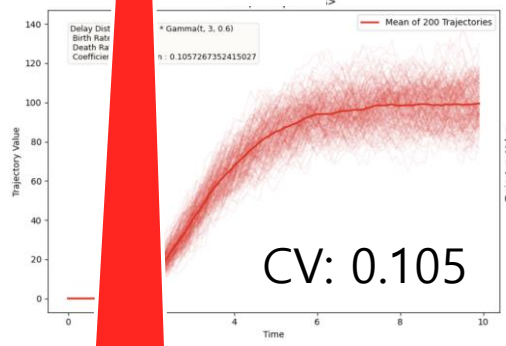
CV: 0.0787



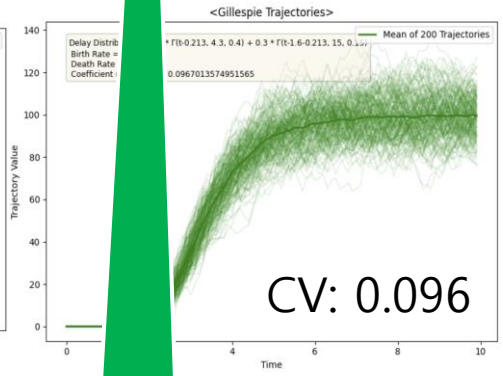
CV: 0.0632

Very little CV difference (200:1)

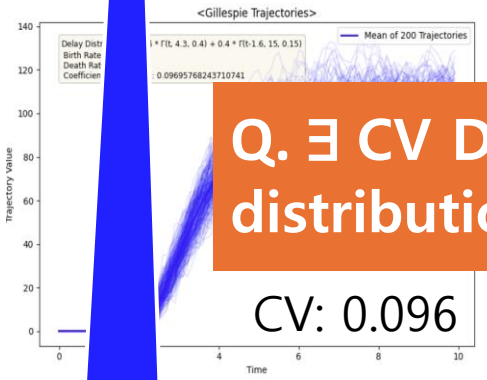
$\lambda_b = 0, \quad \lambda_d = 1$



CV: 0.105



CV: 0.096

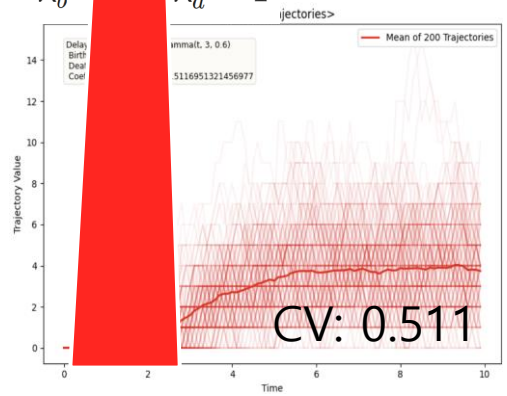


CV: 0.096

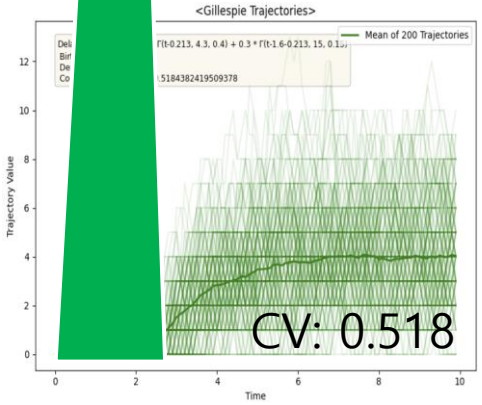
0:1)

Q. ∃ CV Difference when changing distribution variance?

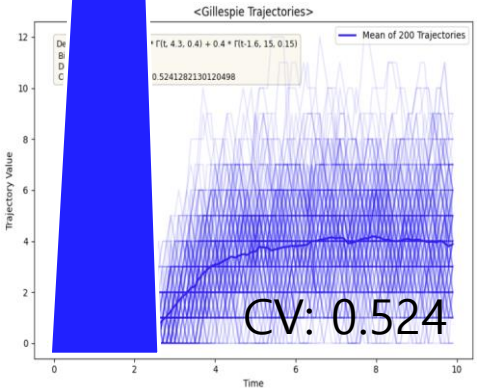
$\lambda_b = \quad \lambda_d = 1$



CV: 0.511



CV: 0.518

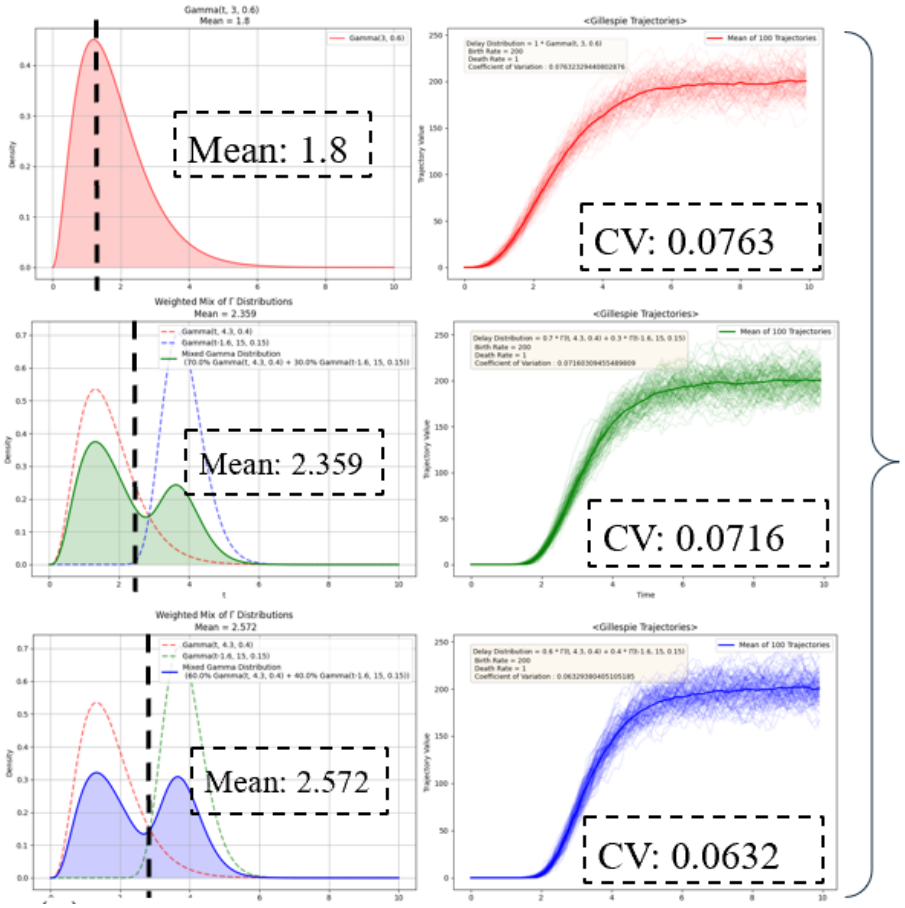


CV: 0.524

Very little CV difference (4:1)

Changing distribution variance yields no significant difference in the final time trace heterogeneity.

Original Γ Distributions



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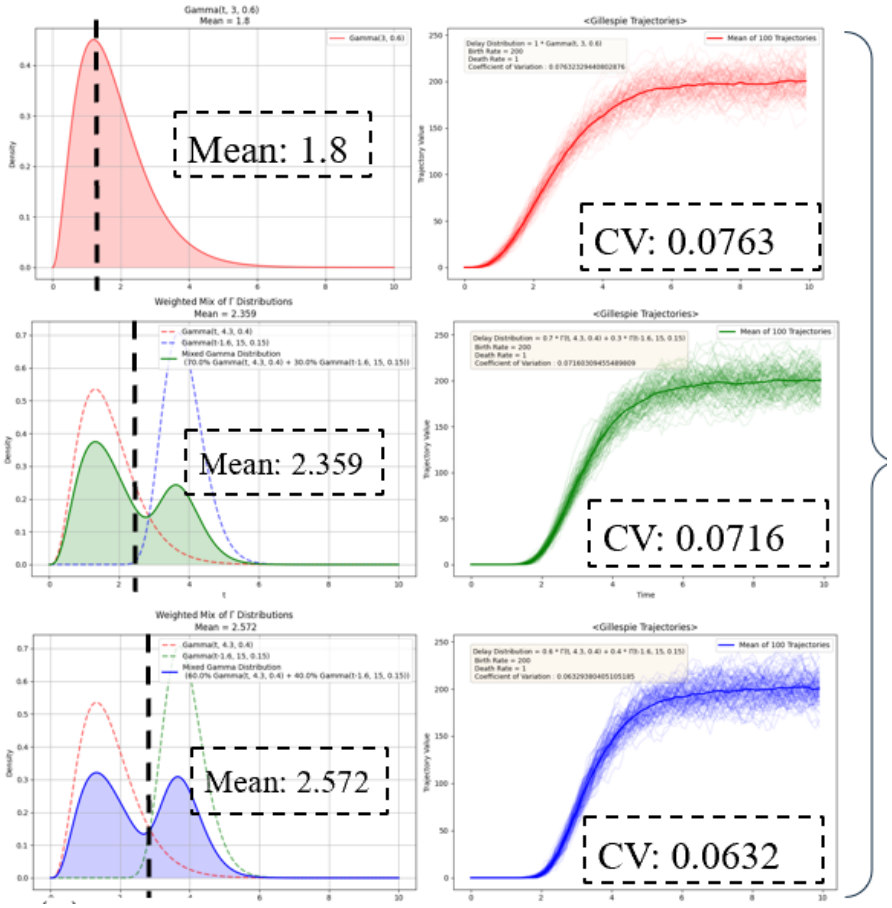
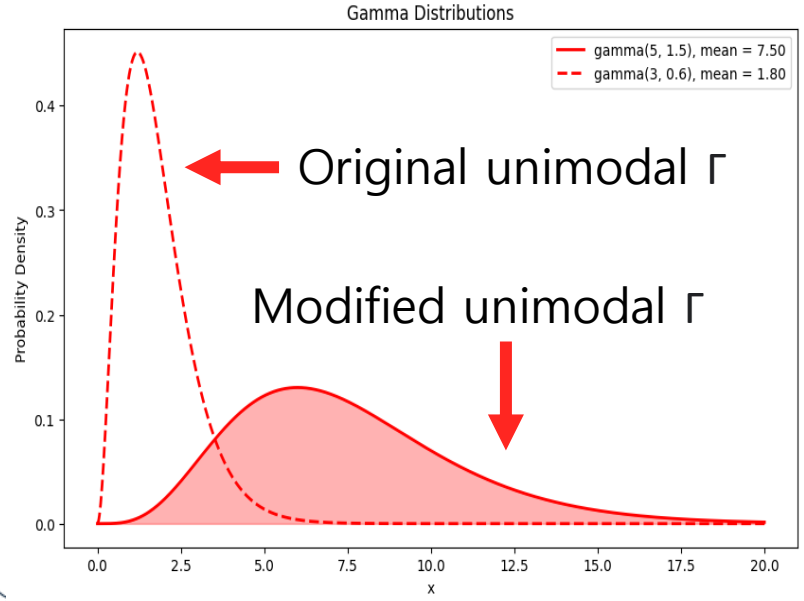
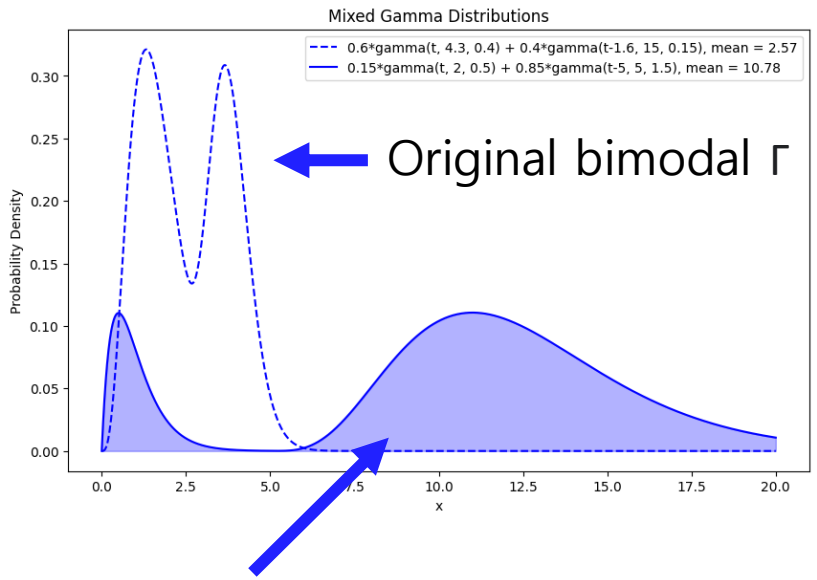
Original Γ Distributions







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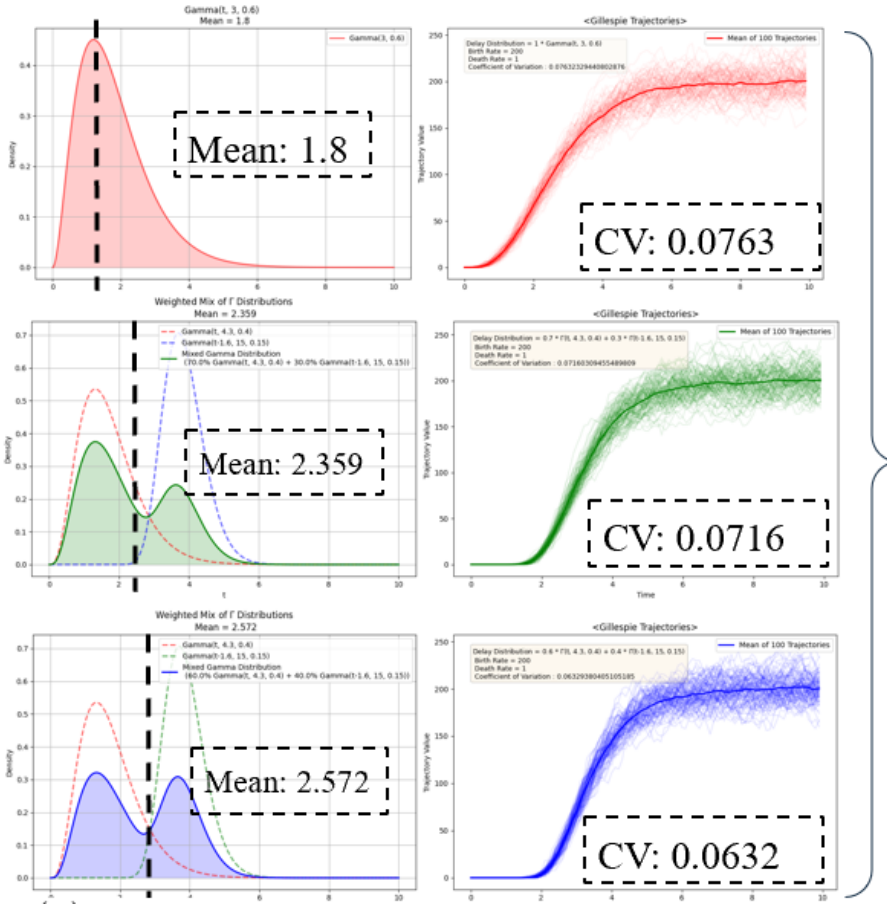
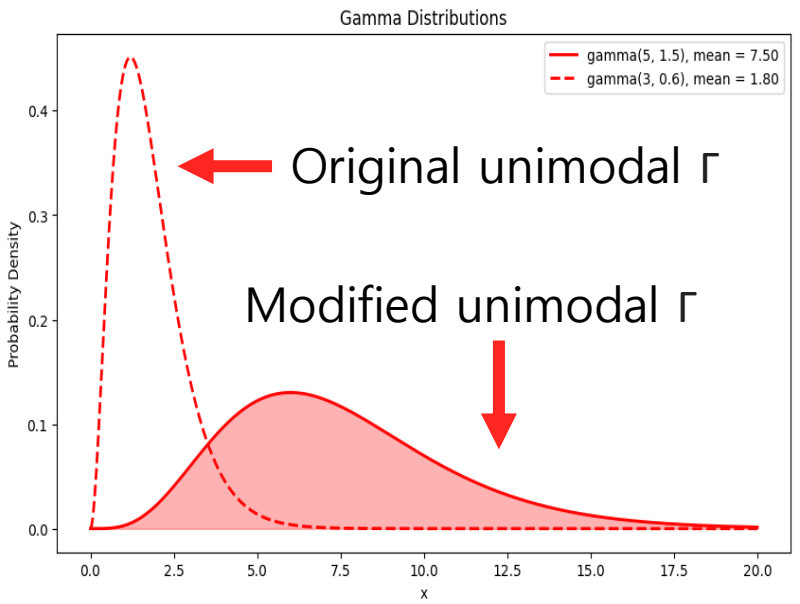
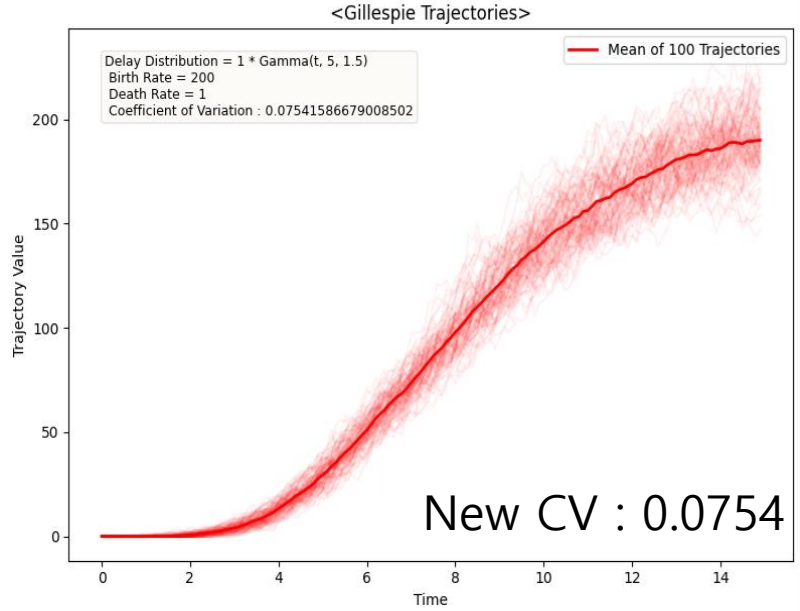
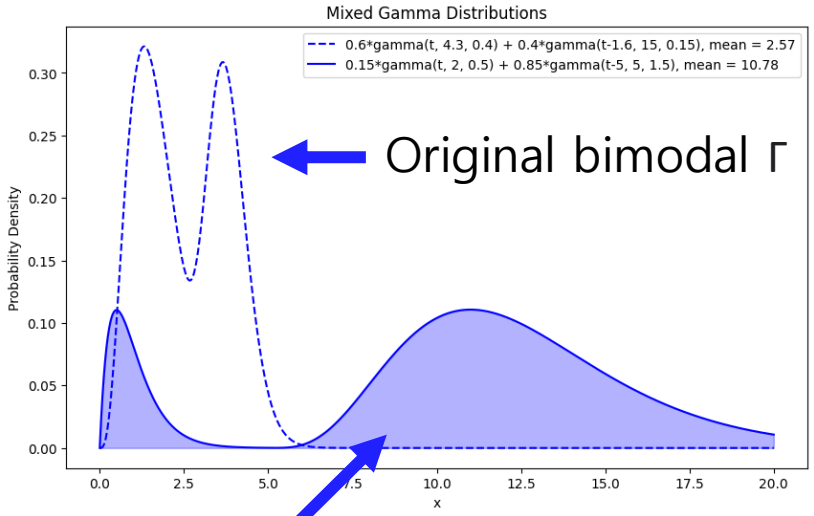
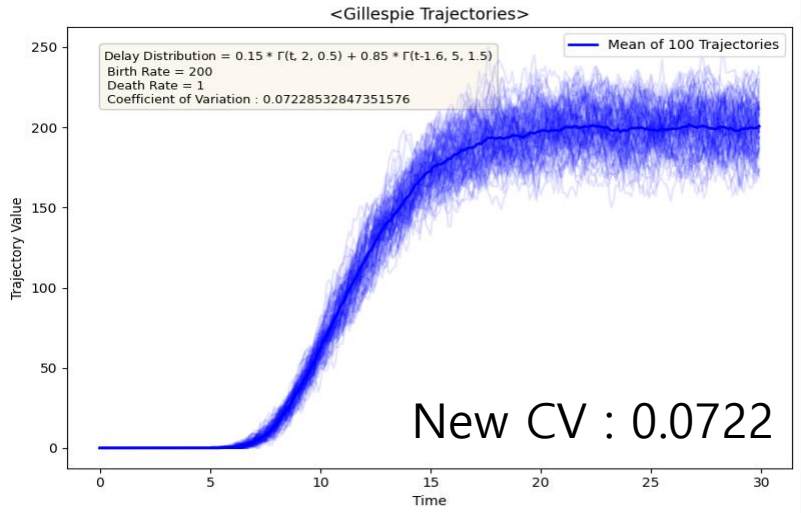
Original Γ Distributions





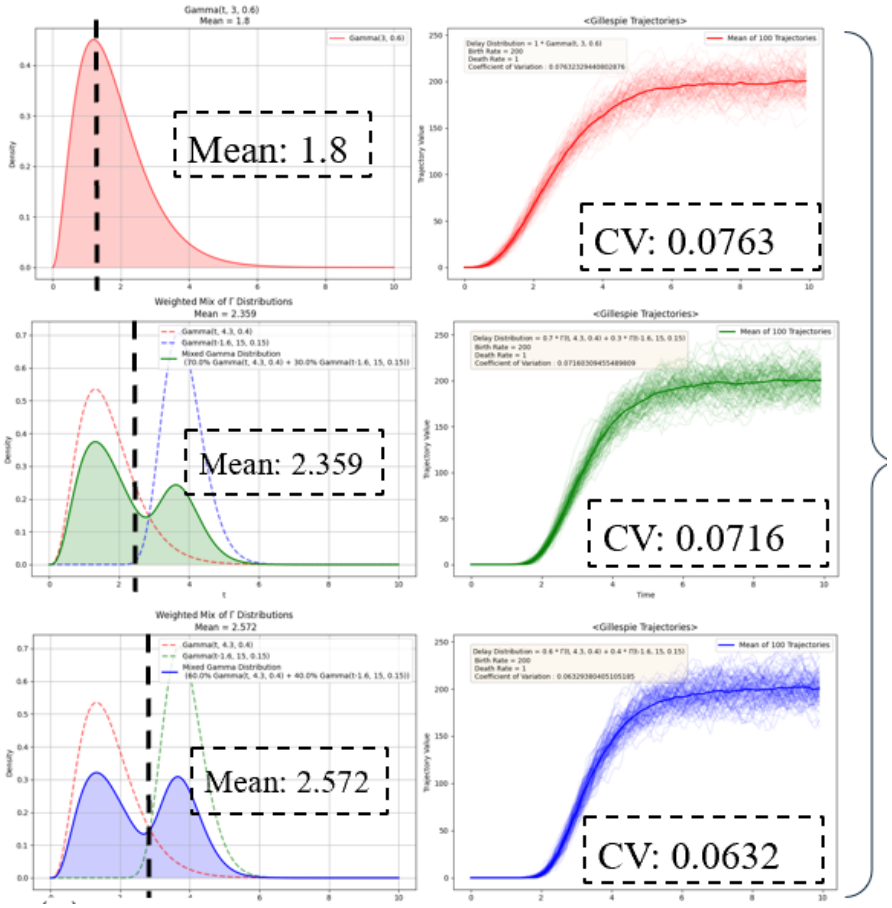


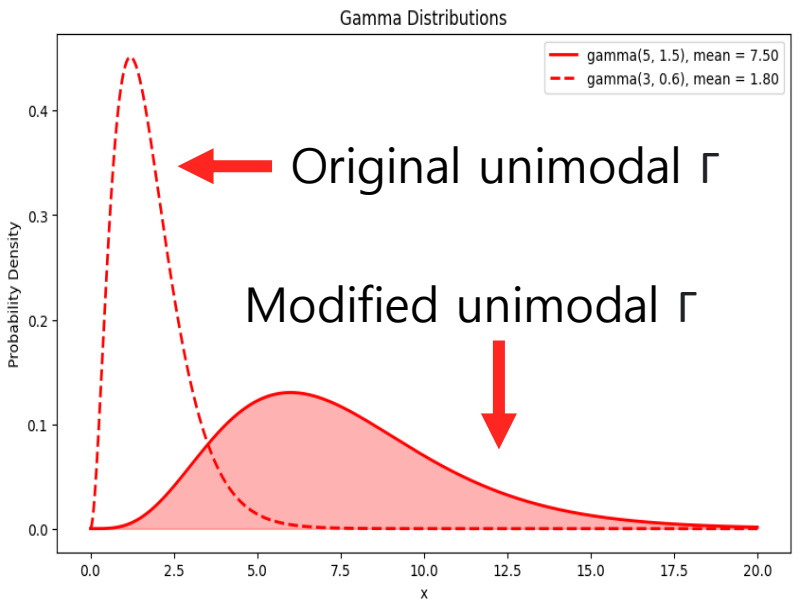


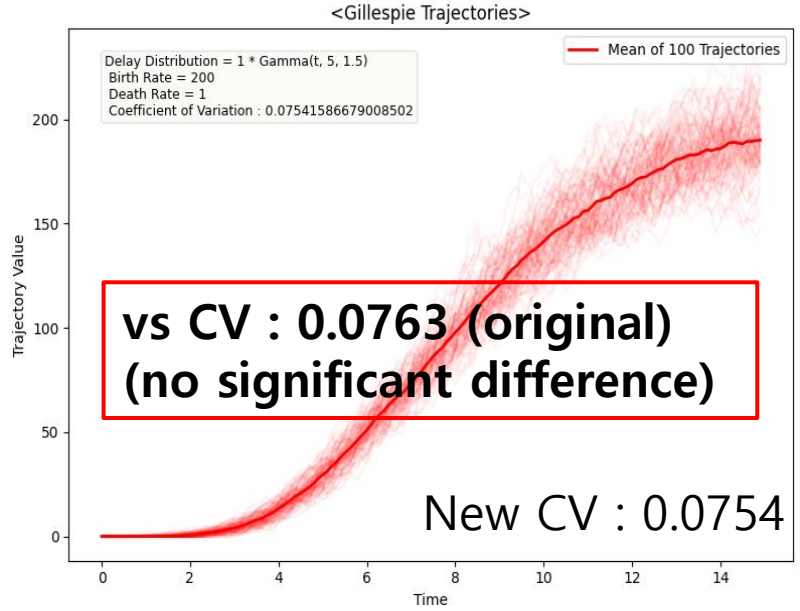


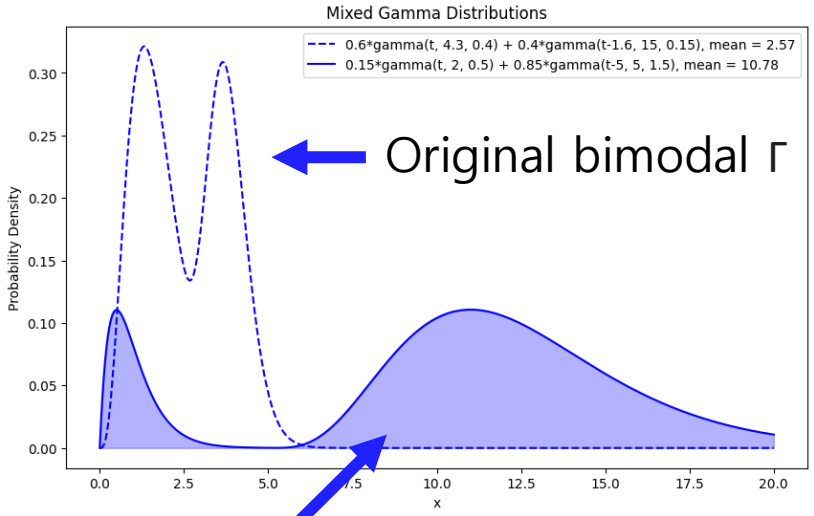
Changing distribution variance yields no significant difference in the final time trace heterogeneity.

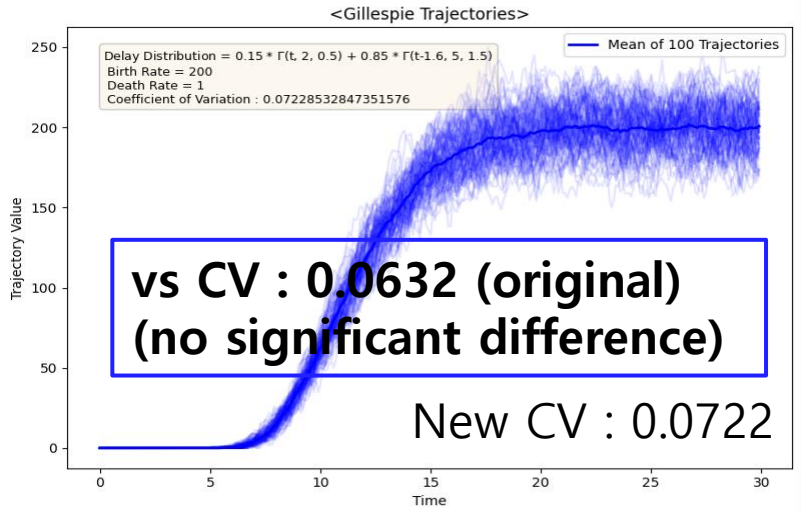
Original Γ Distributions







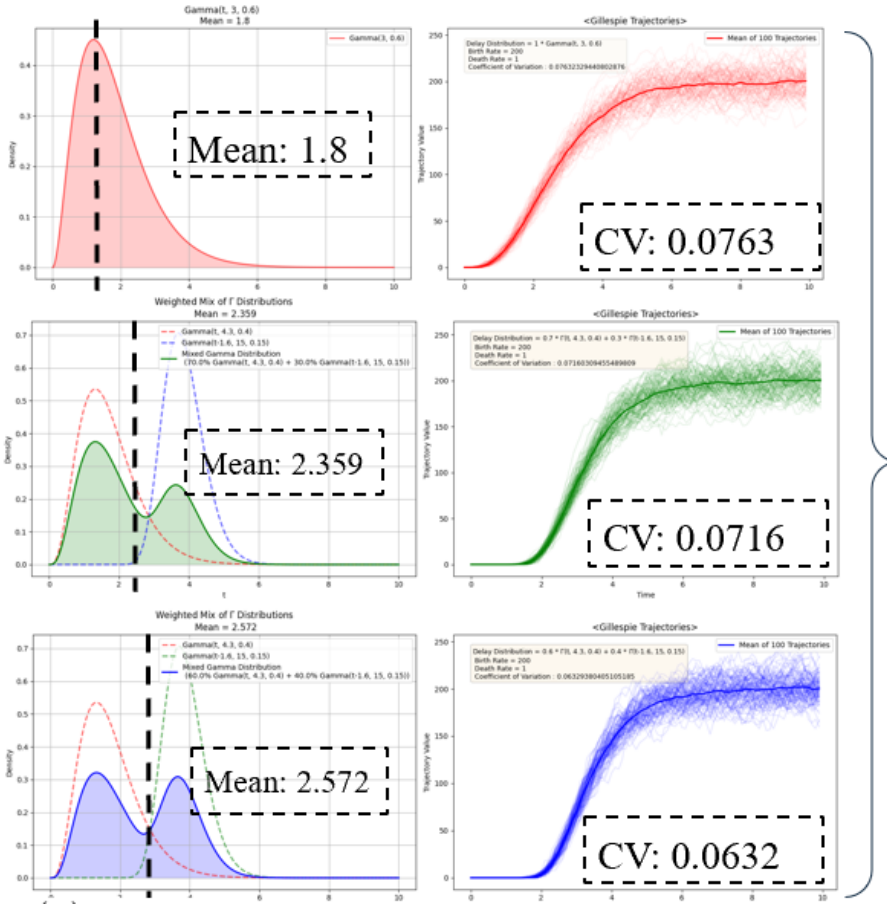


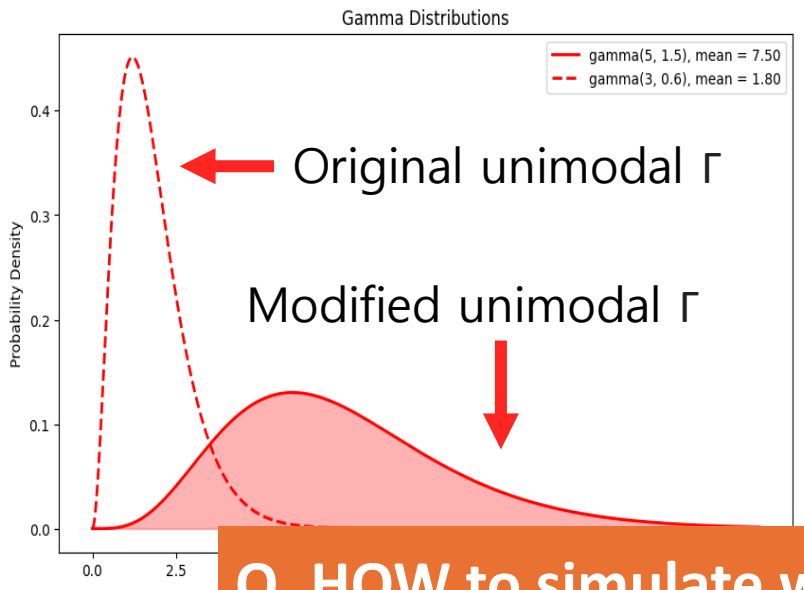


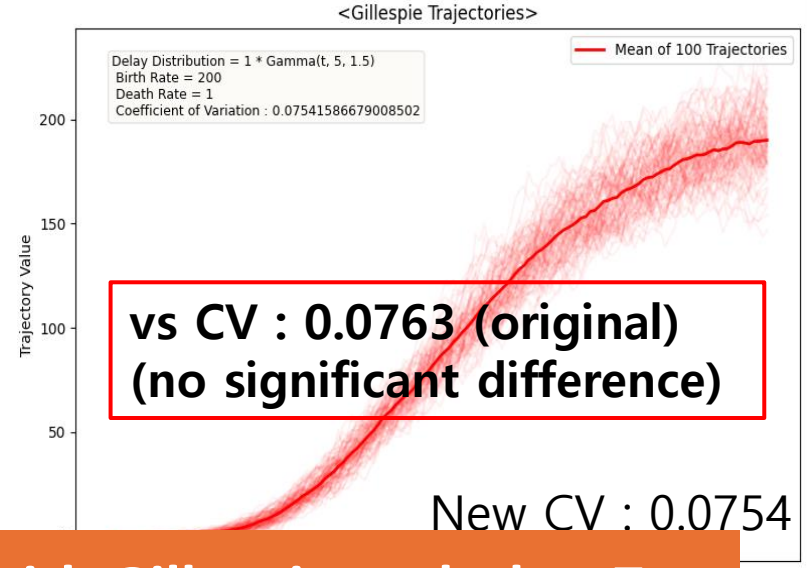
Modified bimodal Γ

Changing distribution variance yields no significant difference in the final time trace heterogeneity.

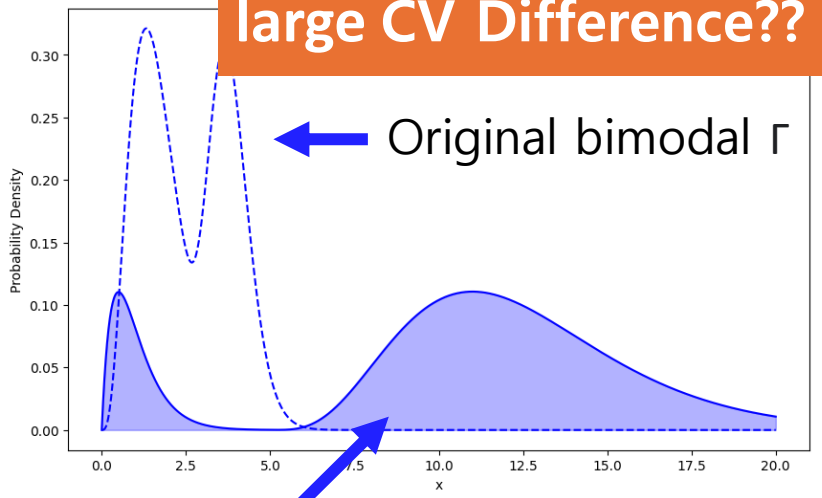
Original Γ Distributions



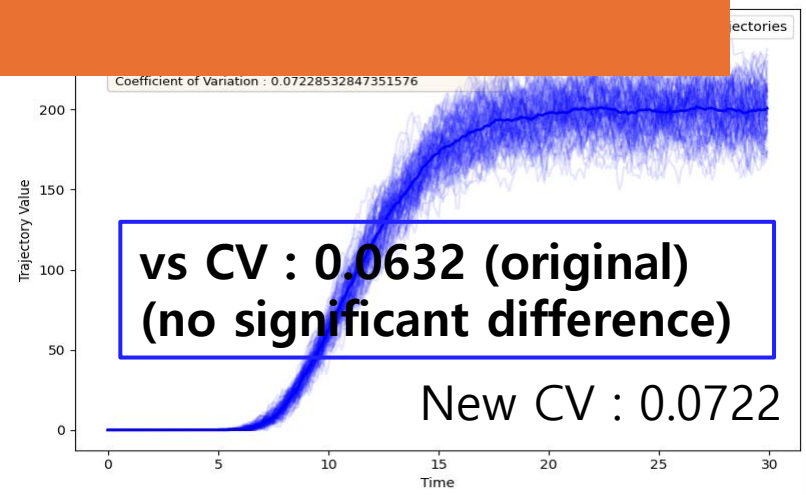




Q. HOW to simulate with Gillespie such that ∃ large CV Difference??



Modified bimodal Γ



Lowering ‘volume’ in Gillespie SSA for single timescale pathways raises heterogeneity and produces closer CV estimates to real data, across different birth/death ratios.

$\lambda_b/\lambda_d = 190$

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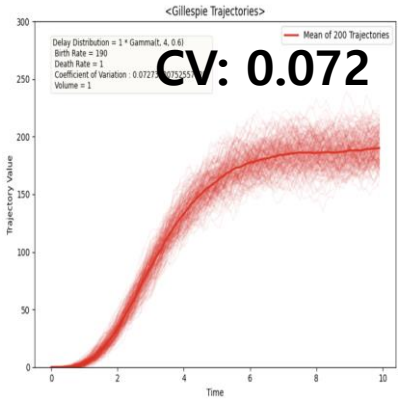
Volume : 1

$\lambda_b/\lambda_d = 190$

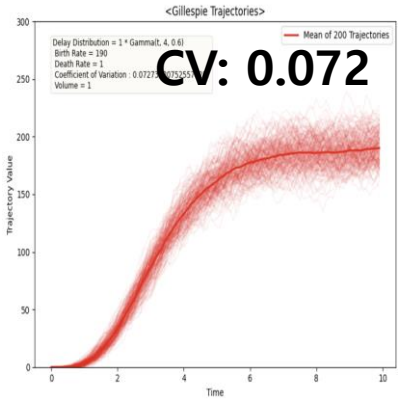


CV: 0.072

Lowering ‘volume’ in Gillespie SSA for single timescale pathways raises heterogeneity and produces closer CV estimates to real data, across different birth/death ratios.

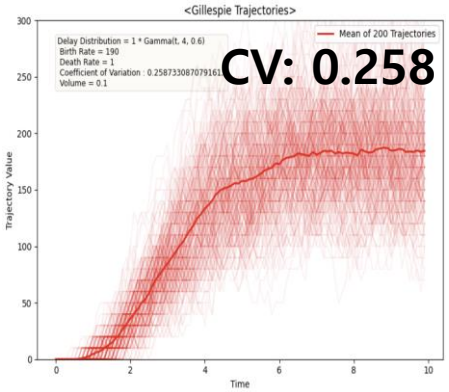
$\lambda_b/\lambda_d = 190$

Volume : 1



CV: 0.072

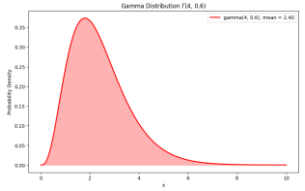
Volume : 0.1



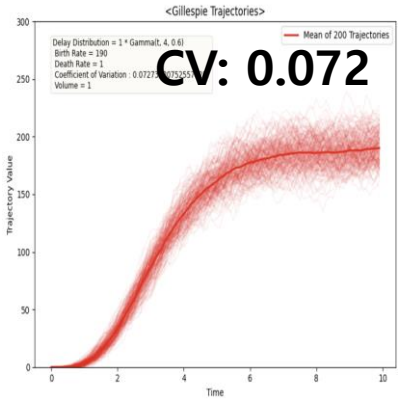
CV: 0.258

Lowering ‘volume’ in Gillespie SSA for single timescale pathways raises heterogeneity and produces closer CV estimates to real data, across different birth/death ratios.

$\lambda_b/\lambda_d = 190$

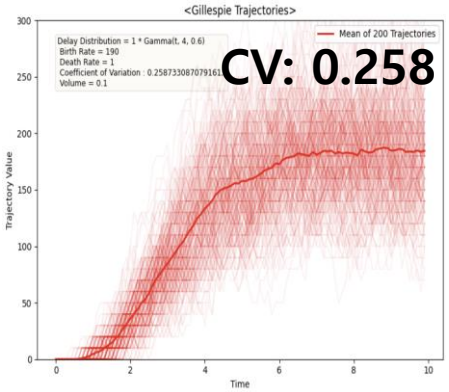


Volume : 1



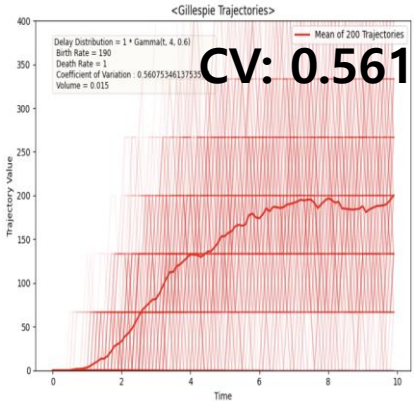
CV: 0.072

Volume : 0.1



CV: 0.258

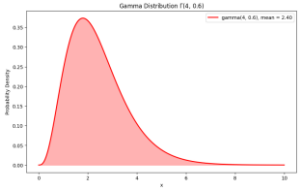
Volume : 0.01



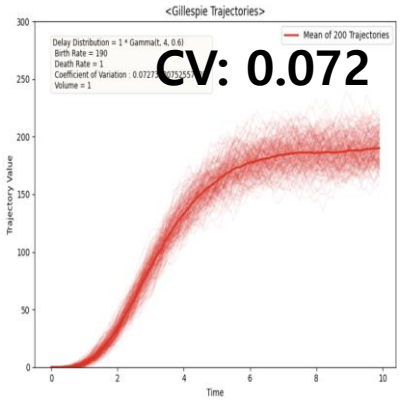
CV: 0.561

Lowering ‘volume’ in Gillespie SSA for single timescale pathways raises heterogeneity and produces closer CV estimates to real data, across different birth/death ratios.

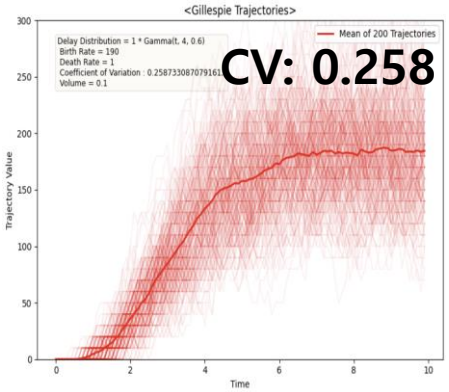
$\lambda_b/\lambda_d = 190$



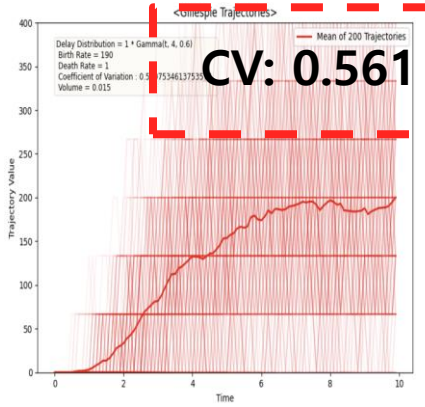
Volume : 1



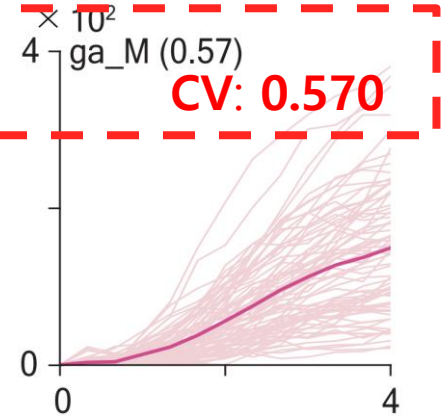
Volume : 0.1



Volume : 0.01



$\lambda_b/\lambda_d = 190$



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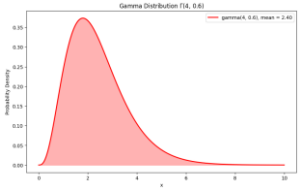
Volume : 1

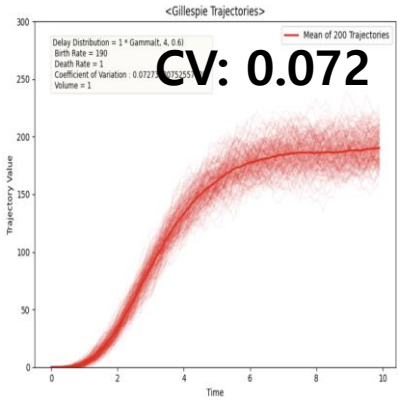
Volume : 0.1

Volume : 0.01

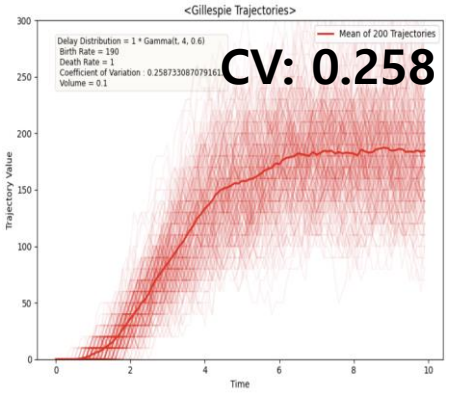
$\lambda_b/\lambda_d = 190$

$\lambda_b/\lambda_d = 190$

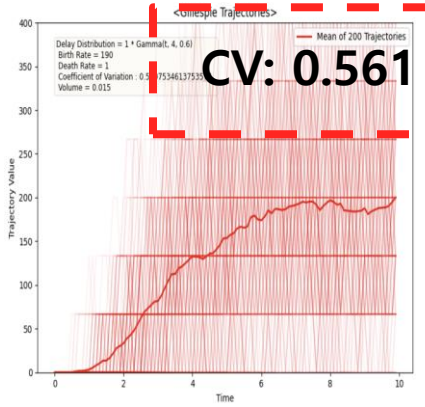




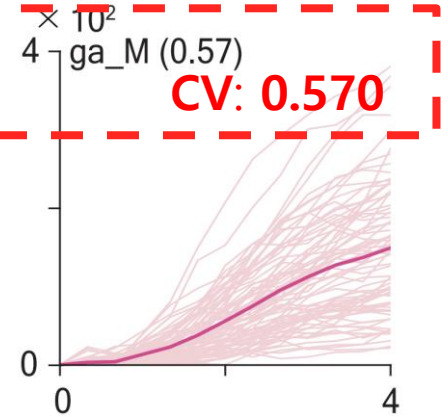
CV: 0.072



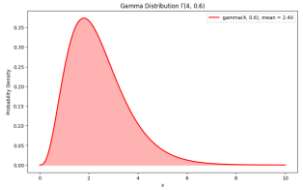
CV: 0.258



CV: 0.561



$\lambda_b/\lambda_d = 350$



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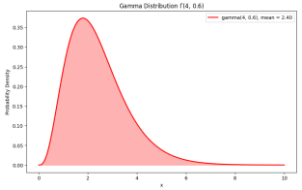
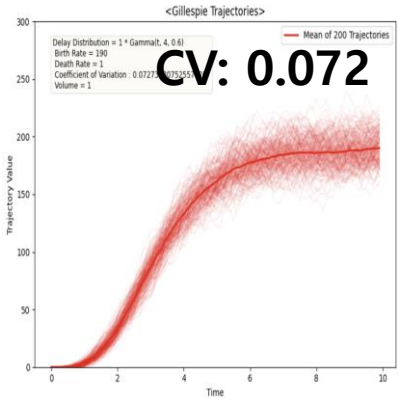
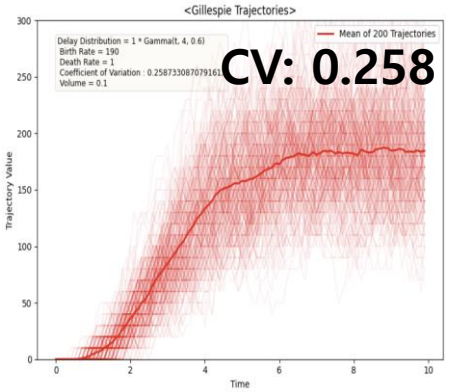


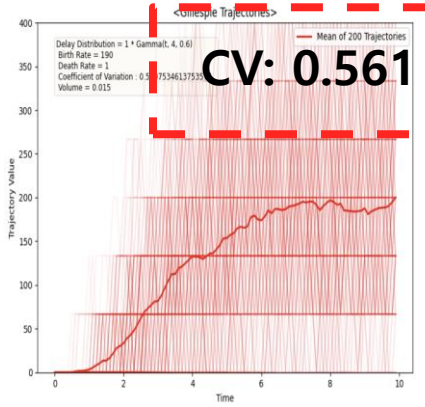
Volume : 1



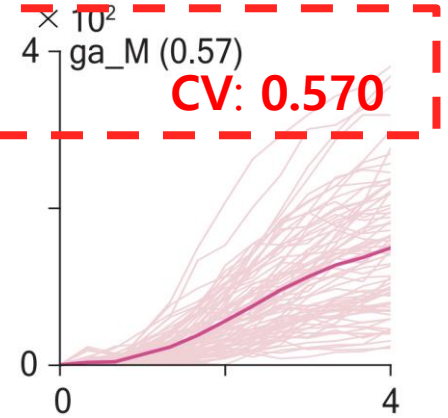
Volume : 0.1



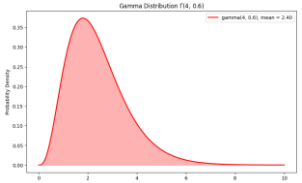
Volume : 0.01



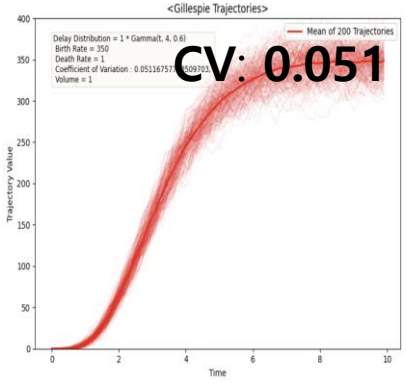
$\lambda_b/\lambda_d = 190$



$\lambda_b/\lambda_d = 350$



Volume : 1



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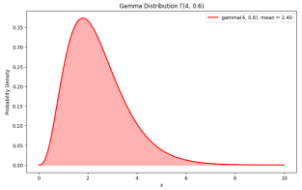
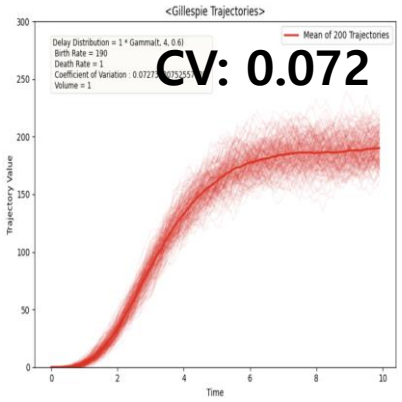
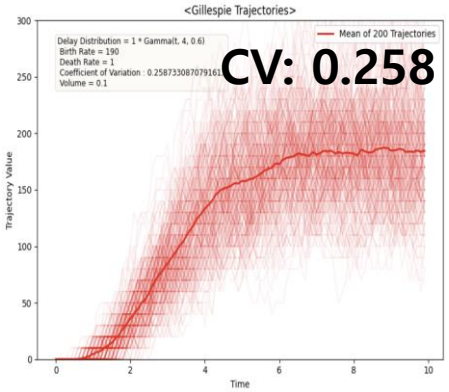


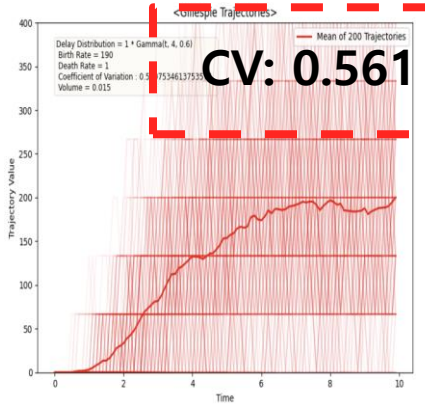
Volume : 1



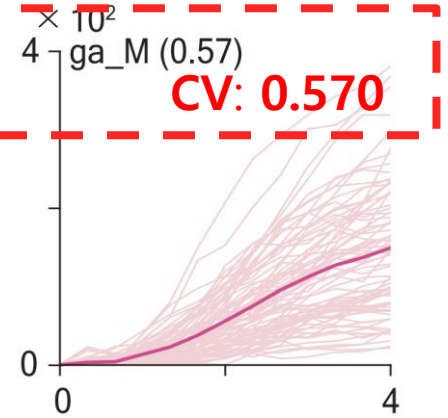
Volume : 0.1



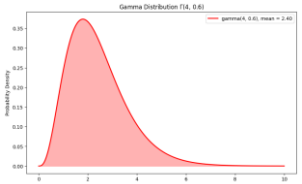
Volume : 0.01



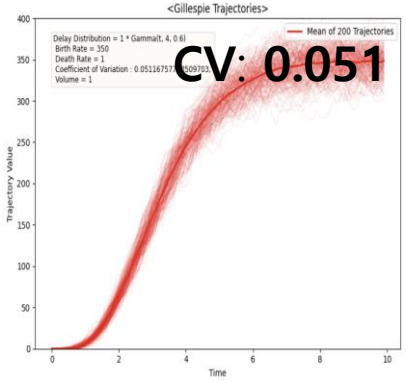
$\lambda_b/\lambda_d = 190$



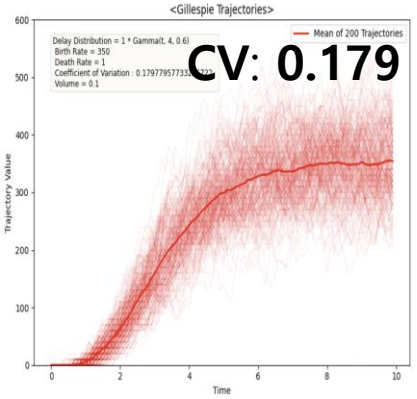
$\lambda_b/\lambda_d = 350$



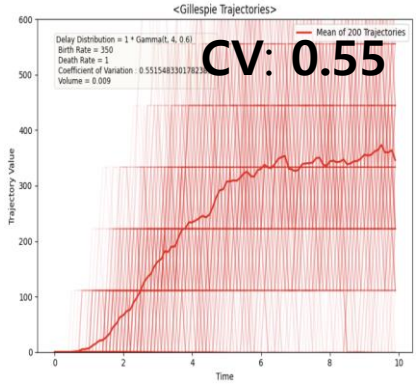
Volume : 1



Volume : 0.1



Volume : 0.01



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Volume : 1

Volume : 0.1

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$\lambda_b/\lambda_d = 190$

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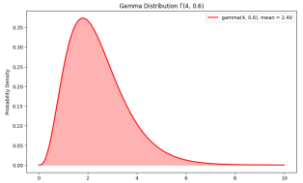
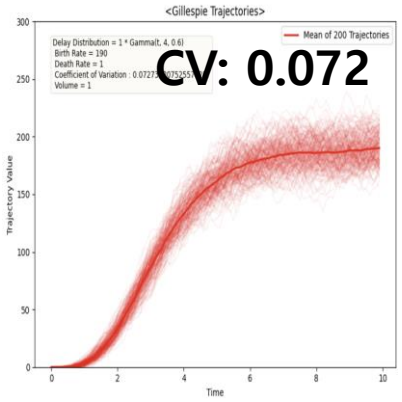
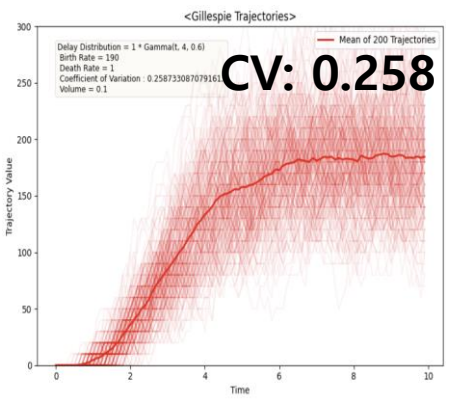
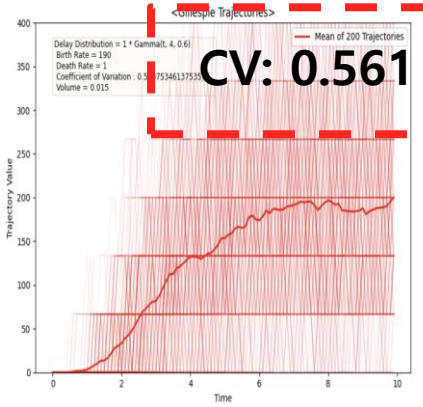




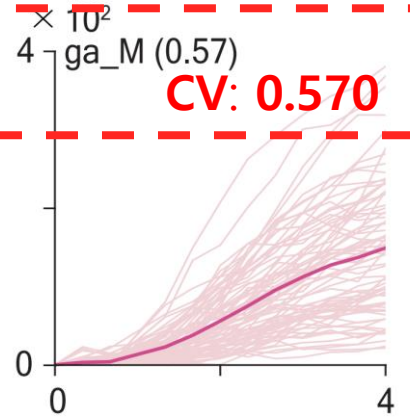
CV: 0.072



CV: 0.258



CV: 0.561



CV: 0.570

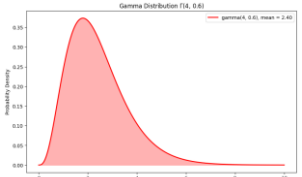
Volume : 1

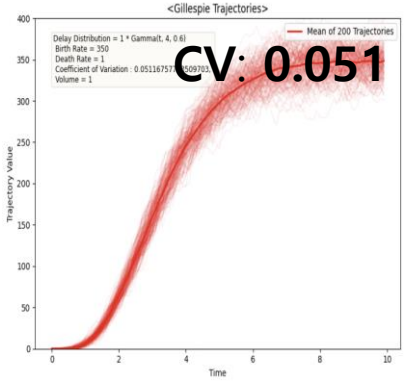
Volume : 0.1

Volume : 0.01

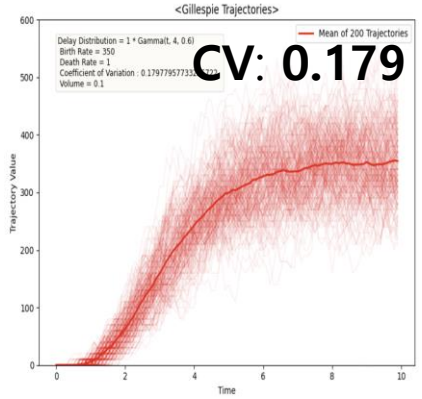
$\lambda_b/\lambda_d = 350$

$\lambda_b/\lambda_d = 350$

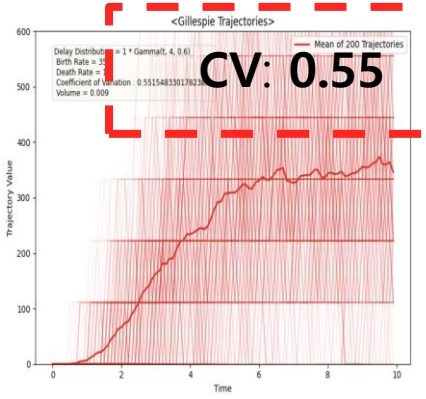




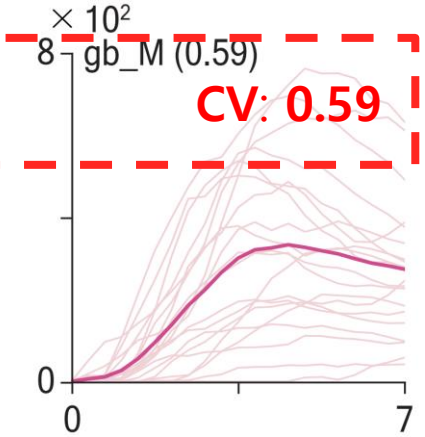
CV: 0.051



CV: 0.179



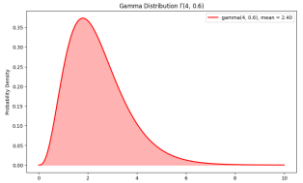
CV: 0.55



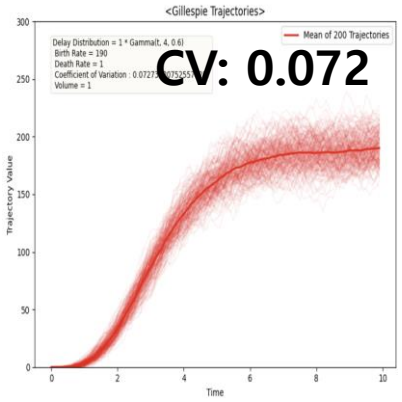
CV: 0.59

Lowering ‘volume’ in Gillespie SSA for single timescale pathways raises heterogeneity and produces closer CV estimates to real data, across different birth/death ratios.

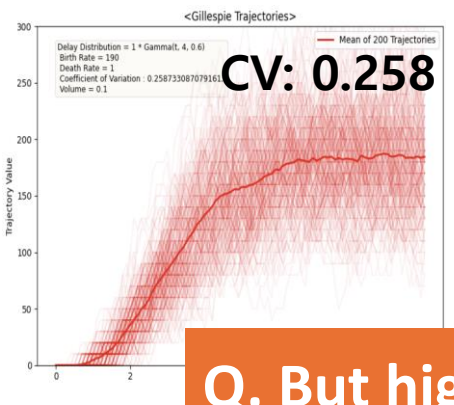
$\lambda_b/\lambda_d = 190$



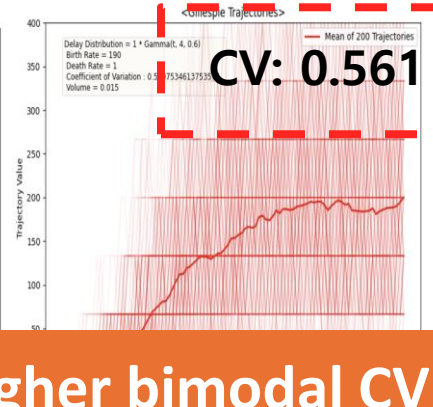
Volume : 1



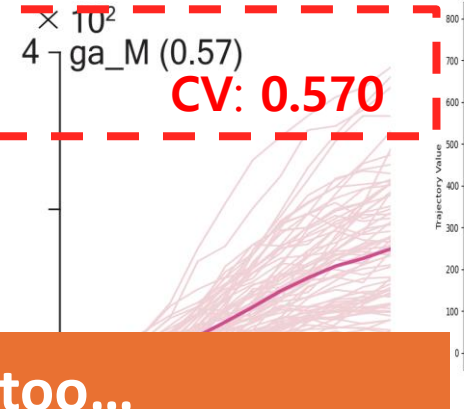
Volume : 0.1



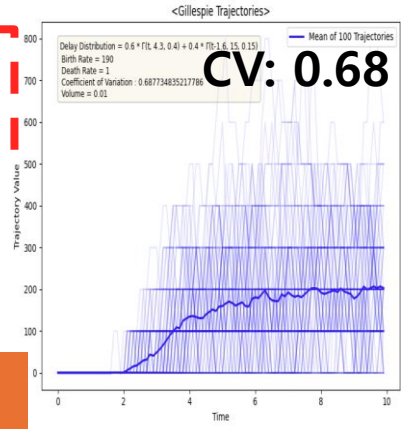
Volume : 0.01



$\lambda_b/\lambda_d = 190$

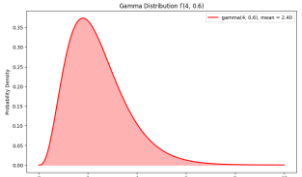


Volume : 0.01

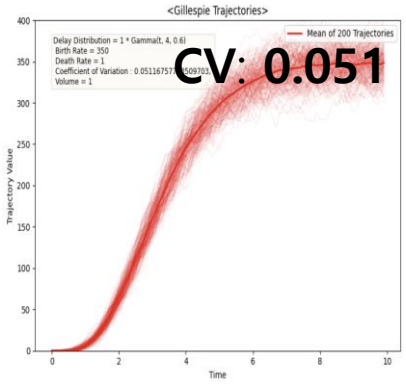


Q. But higher bimodal CV too…

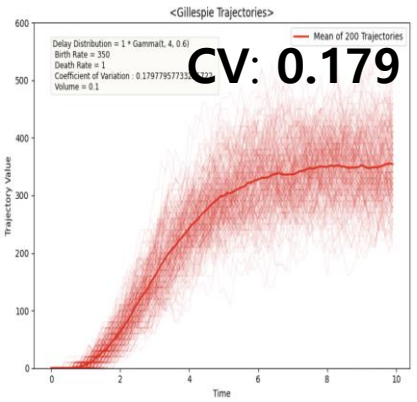
$\lambda_b/\lambda_d = 350$



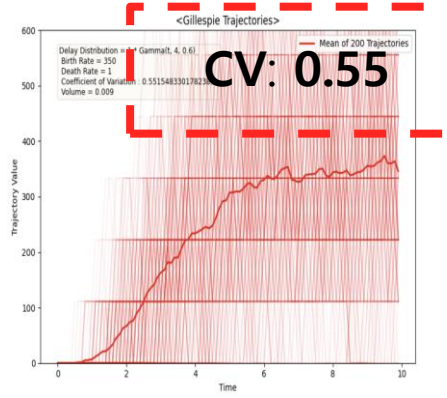
Volume : 1



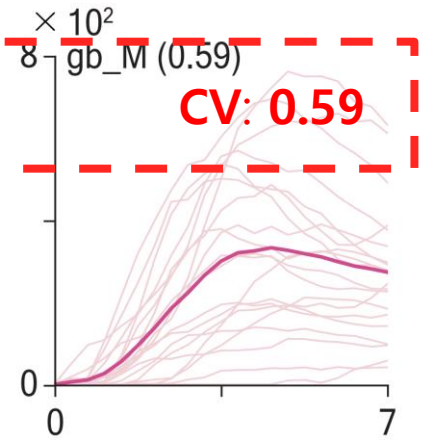
Volume : 0.1



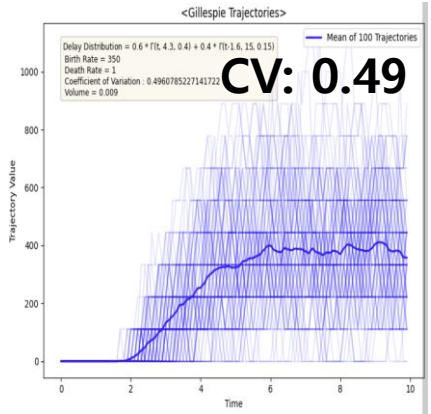
Volume : 0.01



$\lambda_b/\lambda_d = 350$

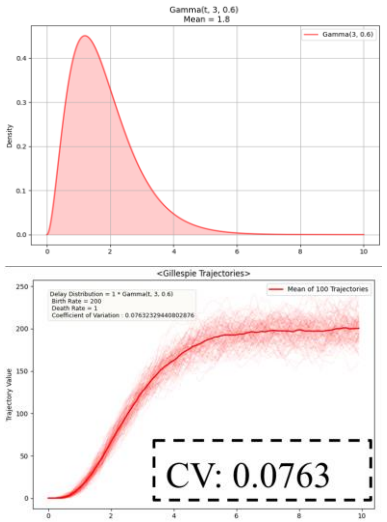


Volume : 0.01



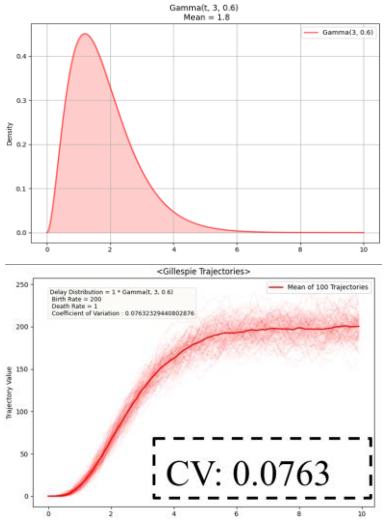
Changing the delay distribution type does not significantly impact heterogeneity.

Gamma

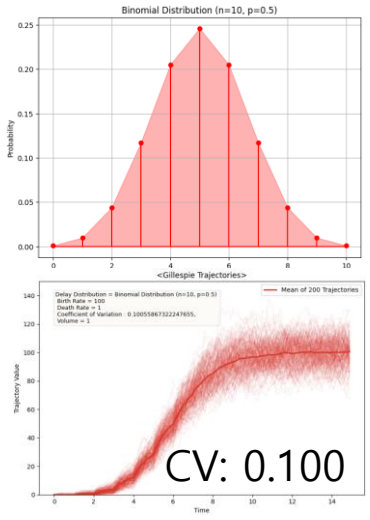


Changing the delay distribution type does not significantly impact heterogeneity.

Gamma

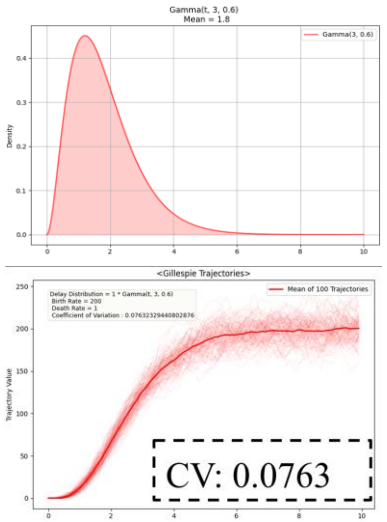


Binomial

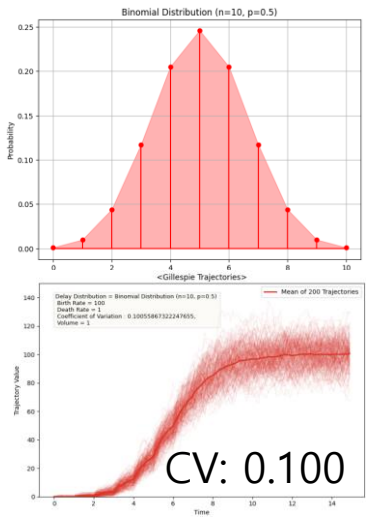


Changing the delay distribution type does not significantly impact heterogeneity.

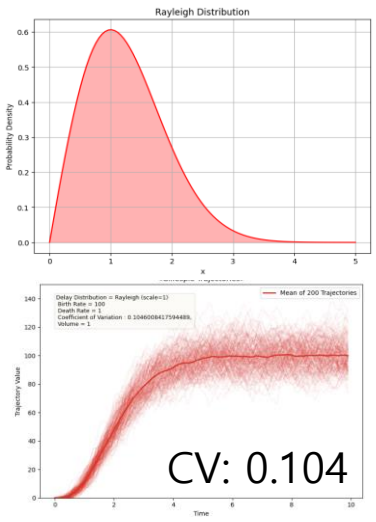
Gamma



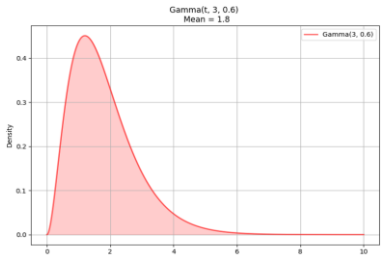
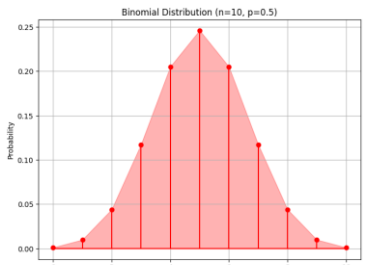
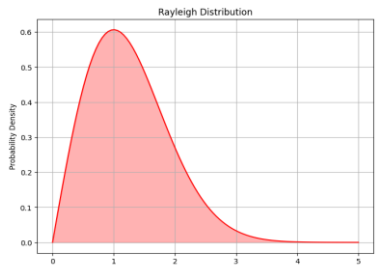
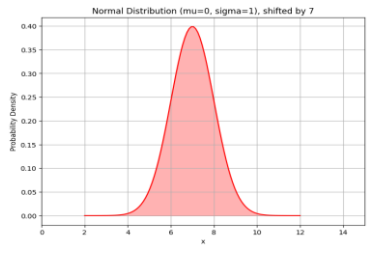
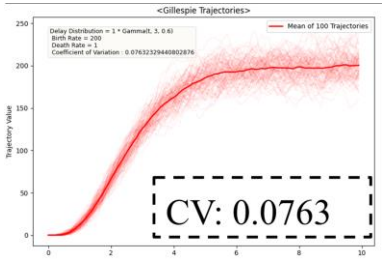
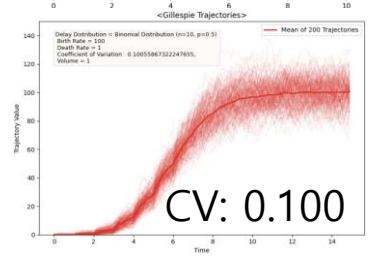
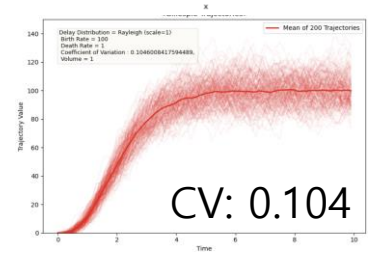
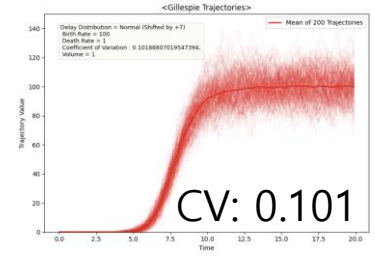
Binomial



Rayleigh

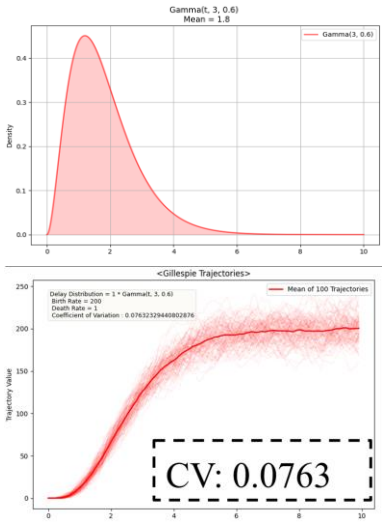


Changing the delay distribution type does not significantly impact heterogeneity.

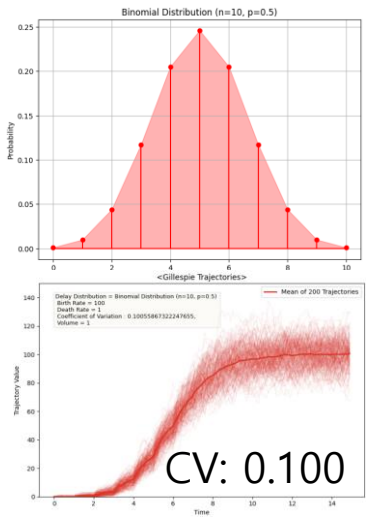
Gamma	Binomial	Rayleigh	Normal
			
			
CV: 0.0763	CV: 0.100	CV: 0.104	CV: 0.101

Changing the delay distribution type does not significantly impact heterogeneity.

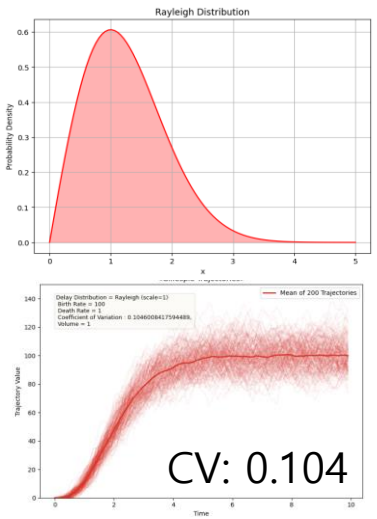
Gamma



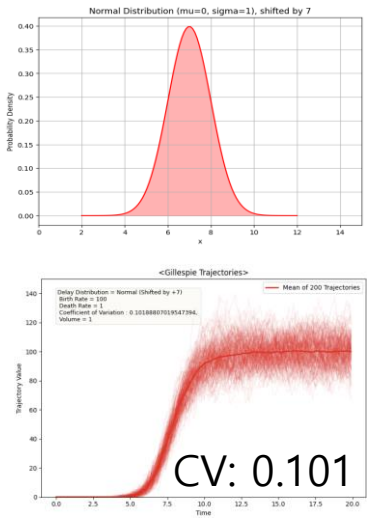
Binomial



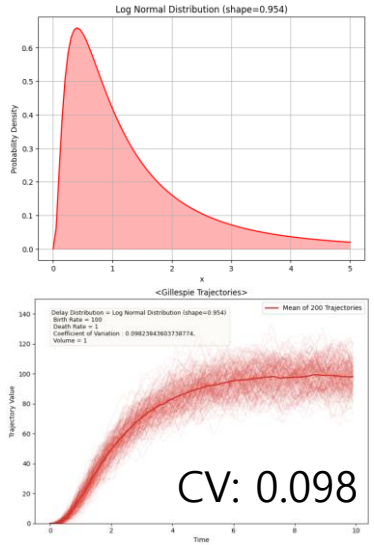
Rayleigh



Normal

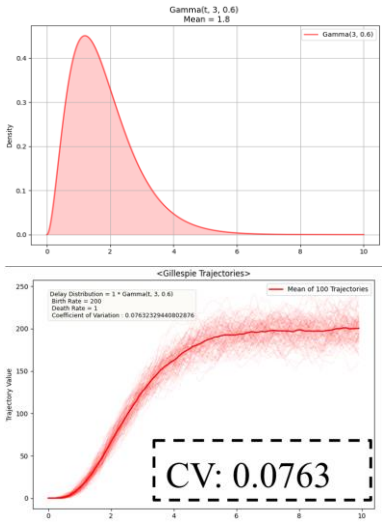


Log Normal

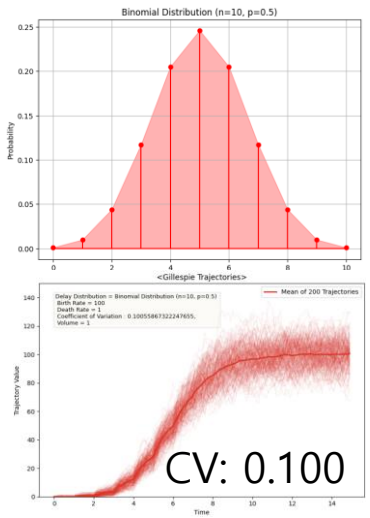


Changing the delay distribution type does not significantly impact heterogeneity.

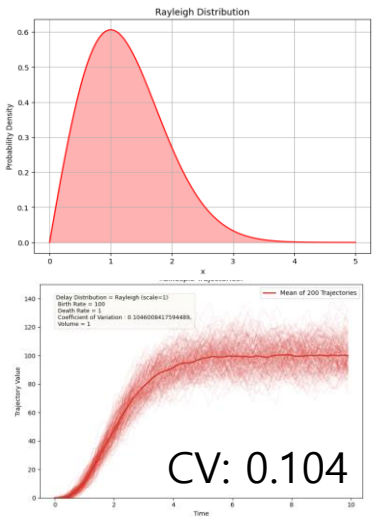
Gamma



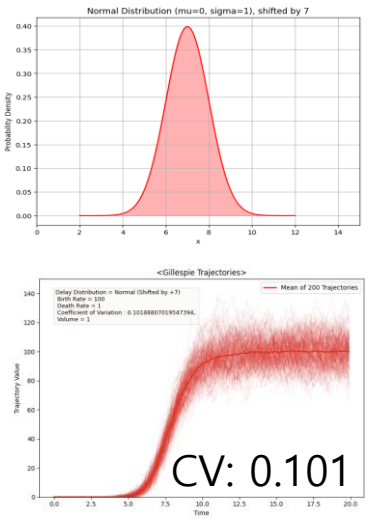
Binomial



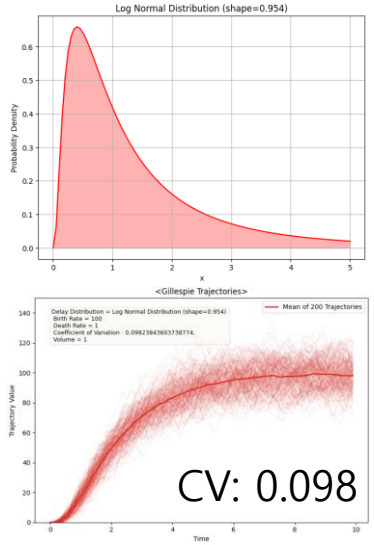
Rayleigh



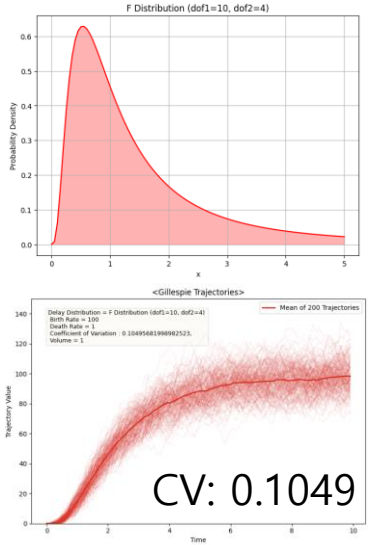
Normal



Log Normal

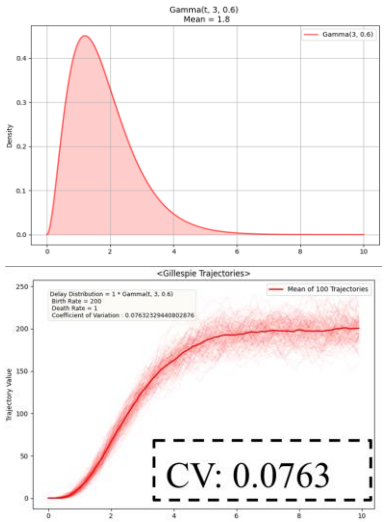


F-distribution

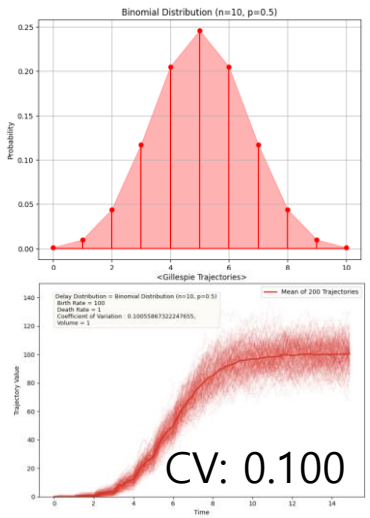


Changing the delay distribution type does not significantly impact heterogeneity.

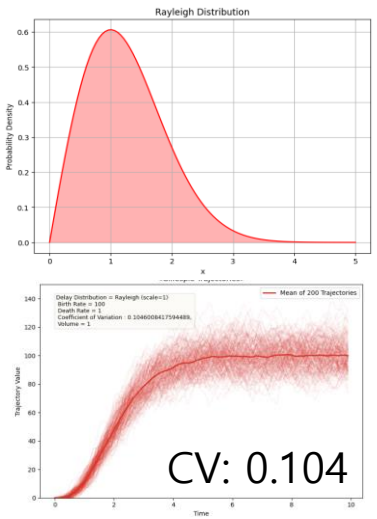
Gamma



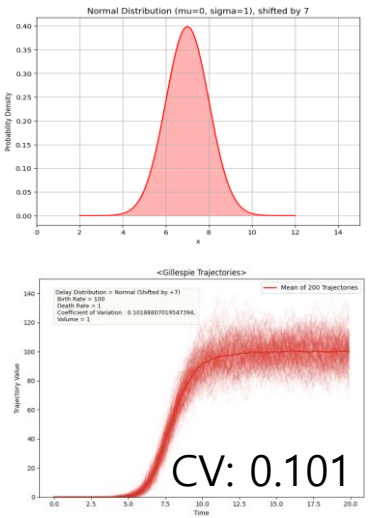
Binomial



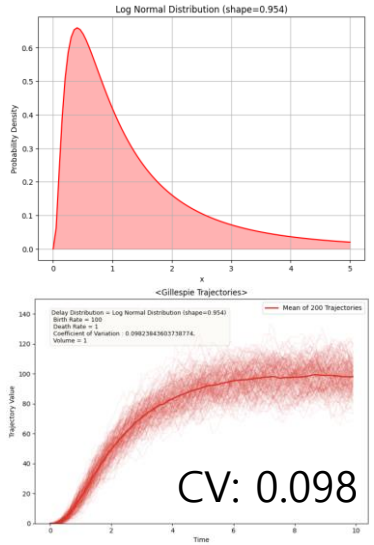
Rayleigh



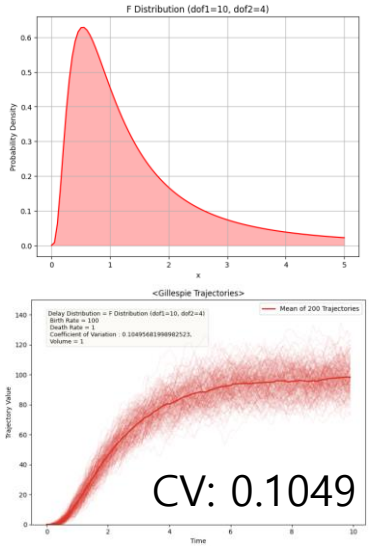
Normal



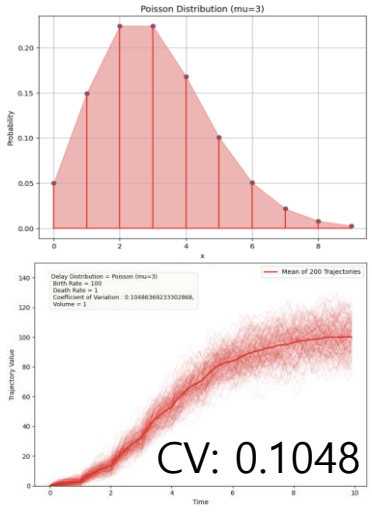
Log Normal



F-distribution

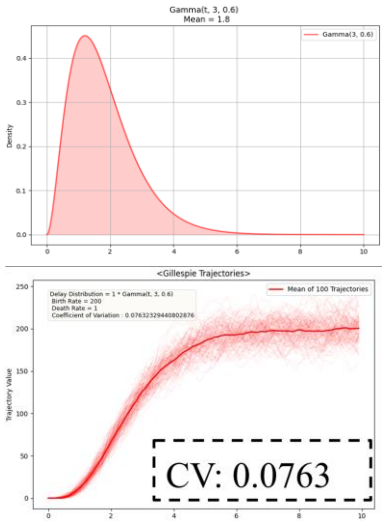


Poisson

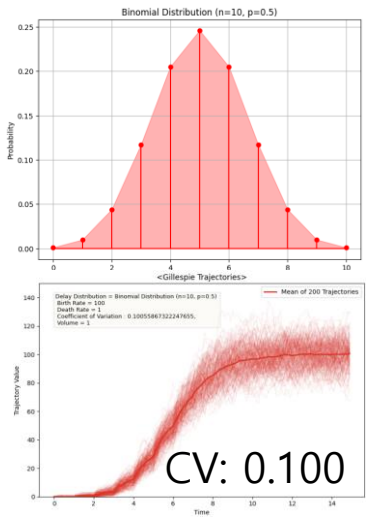


Changing the delay distribution type does not significantly impact heterogeneity.

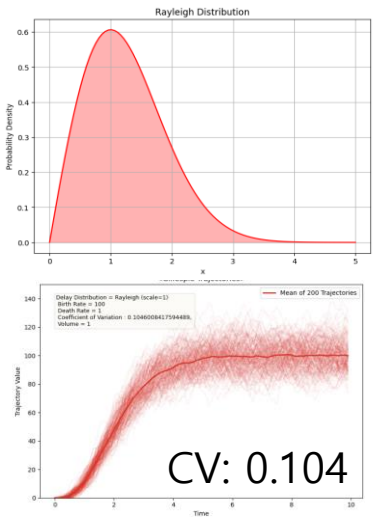
Gamma



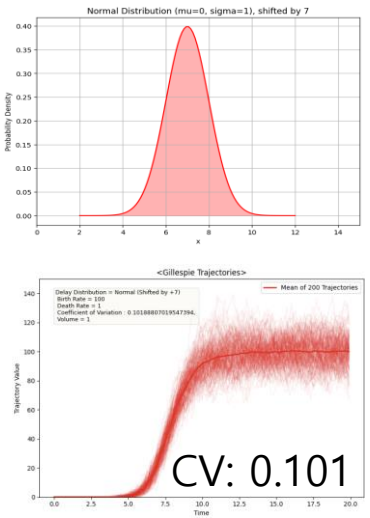
Binomial



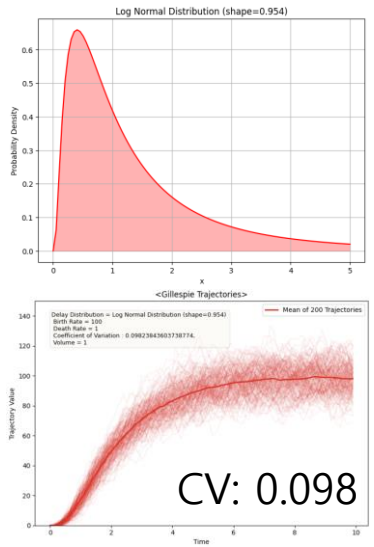
Rayleigh



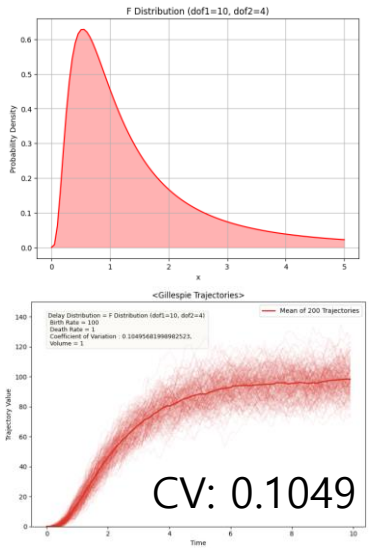
Normal



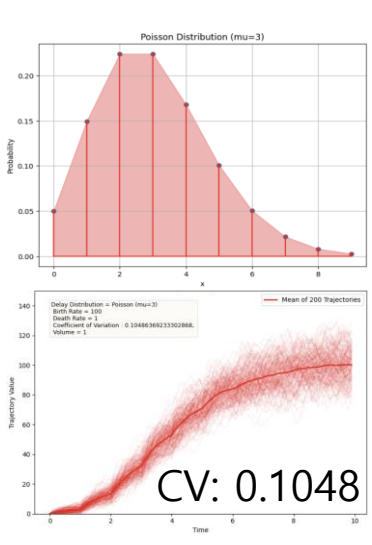
Log Normal



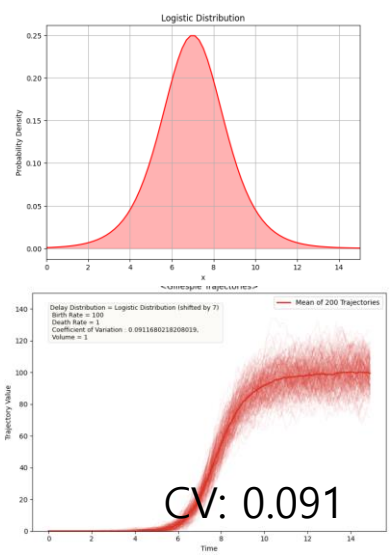
F-distribution



Poisson

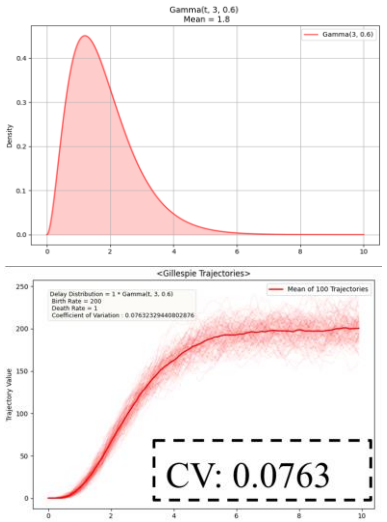


Logistic

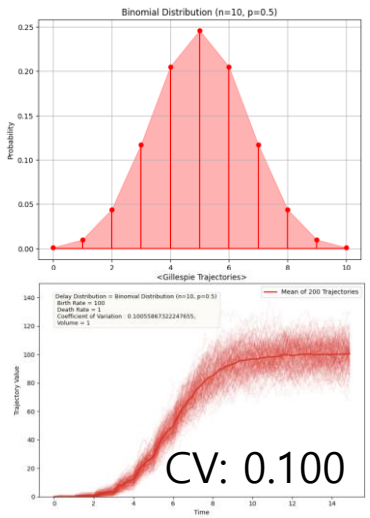


Changing the delay distribution type does not significantly impact heterogeneity.

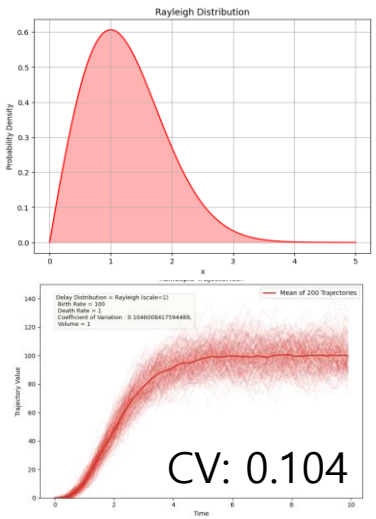
Gamma



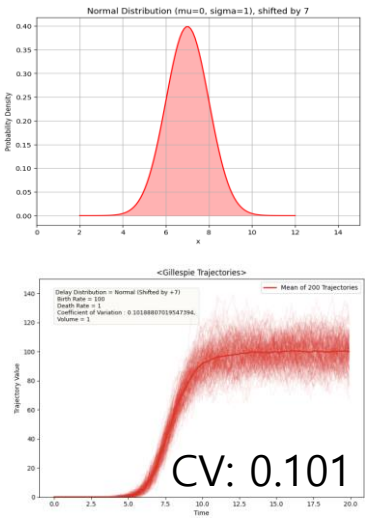
Binomial



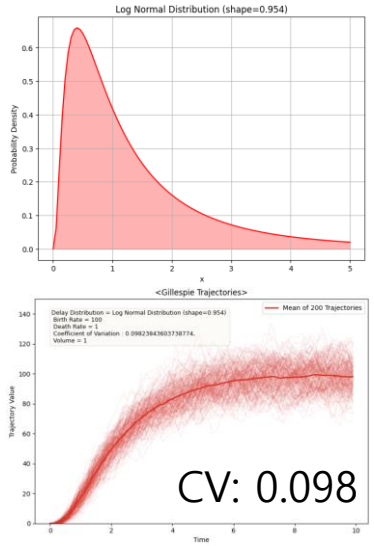
Rayleigh



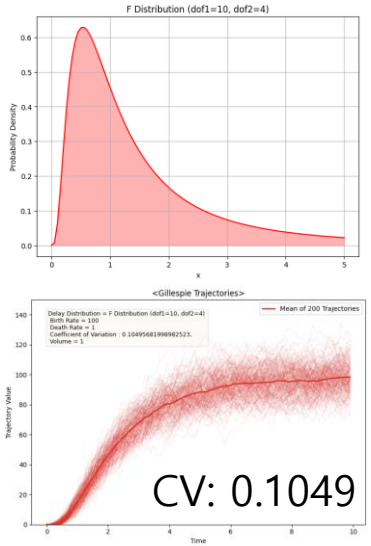
Normal



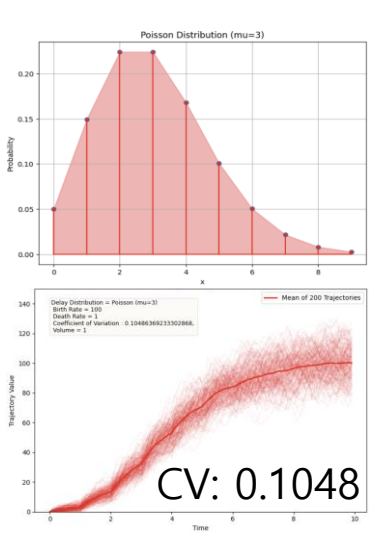
Log Normal



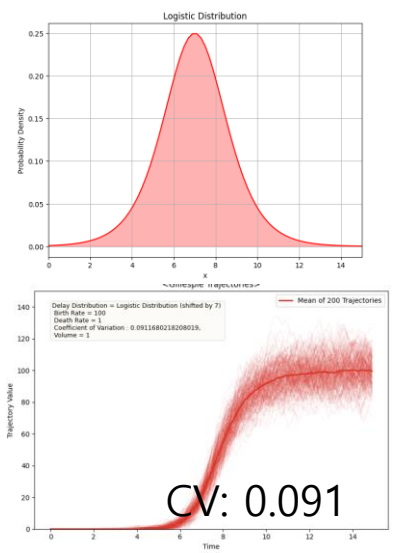
F-distribution



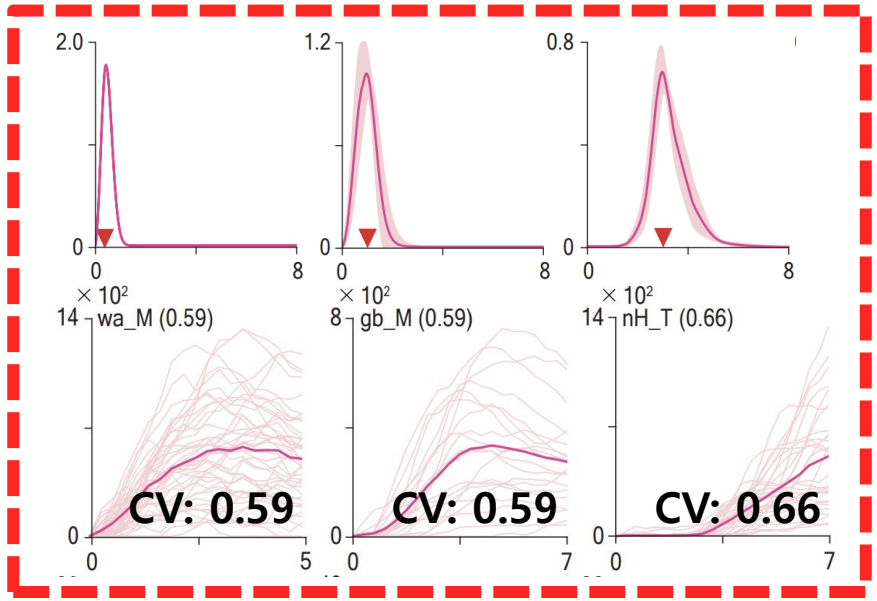
Poisson



Logistic

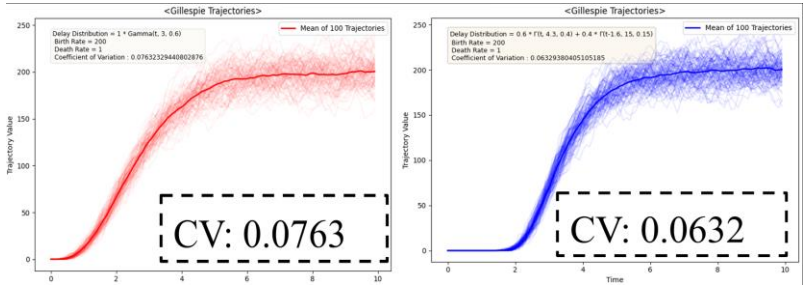


How to generate high CV values??

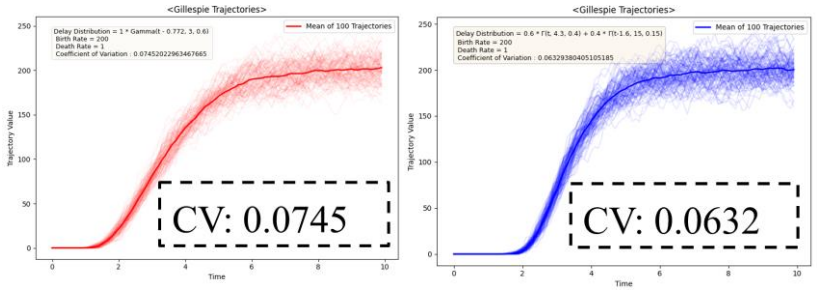


Summary: Modifying delay distribution (mean, variance, type) / volume / birth-death ratio do not work.

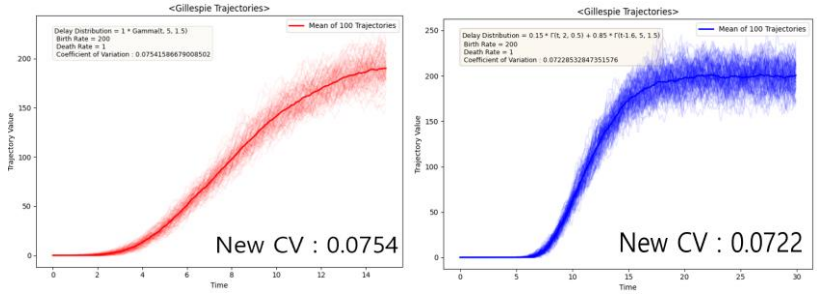
Original [Paper]



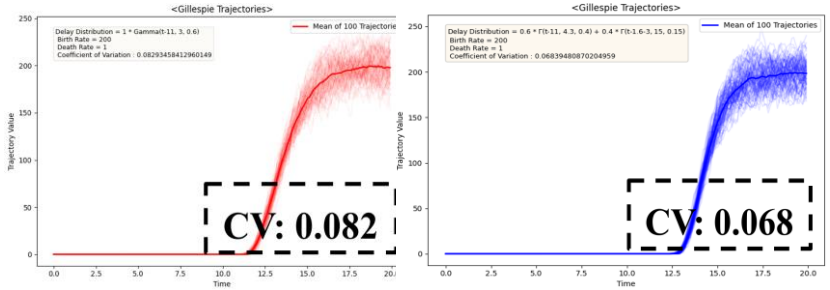
Same Mean



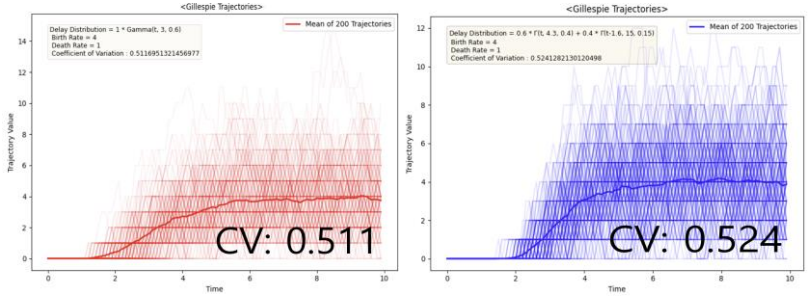
Increased Variance



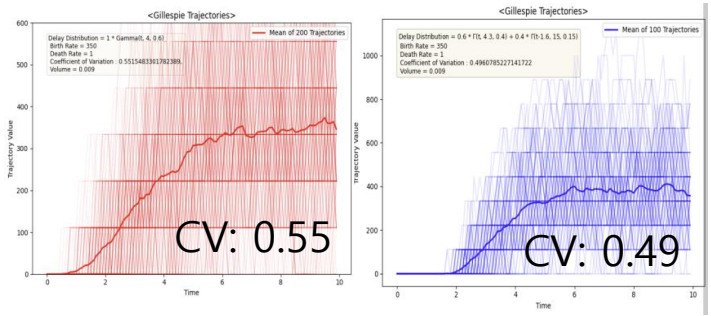
Horizontal Shift



Lower Birth/Death Ratio (4:1)

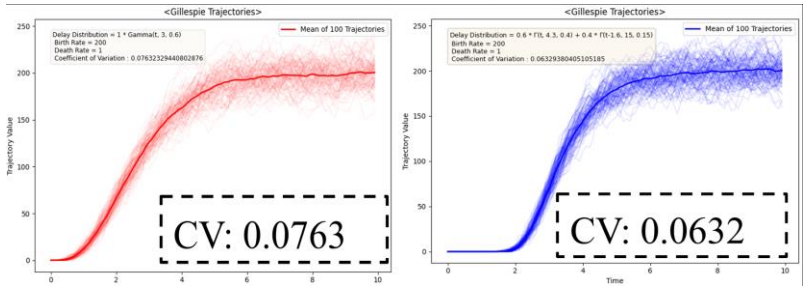


Lower Volume (1 → 0.009)

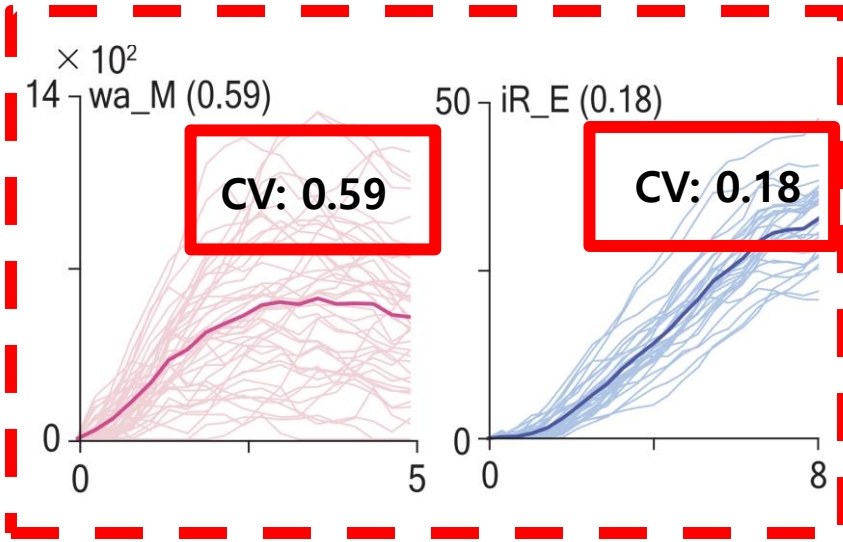


Summary: Modifying delay distribution (mean, variance) / volume / birth-death ratio do not work.

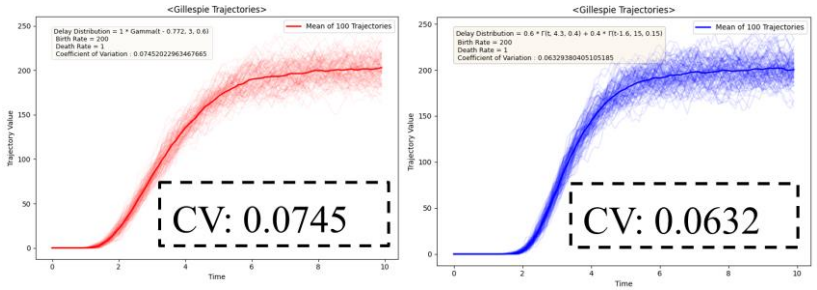
Original [Paper]



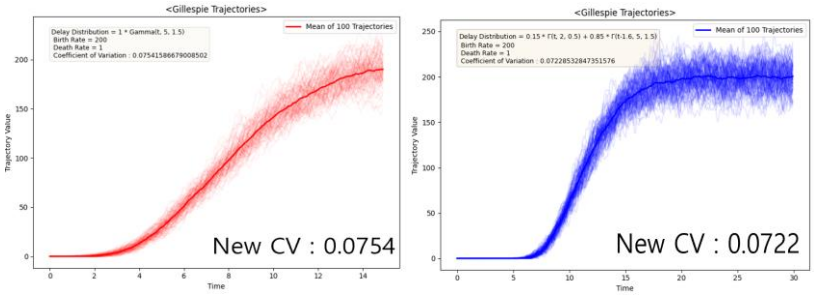
Q. How to get Unimodal CV >> Bimodal CV??



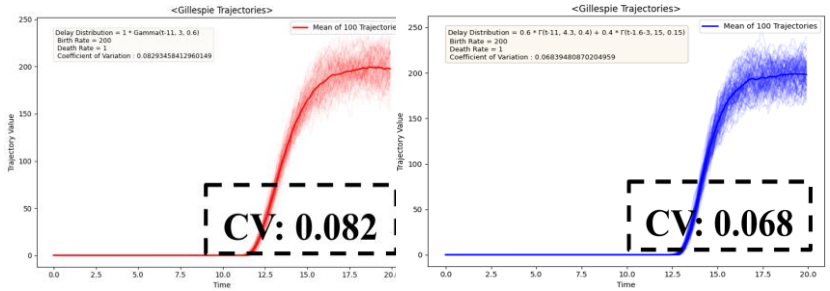
Same Mean



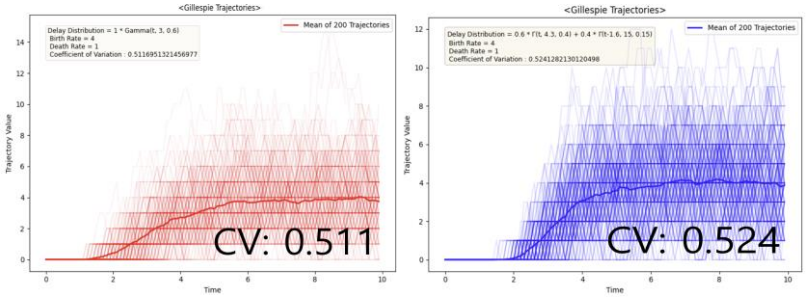
Increased Variance



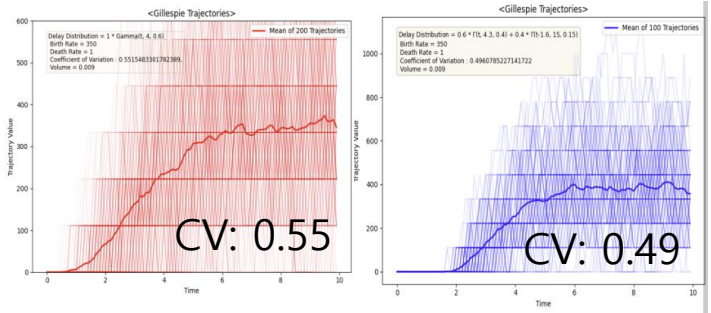
Horizontal Shift



Lower Birth/Death Ratio (4:1)

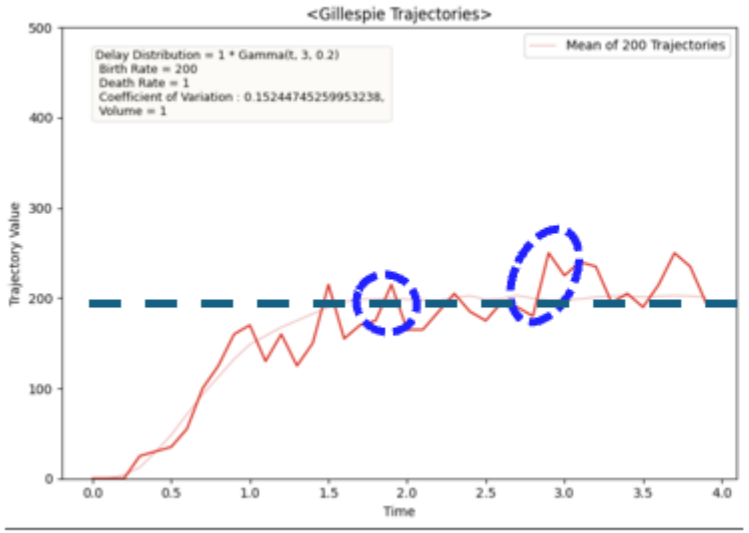


Lower Volume (1 → 0.009)

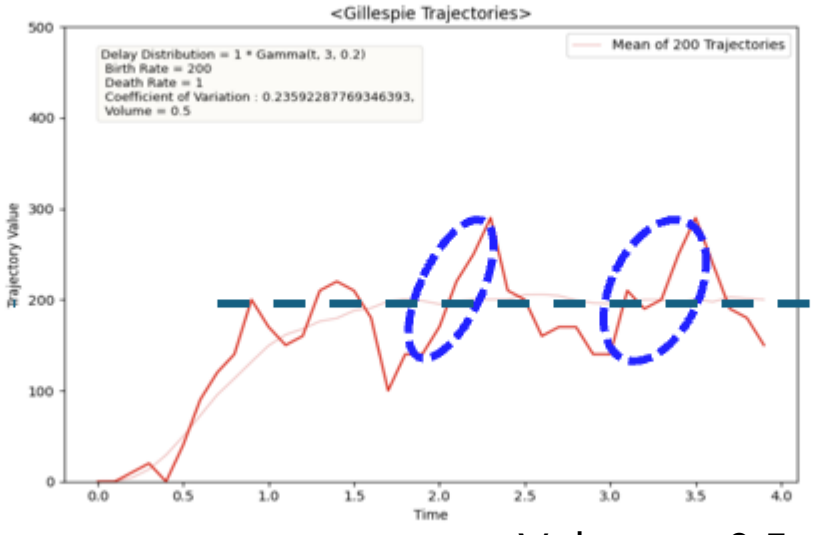


Future Directions : Identify why lowering volume increases CV, find how low volume is related to single timescale pathways.

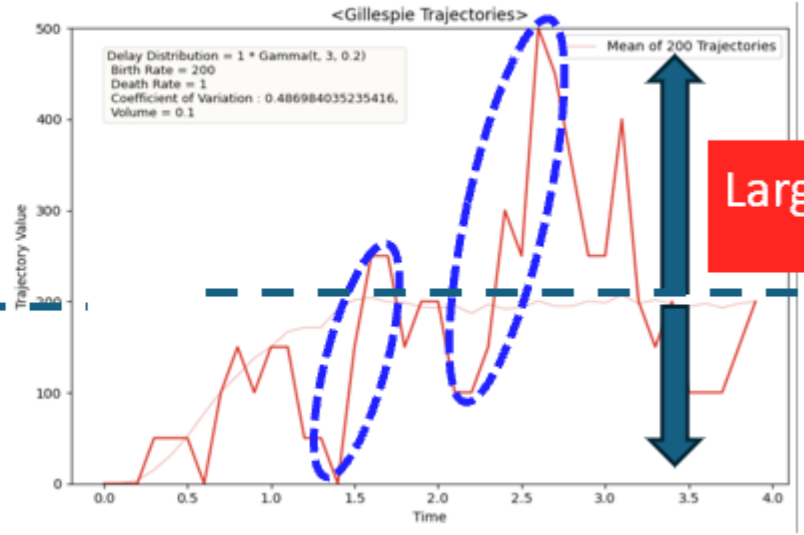
Volume : 1



Volume : 0.5

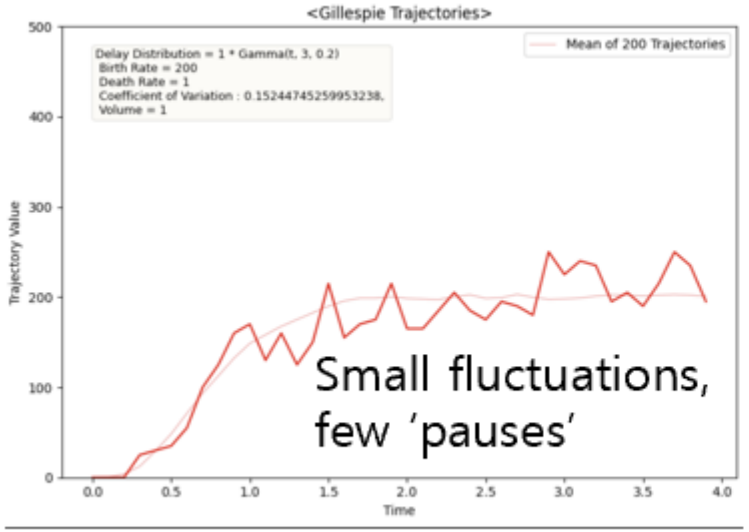


Volume : 0.1

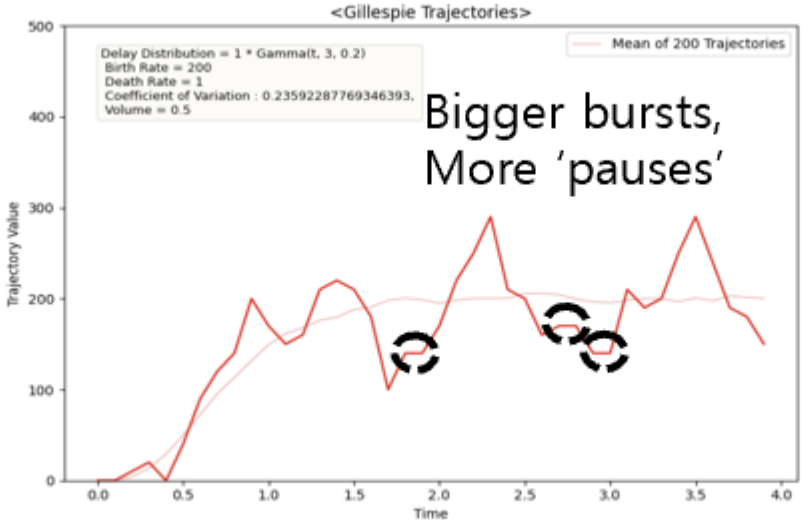


Larger CV

Volume : 1



Volume : 0.5



Volume : 0.1