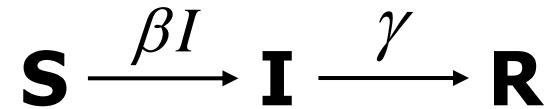


Incorporating representative waiting time distributions in epidemiological models via optimized, **Generalized Erlang-distributions**

Presentation by Vivek Murali

Compartment Models – Underlying Assumptions

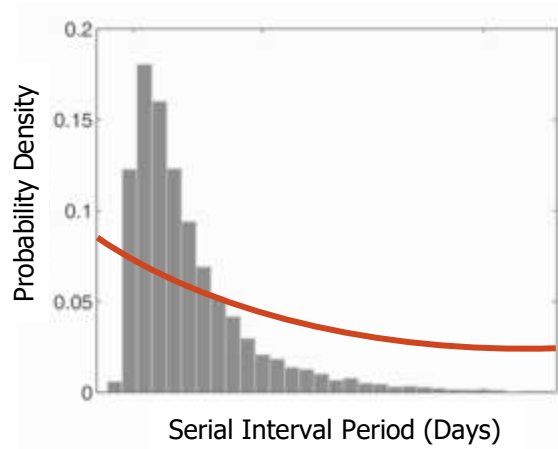
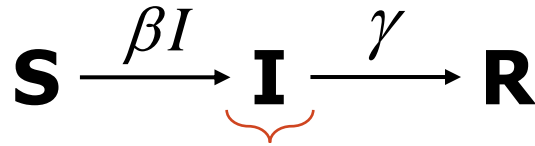


$$\frac{dS}{dt} = -\beta IS$$

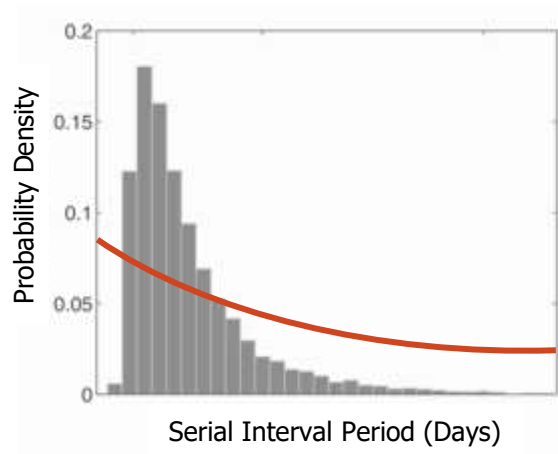
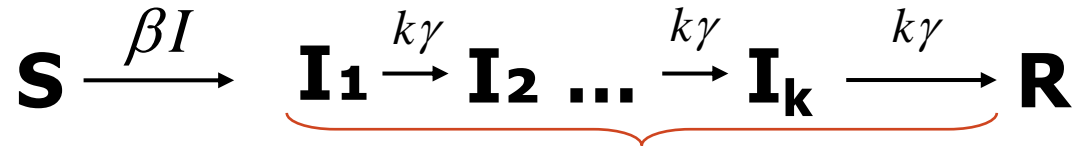
$$\frac{dI}{dt} = \beta IS - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

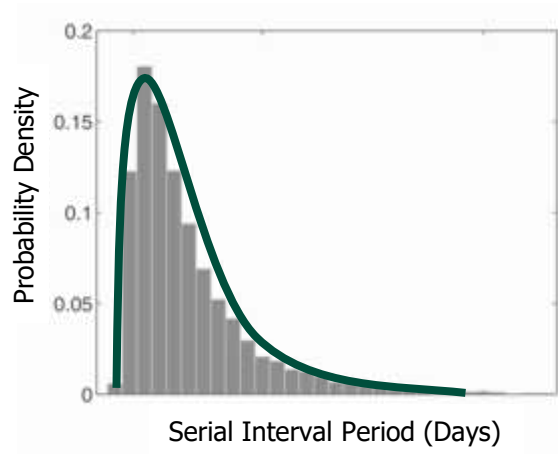
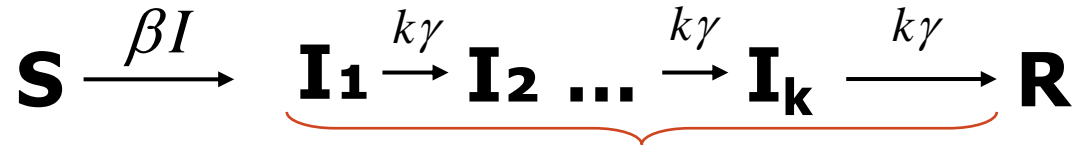
Compartment Models – Underlying Assumptions



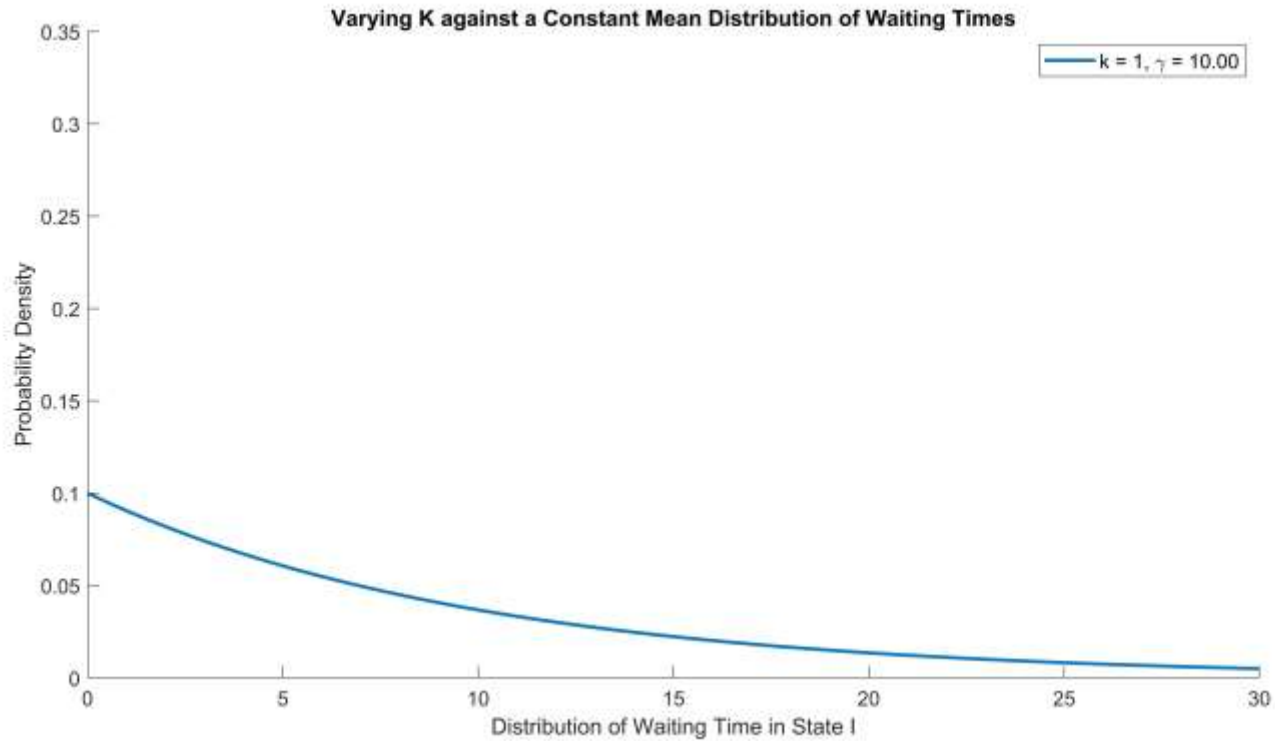
Linear Chain Trick



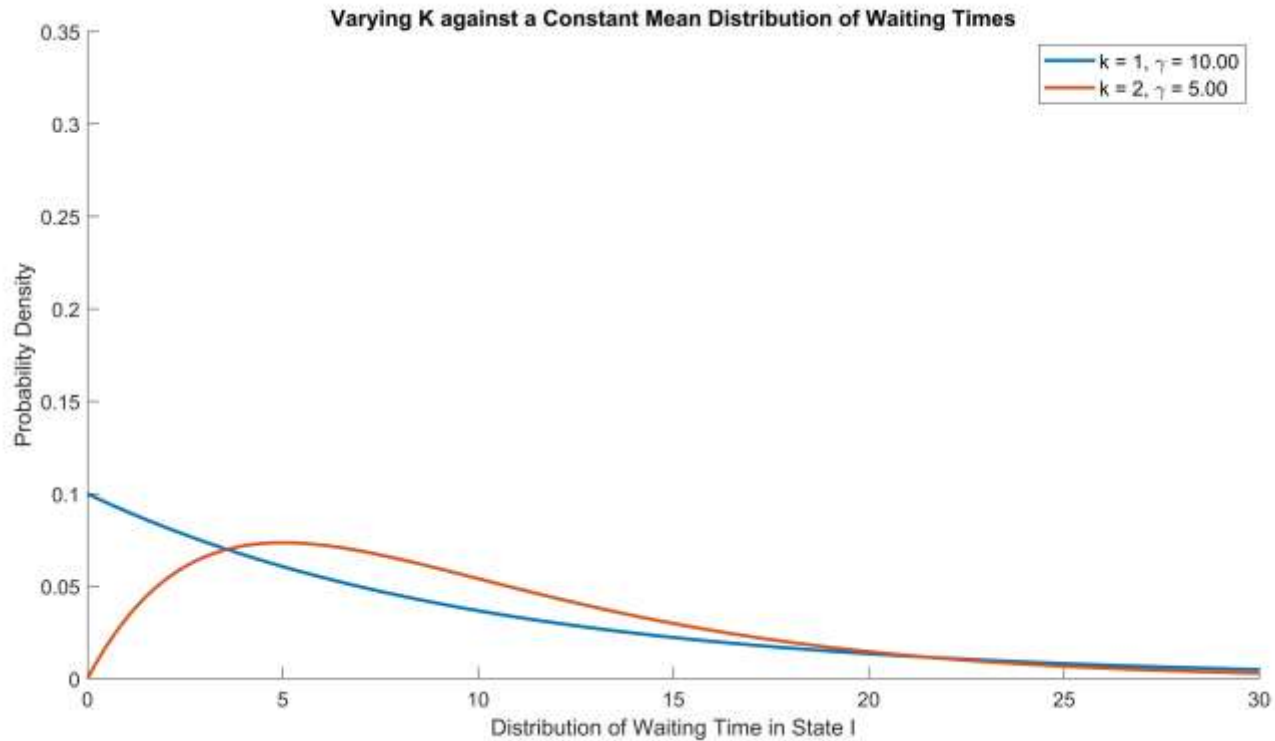
Linear Chain Trick

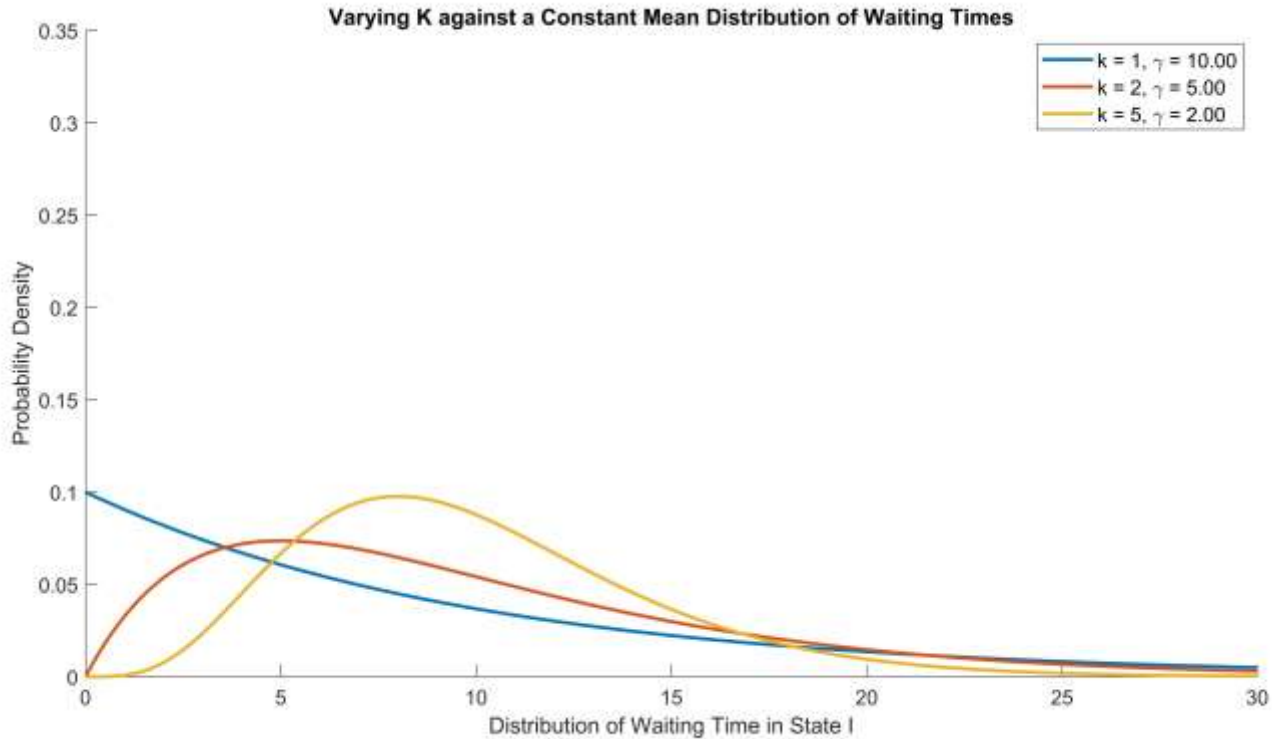
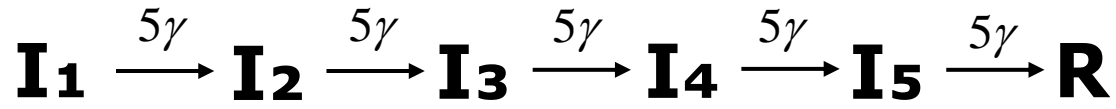


$$\mathbf{I_1} \xrightarrow{\gamma} \mathbf{R}$$

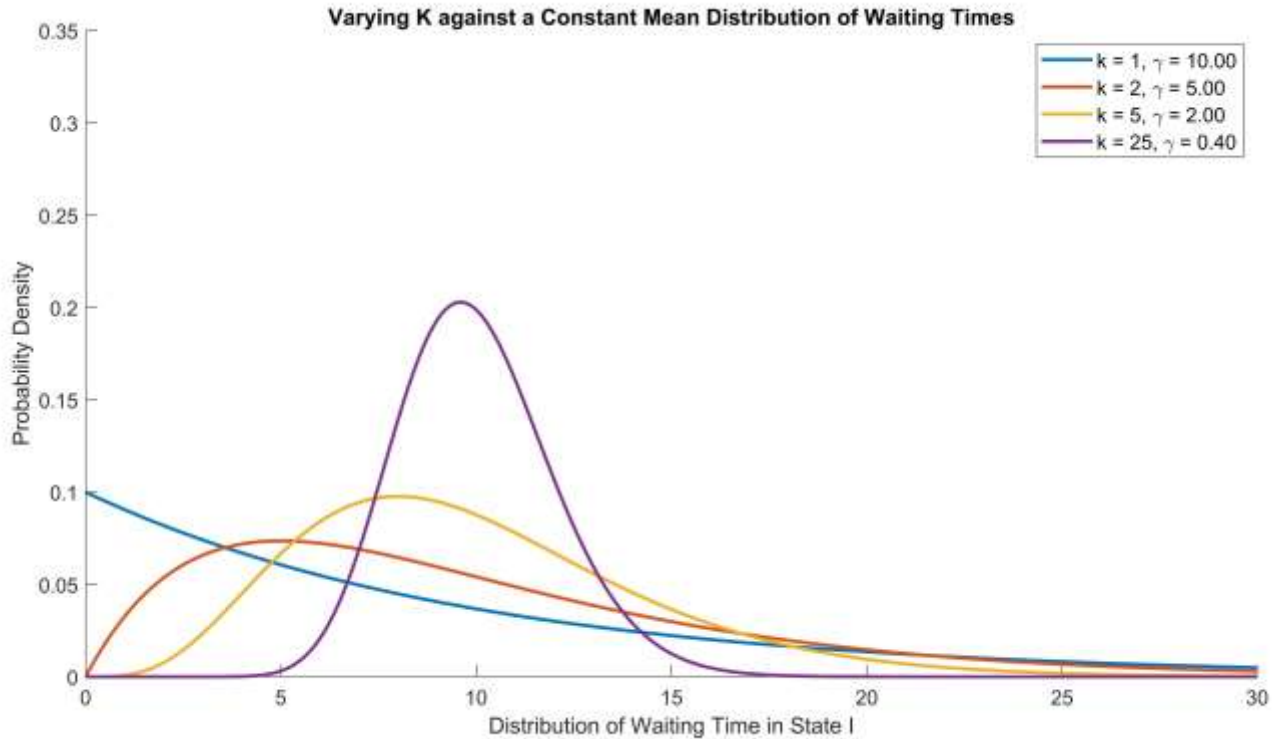


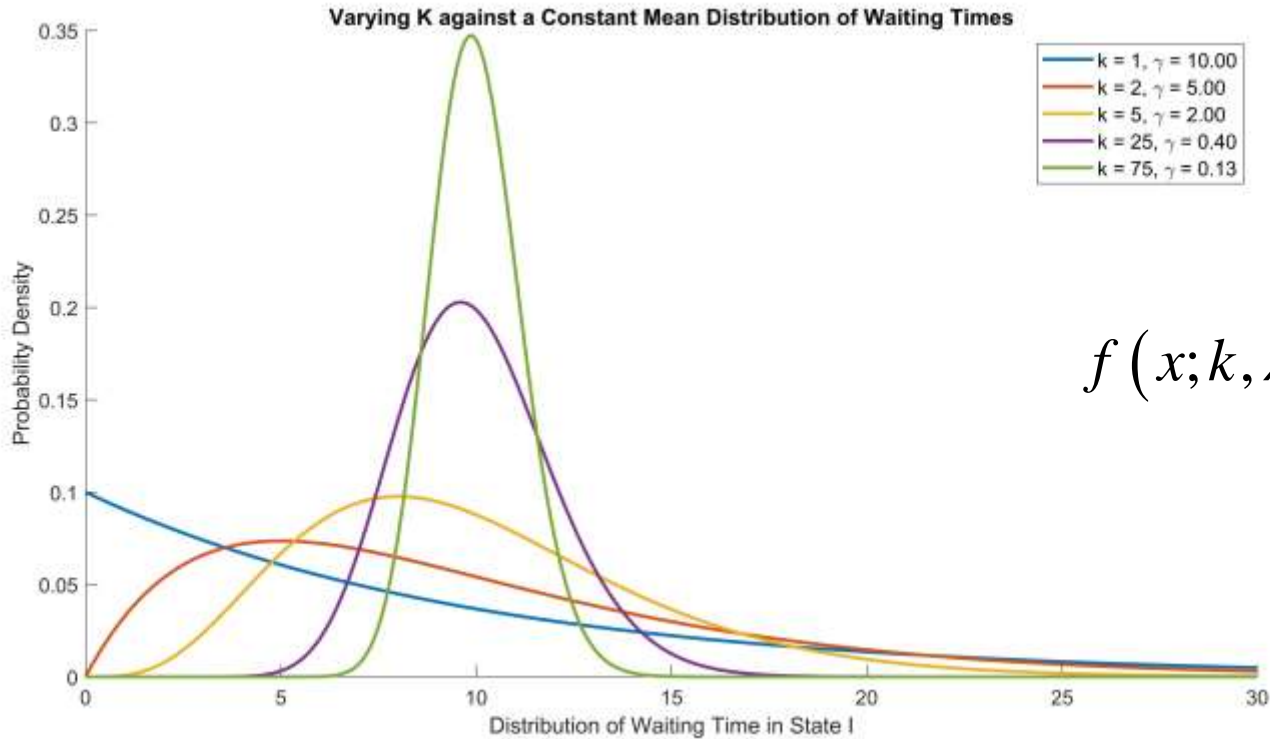
$$\mathbf{I}_1 \xrightarrow{2\gamma} \mathbf{I}_2 \xrightarrow{2\gamma} \mathbf{R}$$





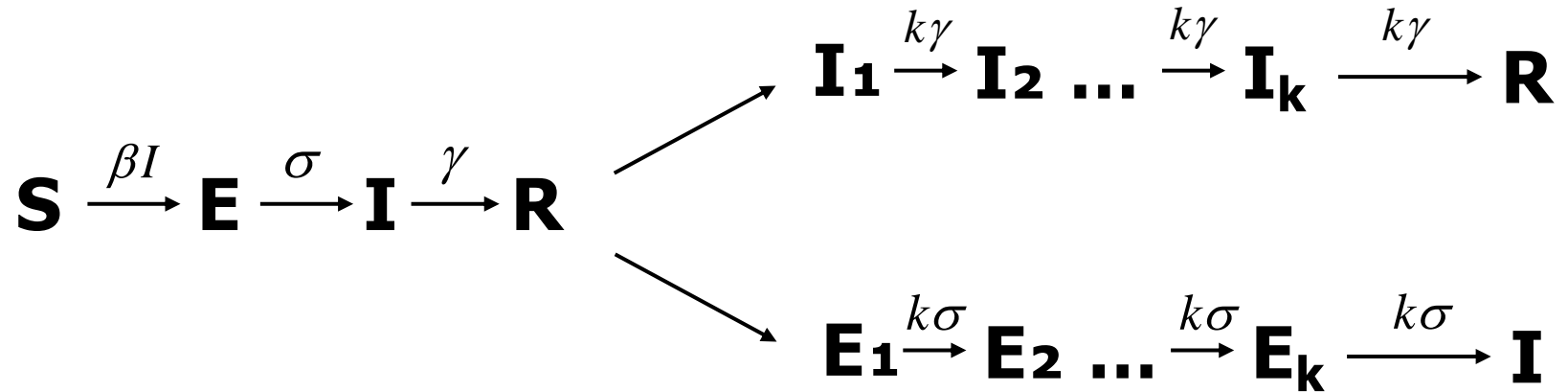
$$\mathbf{I_1} \xrightarrow{25\gamma} \mathbf{I_2} \xrightarrow{25\gamma} \dots \xrightarrow{25\gamma} \mathbf{I_{25}} \xrightarrow{25\gamma} \mathbf{R}$$





$$f(x; k, \lambda) = \frac{\lambda^k x^{k-1} e^{-\lambda x}}{(k-1)!}$$

Capturing Appropriate Time Delays (Erlang)

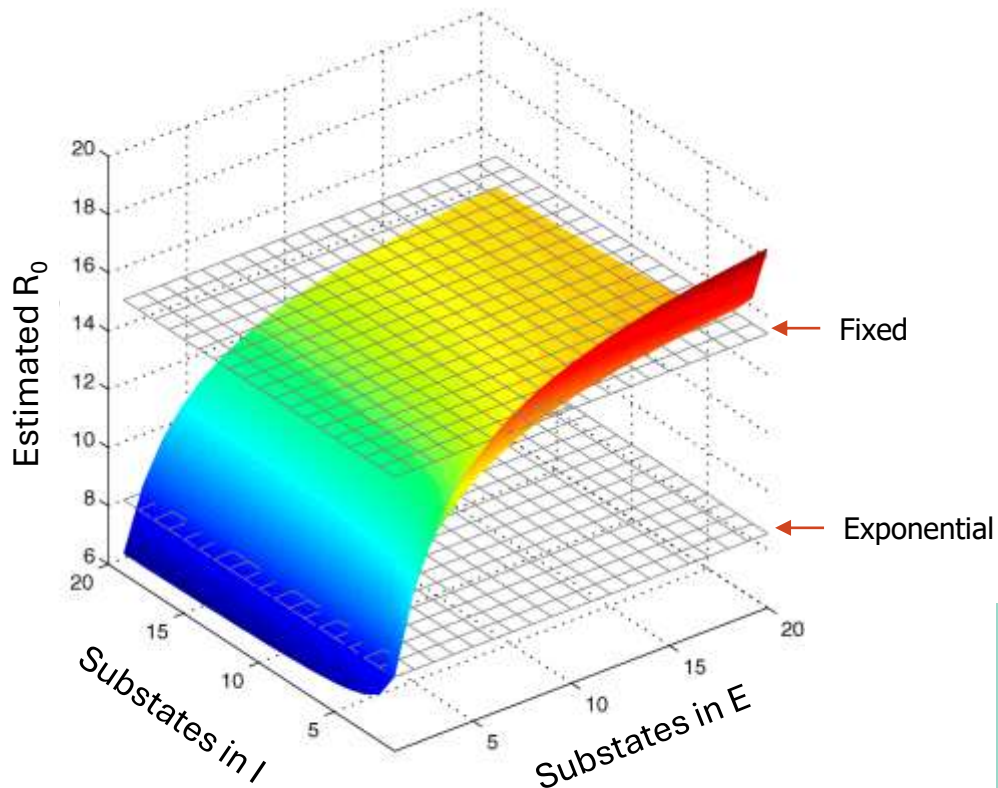




Do different waiting time distributions affect model outcomes?



Erlang vs Exponential

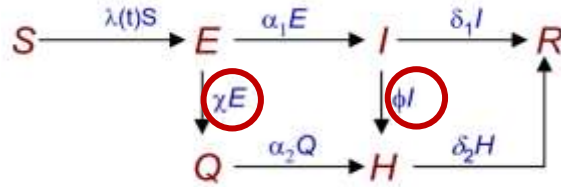


Disease	Latent Period $1/\sigma$ (Days)	m	Infectious Period $1/\gamma$ (Days)	n	Source
Measles	8	~20	5	~20	19
Foot-and-Mouth	3.5	13	4.3	17	39
SARS	5.36	2	5-6	3	34
Smallpox	14	40	8.6	4	48

Wearing, PLOS Medicine, 2005

Assuming exponentially distributed latent and infectious periods results in an underestimation of R_0

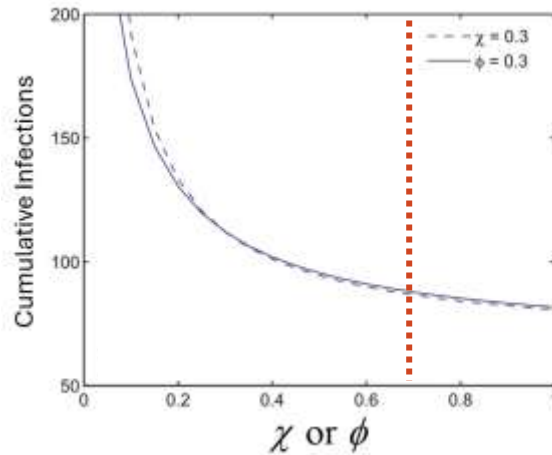
Erlang vs Exponential



χ Rate of being Quarantined
 ϕ Rate of being Isolated

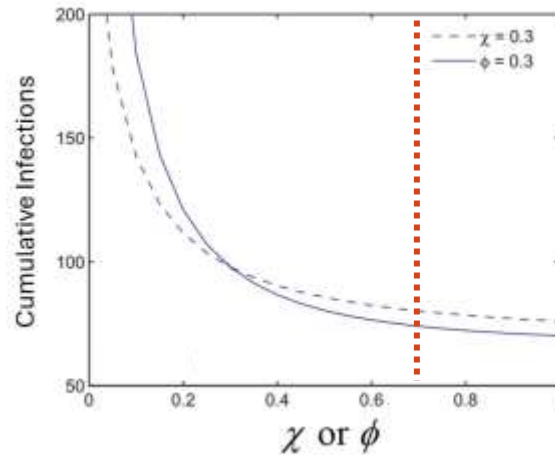
E and I exponentially distributed waiting times

$S \rightarrow E \rightarrow I \rightarrow R$



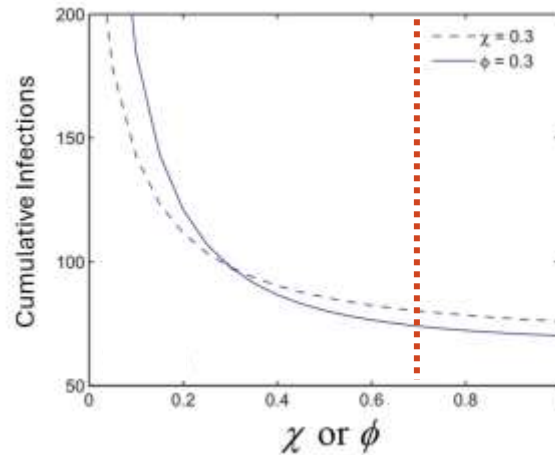
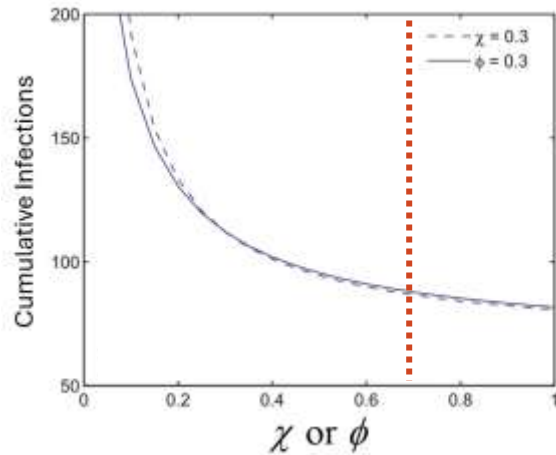
E and I both have 3 substates

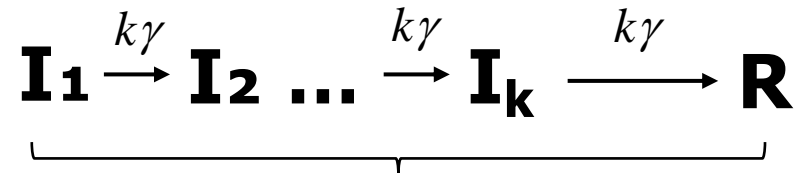
$S \rightarrow E_1 \rightarrow E_2 \rightarrow E_3 \rightarrow I_1 \rightarrow I_2 \rightarrow I_3 \rightarrow R$



Erlang vs Exponential

Assuming different distributions of latent and infectious periods result in conflicting assessments of interventions






How many substates do we choose?

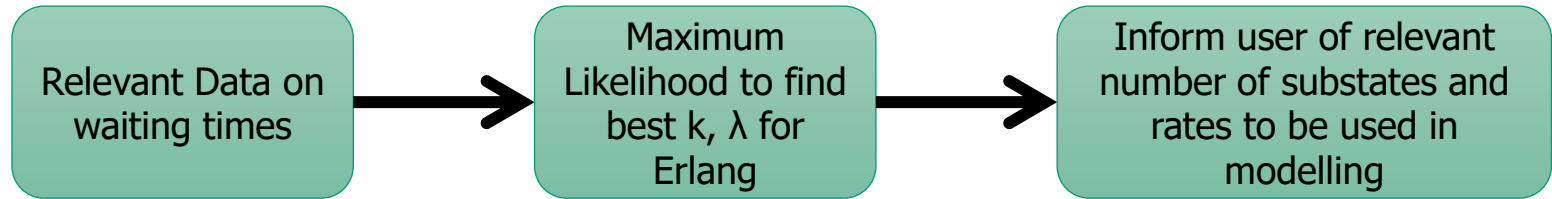


Goal:

Develop a tool to estimate the optimal number of substates
(parameters of an Erlang Distribution) from experimental data
on waiting times



Algorithm Flow



Application Case

Original Paper

*These authors contributed equally to this study.

Cite this article: Yang L, Dai J, Zhao J, Wang Y, Deng P, Wang J (2020). Estimation of incubation period and serial interval of COVID-19: analysis of 178 cases and 131 transmission chains in Hubei province, China. *Epidemiology and Infection* **148**, e117, 1–6. <https://doi.org/10.1017/S0950268820001338>

Received: 1 April 2020

Revised: 8 June 2020

Accepted: 16 June 2020

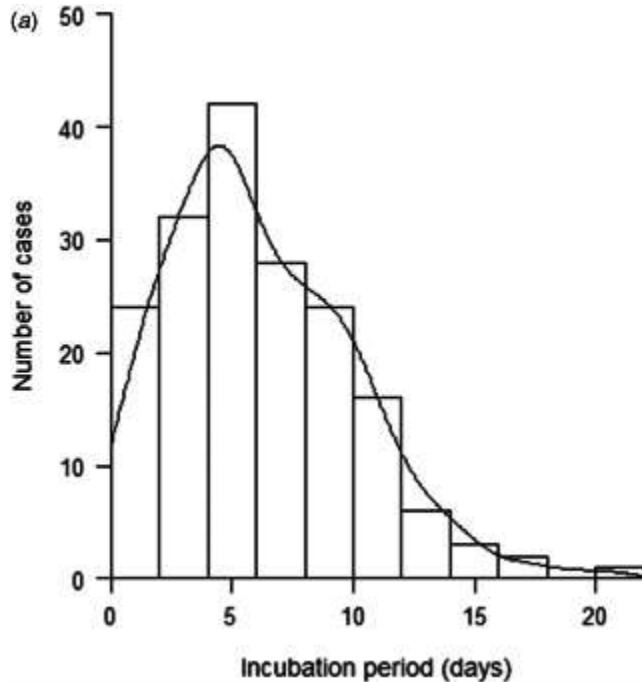
Estimation of incubation period and serial interval of COVID-19: analysis of 178 cases and 131 transmission chains in Hubei province, China

Lin Yang^{1,*}, Jingyi Dai^{2,*}, Jun Zhao¹, Yunfu Wang¹, Pingji Deng¹ and Jing Wang¹

¹School of Public Health and Management, Hubei University of Medicine, Shiyan, Hubei province, China and

²Department of Infectious Diseases, The Third People's Hospital of Kunming City, Kunming, Yunnan province, China

Incubation Period

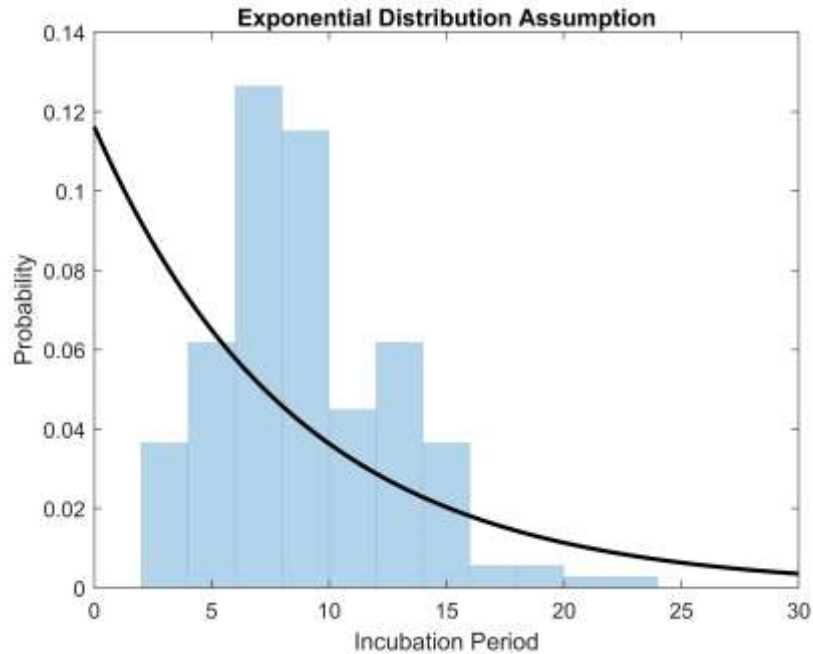


Yang, *Epidemiology and Infection*, 2020

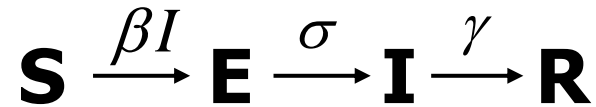
id	sex	age	age_group	symptoms	time_exposure_left	time_exposure_right	time_onset	time_confirm	period	source
1	Male	47	35-64	Yes	2020-01-13	2020-01-15	2020-01-16	2020-01-23	Jan 20 to Jan 31	Wuhan imported
6	Male	30	14-34	Yes	2020-01-11	2020-01-16	2020-01-15	2020-01-23	Jan 20 to Jan 31	Wuhan imported
7	Male	47	35-64	Yes	2020-01-10	2020-01-13	2020-01-17	2020-01-23	Jan 20 to Jan 31	Wuhan imported
8	Male	51	35-64	Yes	2020-01-08	2020-01-15	2020-01-13	2020-01-23	Jan 20 to Jan 31	Contact Wuhan cases
18	Female	52	35-64	Yes	2020-01-17	2020-01-18	2020-01-19	2020-01-24	Jan 20 to Jan 31	Wuhan imported
19	Male	25	14-34	Yes	2020-01-07	2020-01-11	2020-01-10	2020-01-24	Jan 20 to Jan 31	Wuhan imported
20	Female	56	35-64	Yes	2020-01-17	2020-01-20	2020-01-20	2020-01-24	Jan 20 to Jan 31	Wuhan imported
21	Female	70	>64	Yes	2020-01-13	2020-01-15	2020-01-25	2020-01-24	Jan 20 to Jan 31	Contact Wuhan cases
22	Female	27	14-34	Yes	2020-01-13	2020-01-18	2020-01-22	2020-01-24	Jan 20 to Jan 31	Locally infected
33	Male	49	35-64	Yes	2020-01-15	2020-01-18	2020-01-21	2020-01-25	Jan 20 to Jan 31	Wuhan imported
34	Female	43	35-64	Yes	2020-01-12	2020-01-19	2020-01-18	2020-01-25	Jan 20 to Jan 31	Contact Wuhan cases
35	Male	43	35-64	Yes	2020-01-14	2020-01-18	2020-01-17	2020-01-25	Jan 20 to Jan 31	Contact Wuhan cases
38	Male	47	35-64	Yes	2020-01-14	2020-01-18	2020-01-19	2020-01-25	Jan 20 to Jan 31	Contact Wuhan cases
50	Female	50	35-64	Yes	2020-01-16	2020-01-19	2020-01-23	2020-01-26	Jan 20 to Jan 31	Wuhan imported
51	Male	38	35-64	Yes	2020-01-10	2020-01-11	2020-01-11	2020-01-26	Jan 20 to Jan 31	Wuhan imported

Yang, *Epidemiology and Infection*, 2020

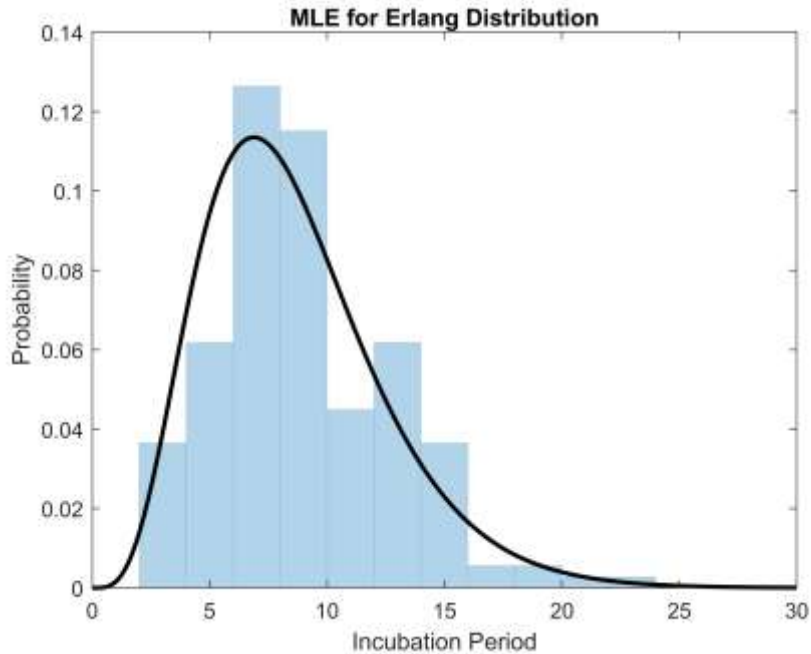
Application Case 1 – Assumption of Exponential Waiting Time



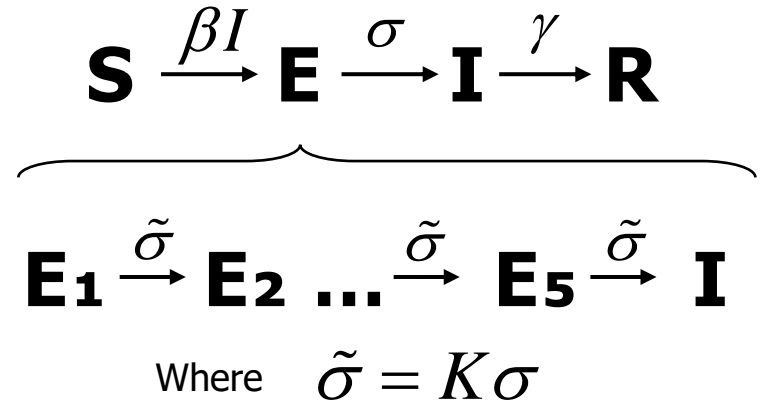
$$\sigma = 1 / \text{Mean}(\text{data})$$



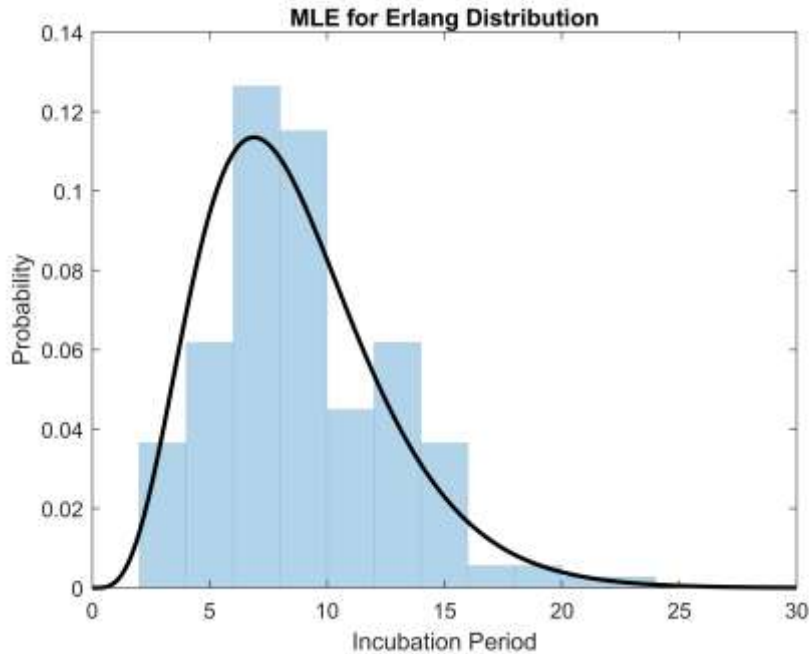
Application Case 1 – Assumption of Erlang Waiting Time



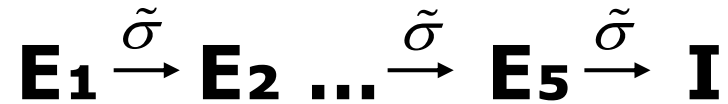
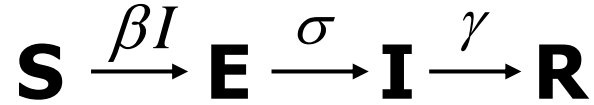
$$K = 5, \quad \tilde{\sigma} = 0.581$$



Application Case 1



$$K = 5, \quad \tilde{\sigma} = 0.581$$



$$\frac{dS}{dt} = -\beta IS$$

$$\frac{dE_1}{dt} = \beta IS - \tilde{\sigma} E_1$$

$$\frac{dE_2}{dt} = \tilde{\sigma} E_1 - \tilde{\sigma} E_2$$

$$\frac{dE_3}{dt} = \tilde{\sigma} E_2 - \tilde{\sigma} E_3$$

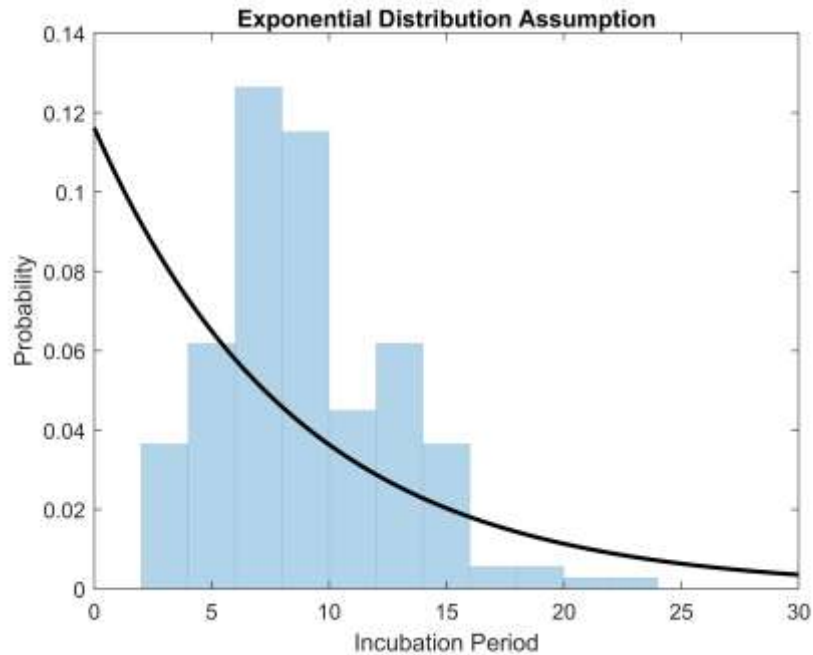
$$\frac{dE_4}{dt} = \tilde{\sigma} E_3 - \tilde{\sigma} E_4$$

$$\frac{dE_5}{dt} = \tilde{\sigma} E_4 - \tilde{\sigma} E_5$$

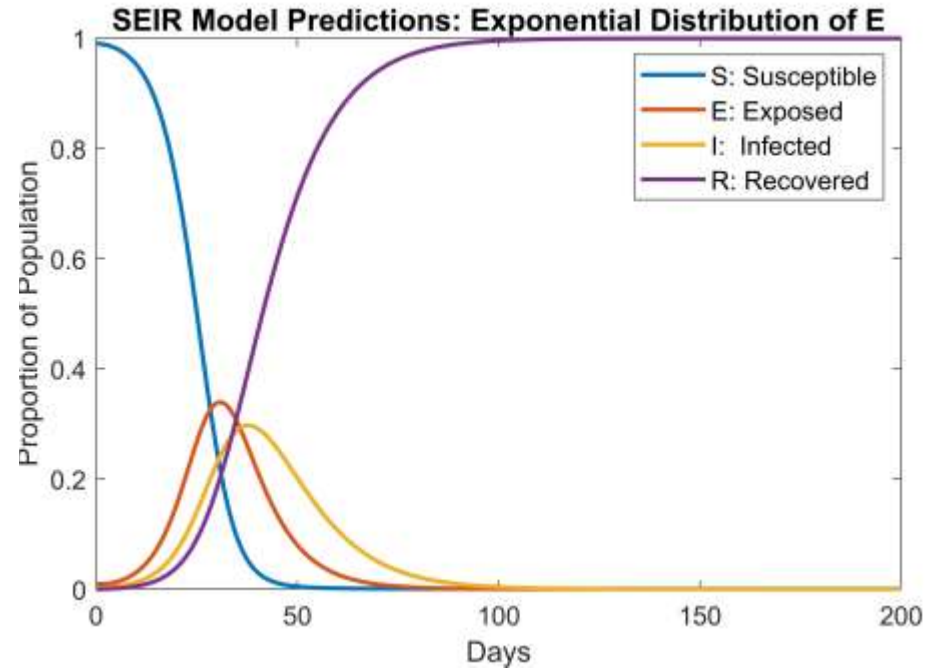
$$\frac{dI}{dt} = \tilde{\sigma} E_5 - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

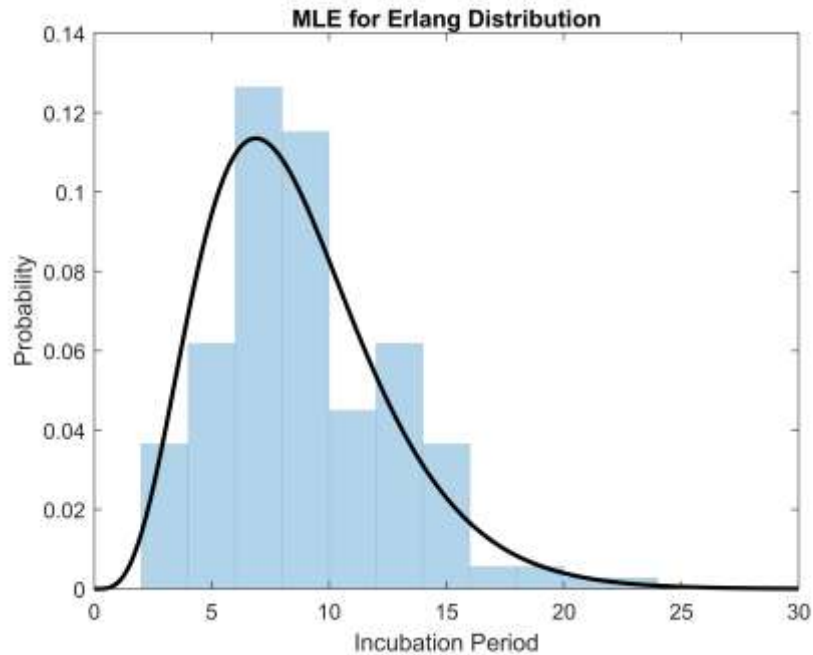
Application Case 1



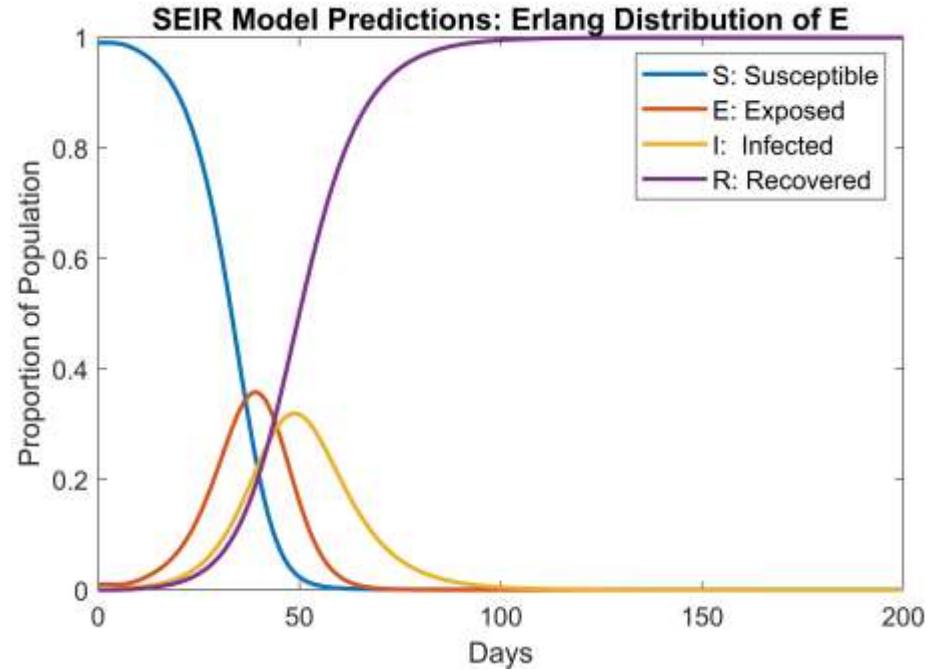
$$\sigma = 1 / \text{Mean}(\text{data})$$



Application Case Simulation



$$K = 5, \sigma = 0.581$$



Applications in other fields

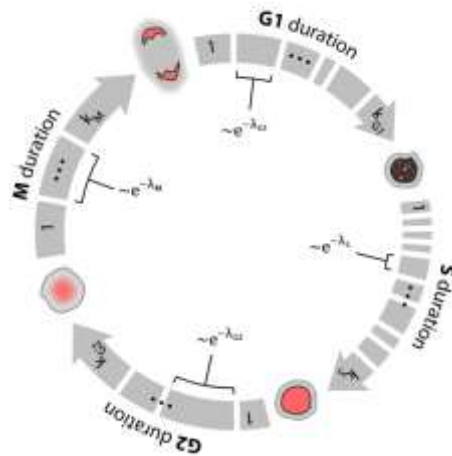
Article



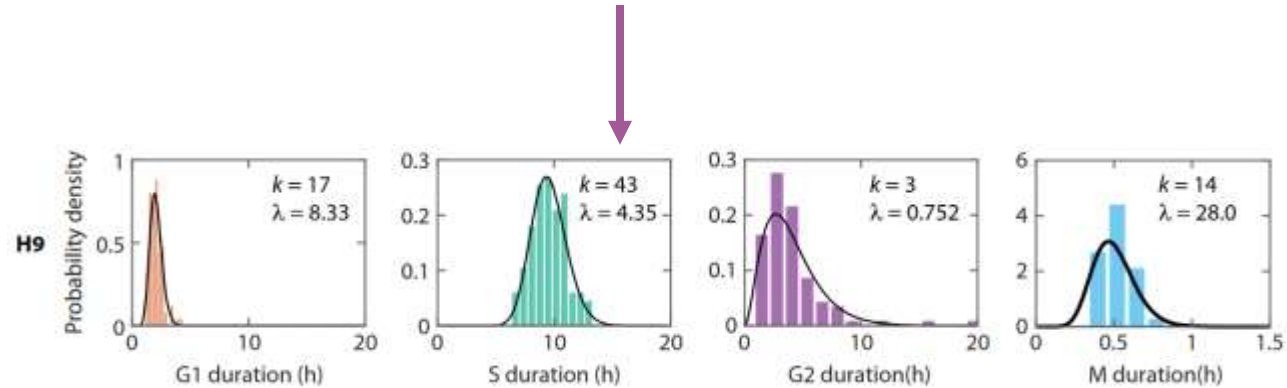
molecular
systems
biology

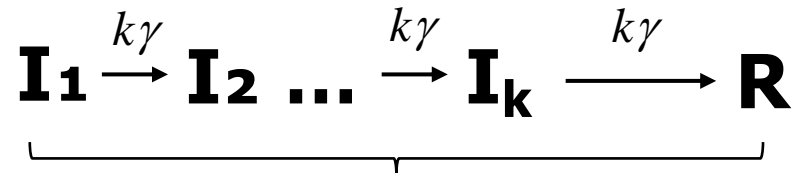
Evidence that the human cell cycle is a series of uncoupled, memoryless phases

Hui Xiao Chao^{1,2}, Randy I Fakhreddin¹, Hristo K Shimerov¹, Katarzyna M Kedziora¹, Rashmi J Kumar^{1,3}, Joanna Perez⁴, Juanita C Limas⁵, Gavin D Grant^{4,6}, Jeanette Gowen Cook^{4,6}, Gaorav P Gupta^{6,7} & Jeremy E Purvis^{1,2,3,6,*}



Chao, Mol. Syst. Biol, 2019

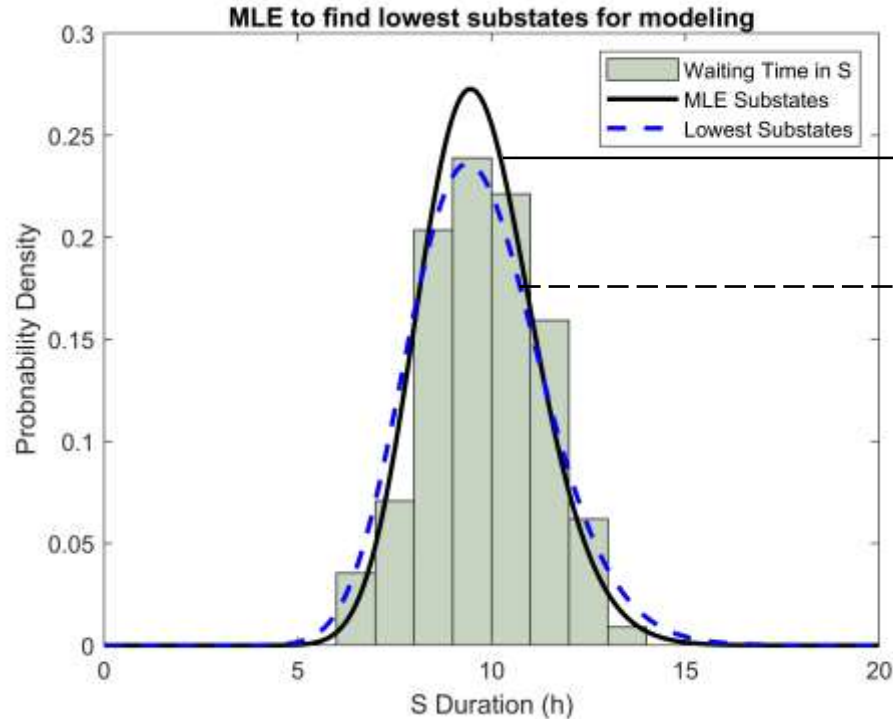




How many substates do we choose?

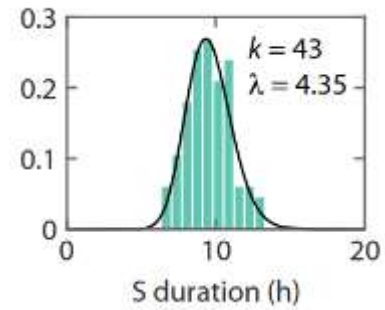
What is the lowest number of substates we could choose?

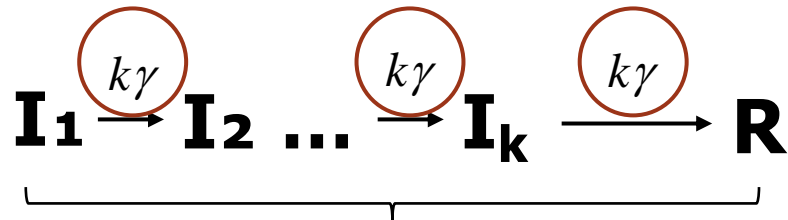
Choosing Smallest K



43 Substates

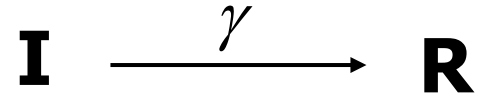
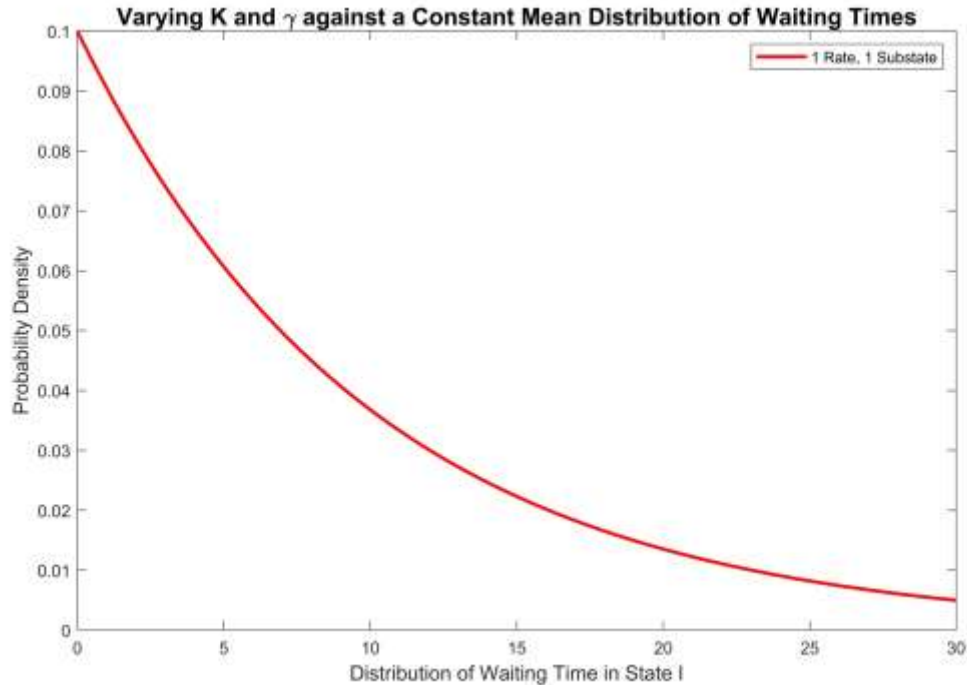
32 Substates



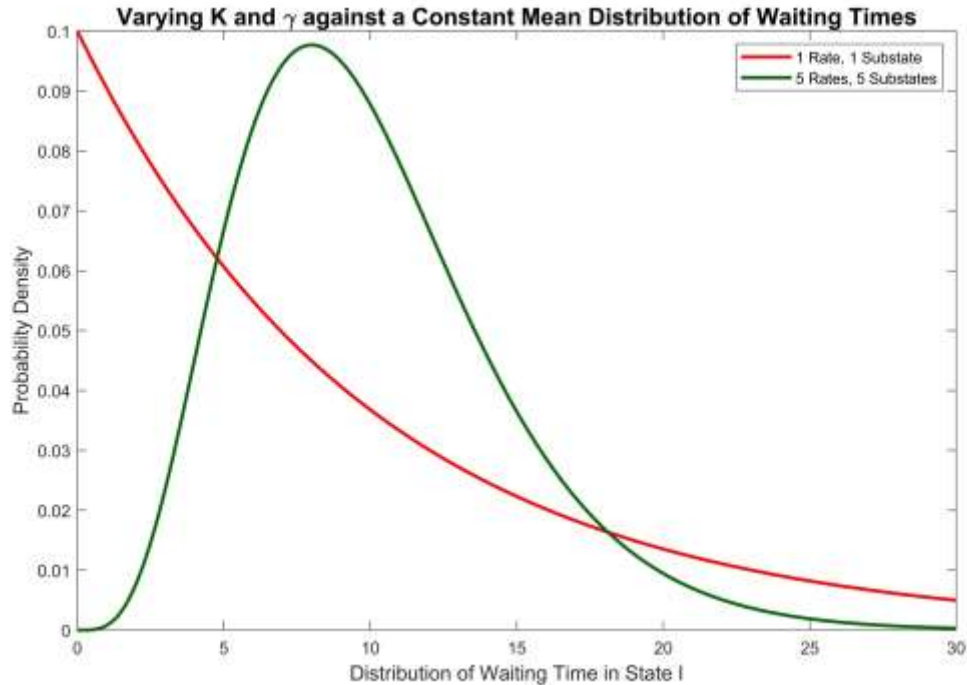


Do rates need to be constant?

Future Work: Extension to Generalized Erlang

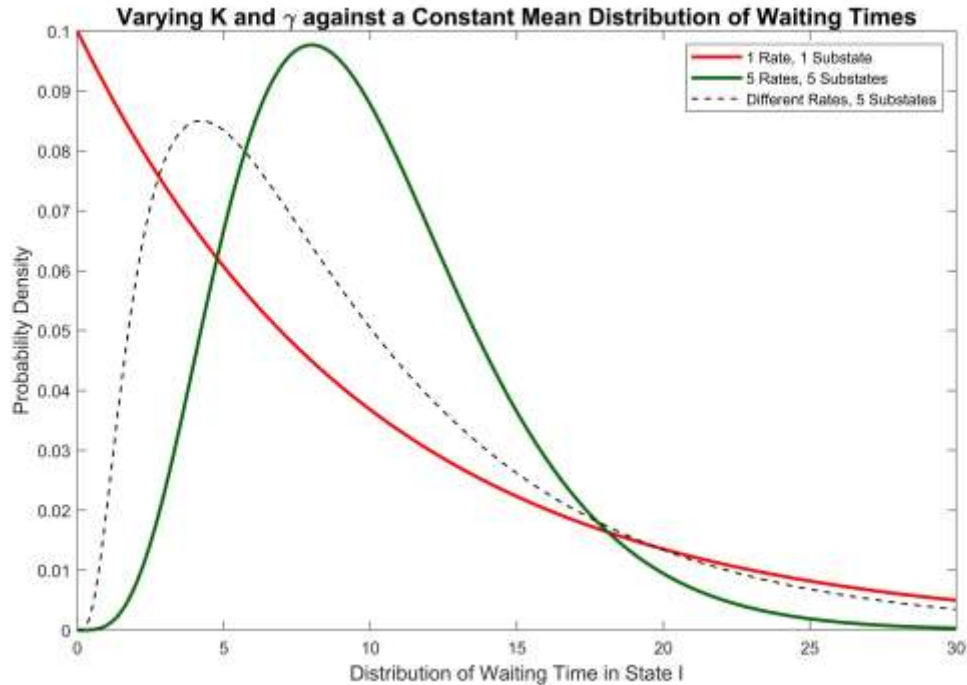


Future Work: Extension to Generalized Erlang



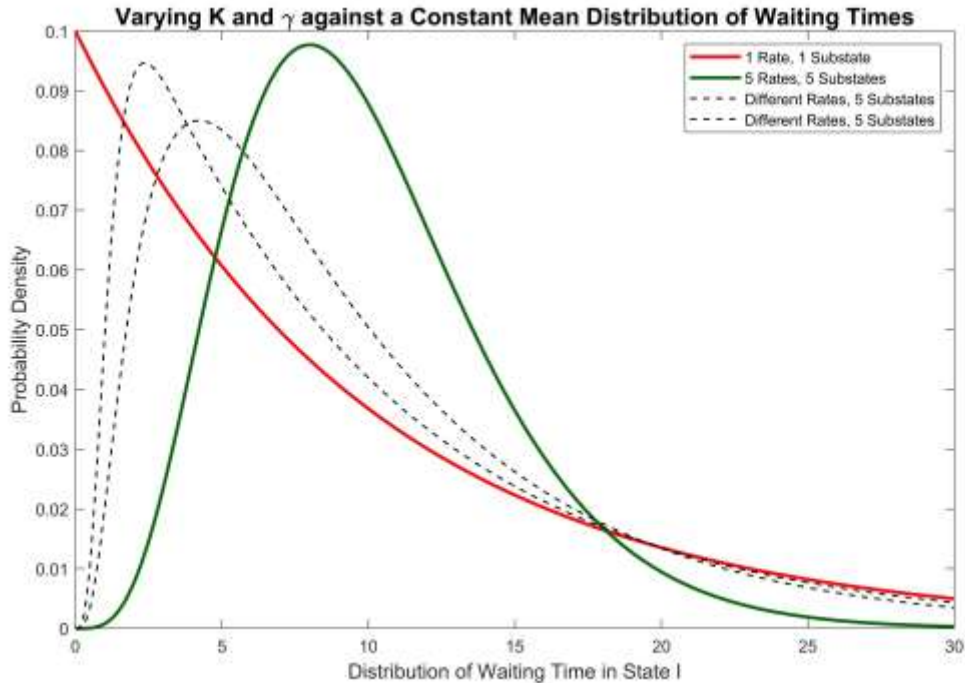
$$\mathbf{I}_1 \xrightarrow{k\gamma} \mathbf{I}_2 \dots \xrightarrow{k\gamma} \mathbf{I}_k \xrightarrow{k\gamma} \mathbf{R}$$

Future Work: Extension to Generalized Erlang



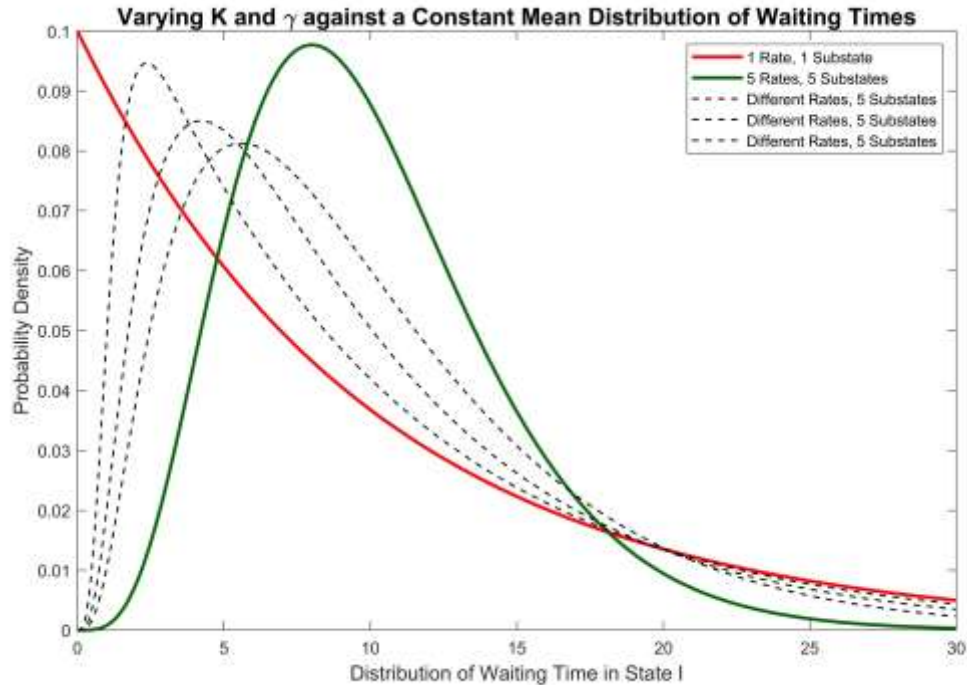
$$\mathbf{I}_1 \xrightarrow{\gamma_1} \mathbf{I}_2 \dots \xrightarrow{\gamma_2} \mathbf{I}_k \xrightarrow{\gamma_K} \mathbf{R}$$

Future Work: Extension to Generalized Erlang



$$\mathbf{I}_1 \xrightarrow{\tilde{\gamma}_1} \mathbf{I}_2 \dots \xrightarrow{\tilde{\gamma}_2} \mathbf{I}_k \xrightarrow{\tilde{\gamma}_K} \mathbf{R}$$

Future Work: Extension to Generalized Erlang



$$\mathbf{I}_1 \xrightarrow{\check{\gamma}_1} \mathbf{I}_2 \dots \xrightarrow{\check{\gamma}_2} \mathbf{I}_k \xrightarrow{\check{\gamma}_K} \mathbf{R}$$

Future Work in progress

- Model simplification by choosing the lowest K that remains statistically significant
- Extension of Generalized Erlang to Exponential * Erlang & Erlang * Erlang
- Sensitivity of model to noise and data size
- Exploring Key outputs from SEIR models and how sensitive these outputs are to such model assumptions.

Current Work in the field

Bioinformatics, 2020, 2020, 1048–1054
doi: 10.1093/bioinformatics/btaz538
Advance Access Publication Date: 14 November 2019
Original Paper



Systems biology

Estimating chain length for time delays in dynamical systems using profile likelihood

Adrian L. Hauber ^{1,*}, Raphael Engesser^{1,2}, Joep Vanlier¹ and Jens Timmer^{1,2}

- Requires some manual iteration to get optimal number of substates
- Only fits Erlang Distributions (Same rates between substates)
- Matlab Package Implementation

Our Work

- Automatically provides optimal number of states and rates
- Extension to Generalized Erlang Distributions
- Working towards Python and R integration

Acknowledgements

- Alison Hill
- Anjalika Nande
- Sara Loo
- Madeline Gastonguay
- Thayer Anderson



Thank you!

References

- Images Reference:
- [1]: Hurtado, P. J., & Kiro Singh, A. S. (2019). Generalizations of the 'Linear Chain Trick': Incorporating more flexible dwell time distributions into mean field ODE models. *Journal of Mathematical Biology*, 79(5), 1831–1883. <https://doi.org/10.1007/s00285-019-01412-w>
- [2] Wearing, H. J., Rohani, P., & Keeling, M. J. (2005). Appropriate Models for the Management of Infectious Diseases. *PLOS Medicine*, 2(7), e174. <https://doi.org/10.1371/journal.pmed.0020174>
- [3]: Feng, Z., Xu, D., & Zhao, H. (2007). Epidemiological Models with Non-Exponentially Distributed Disease Stages and Applications to Disease Control. *Bulletin of Mathematical Biology*, 69(5), 1511–1536. <https://doi.org/10.1007/s11538-006-9174-9>
- [4]: Yang, L., Dai, J., Zhao, J., Wang, Y., Deng, P., & Wang, J. (2020). Estimation of incubation period and serial interval of COVID-19: Analysis of 178 cases and 131 transmission chains in Hubei province, China. *Epidemiology & Infection*, 148, e117. <https://doi.org/10.1017/S0950268820001338>
- [5]: Chao, H. X., Fakhreddin, R. I., Shimerov, H. K., Kedziora, K. M., Kumar, R. J., Perez, J., Limas, J. C., Grant, G. D., Cook, J. G., Gupta, G. P., & Purvis, J. E. (2019). Evidence that the human cell cycle is a series of uncoupled, memoryless phases. *Molecular Systems Biology*, 15(3), e8604. <https://doi.org/10.15252/msb.20188604>



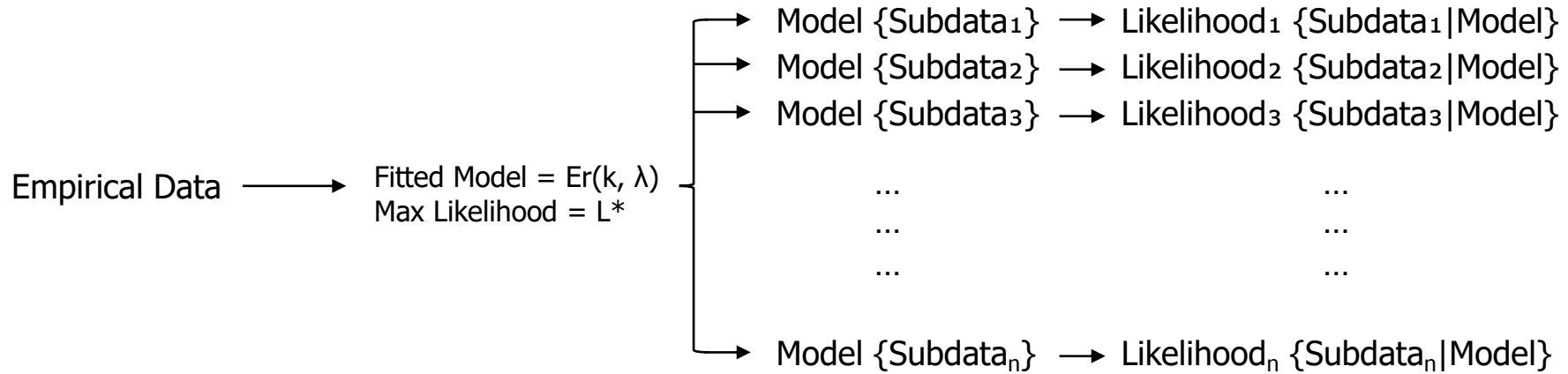
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Reference Slides

Algorithm Flow – Quick note on Benchmarking



$L^* = \text{Likelihood}\{\text{Empirical Data} \mid \text{Model}\}$

Algorithm Flow – Quick note on Benchmarking

Likelihood₁ {Subdata₁ | Model}

Likelihood₂ {Subdata₂ | Model}

Likelihood₃ {Subdata₃ | Model}

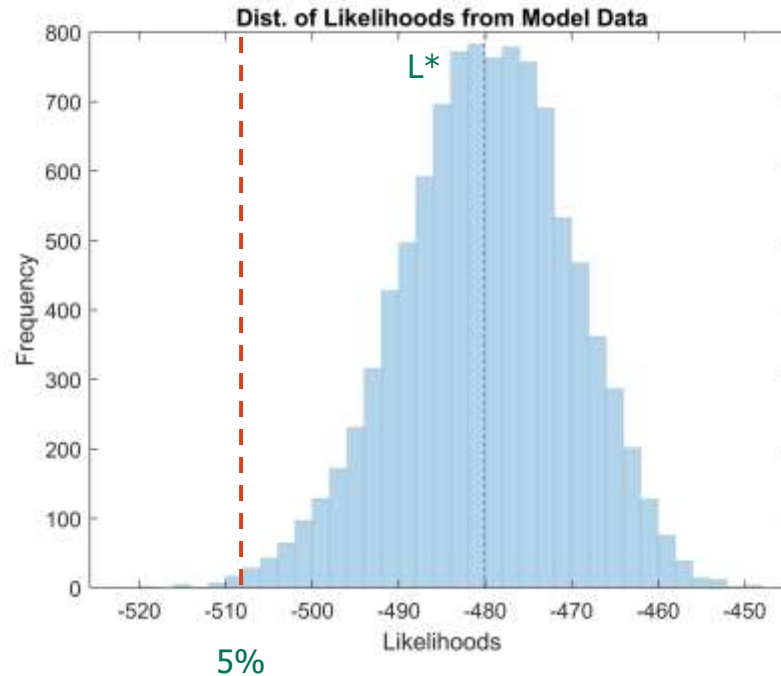
...

...

...

Likelihood_n {Subdata_n | Model}

$L^* = \text{Likelihood}\{\text{Empirical Data} \mid \text{Model}\}$





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