On the characterization of censored survival curves in system dynamics models

Radboud J. Duintjer Tebbens and Kimberly M. Thompson
Kid Risk, Inc., 10524 Moss Park Rd., Ste. 204-364, Orlando, FL 32832, www.kidrisk.org

Abstract

System dynamics (SD) models typically use one or more sequential exponential processes to characterize survival or other expiry processes. These processes imply gamma distributions of the time until death, including the special case of exponential distributions for single-stage processes. For many applications, this provides an adequate representation of the survival process. However, in the context of characterizing risks associated with rare events, the shape of the distribution, and in particular the tail, may carry important implications. We explore a number of different ways to characterize survival in an SD framework to fit a set of censored survival data for a medical condition that may lead to low probability-high consequence events of re-introduction of poliovirus after global polio eradication. We find that most survival characterizations reasonably match the limited data, but the choice of characterization can lead to significantly different behavior in the tail of the survival curve, which could result in widely different implications for risk management.

Introduction

Deterministic, differential-equation based system dynamics (SD) models typically characterize outflow from stocks using fractional rates that represent the proportion that exits the stock per time unit.(Sterman 2001) Characterizing expiry from a single stock using constant fractional rates results in an exponentially-distributed residence time in the stock and leads to appropriate and adequate representation of the survival process in some applications.(Sterman 2001) Division of the expiry process into multiple, sequential stages with the same fractional expiry rate results in gamma-distributed residence times, which provides a more realistic representation for other processes.(Lloyd 2001, Sterman 2001) Chained processes, such as an aging chain, allow further flexibility by characterizing appropriate fractional expiry rates at different stages of the process.(Sterman 2001) In deterministic SD models, regardless of the choice of expiry process, the number remaining in any stage of the process represents a fractional number at any time, which implies an infinite tail of the residence time. Stochastic formulations of SD models circumvent this limitation by allowing only for discrete units in each stock (e.g., people, widgets, vaccine doses) and they can achieve a value of 0 units, but attain the same distributions of residence times if they utilize rate-based transition probabilities. The method of "continuous cohorting" (Eberlein, Thompson et al. 2012) breaks downs the expiry process into one stage for each time step and can characterize any desired survival function and truncate the residence time at some pre-determined maximum.

Statistical survival analysis for medical conditions typically relies either on competing risk survival analysis or uses excess hazard rates.(Sandin 2008) Competing risk survival analysis requires teasing out the cause of death of patients as either related to the medical condition or unrelated through analysis of death certificates. Estimating of the excess hazard rates occurs by comparing survival rates of patients with the medical condition with the background survival rates of the general population. Both of these methods results in survival rates specific to the medical condition that SD models can take into account, assuming that the data exist to support the analysis.

In the context of some risk analysis applications of SD models, consideration of the expiry process deserves particular attention if the tail of the distribution generates low probability events with high consequences. For example, decay of radioactive material may involve a very long tail and the probability that high enough amounts of material remains beyond the expected duration of effective containment measures may drive the long-term risk of catastrophic events. In dynamic epidemiologic modeling, the existence of "super spreaders" with much longer than average infectious periods drives the pattern of outbreaks and persistence of certain infectious diseases.(Lloyd-Smith, Schreiber et al. 2005) We explore different characterizations of survival for a rare medical condition that may potentially lead to major global public health implications by re-introducing eradicated poliovirus.(Duintjer Tebbens, Pallansch et al. 2006) We focus on deterministic SD characterizations while noting that stochastic formulations of the same processes imply similar distributional behavior. We consider how well each characterization reproduces a censored survival data set for this medical condition, and report the tail behavior that drives the risk. Finally, we discuss pros and cons of each approach and possible areas of future research.

Problem description

The Global Polio Eradication Initiative (GPEI) represents one of the largest global public health ever undertaken. With the apparent global eradication of 2 of the 3 wild poliovirus (WPV) serotypes (World Health Organization 2001, Kew, Cochi et al. 2014) and indigenous transmission of the last remaining WPV serotype confined to 2 countries,(World Health Organization 2015) the GPEI increasingly focuses on transitioning to a polio-free world.(World Health Organization 2013) Oral poliovirus vaccine (OPV) represents the current vaccine of choice for most GPEI activities. Inexpensive and easy-to-administer OPV successfully interrupted WPV in the most challenging environments, but it contains attenuated (weakened) live polioviruses that cause vaccine-associated paralytic poliomyelitis (VAPP) disease in a small fraction of recipients and their close contacts.(Platt, Estivariz et al. 2014) In populations with very low immunity, the OPV viruses can continue to spread and evolve to cause paralytic outbreaks of circulating vaccine-derived polioviruses (cVDPVs) that behave like WPVs.(Kew, Morris-Glasgow et al. 2002, Duintjer Tebbens, Pallansch et al. 2013, Burns, Diop et al. 2014) Because of these risks, the GPEI plans to globally coordinate the cessation of OPV,(World Health Organization 2013) which requires high enough population immunity everywhere to avoid cVDPV outbreaks after OPV cessation.(Thompson and Duintjer Tebbens 2014) Because of the typical infectious period of approximately one month for most individuals, dynamic poliovirus transmission and OPV evolution modeling suggests any cVDPVs would emerge within approximately one year of OPV cessation.(Thompson and Duintjer Tebbens 2014) Thus, if the GPEI successfully manages OPV cessation to prevent or contain cVDPV outbreaks, the risks of cVDPVs and VAPP will disappear within a few years of OPV cessation, and only long-term poliovirus re-introduction risks will remain. These include intentional or unintentional release of poliovirus from laboratories or poliovirus vaccine manufacturing sites and introductions of immunodeficiency-associated vaccine-derived poliovirus (iVDPV) from a small number of individuals with primary B-cell immunodeficiencies.(Duintjer Tebbens, Pallansch et al. 2006) Given that population immunity will decline after OPV cessation,(Duintjer Tebbens and Thompson 2014) any poliovirus re-introduction long after OPV cessation could potentially spread rapidly, resulting in a major global health emergency and presenting a serious challenge to contain.

While immunocompetent individuals excrete poliovirus for less than 3 months,(Alexander, Gary et al. 1997) as of late 2014 the GPEI identified 73 immunodeficient patients who excreted for at least 6 months.(Burns, Diop et al. 2014) The iVDPV viruses excreted appear to possess similar properties as WPV and cVDPVs and thus could spread and cause paralytic poliomyelitis disease if introduced after OPV cessation.(Burns, Diop et al. 2014) To date no known outbreaks of paralytic poliomyelitis occurred as a result of virus introductions from these patients into the general population, which could reflect population immunity in the communities surrounding these patients rather than absence of iVDPV introductions or limited transmissibility of these viruses. The GPEI defines prolonged excretors as immunodeficient patients who excreted at least 6 months and chronic excretors as immunodeficient patients who excreted for at least 5 years.(Burns, Diop et al. 2014). Only 5 of the 73 known prolonged and chronic excretors exhibited chronic excretion, all diagnosed with one category of primary immunodeficiency disease, i.e., common-variable immunodeficiency disease (CVID). While at least one of the five chronic excretors spontaneously stopped excreting,(Bellmunt, May et al. 1999) others continued

to excrete until they died (in some cases by contracting paralytic poliomyelitis), and one began excreting in approximately 1978 and continues to date without contracting paralytic poliomyelitis.(MacLennan, Dunn et al. 2004) Given the potentially serious consequences of poliovirus re-introductions long after OPV cessation, the global prevalence of CVID patients with chronic poliovirus excretion represents an important risk for reintroduction.(Duintjer Tebbens, Pallansch et al. 2015) Polio antiviral compounds may offer the possibility to clear chronic infections, but require significant investments to develop.(McKinlay, Collett et al. 2014) Moreover, using polio antiviral drugs requires identification of prolonged and chronic excretors, which remains costly, because the majority excrete asymptomatically for many years.(Duintjer Tebbens, Pallansch et al. 2015) In the context of modeling the prevalence of prolonged and chronic excretors,(Duintjer Tebbens, Pallansch et al. 2015) the survival of CVID patients in different settings emerged as a major uncertainty that warrants modeling attention given the important risk management implications.

CVID represents the most prevalent of the many types of primary immunodeficiency diseases accounting for approximately 20%.(Gathmann, Grimbacher et al. 2009) CVID is a progressive disease that typically does not result in any symptoms until the second decade of life, with an average age of onset of approximately 25 years.(Chapel, Lucas et al. 2008) Due to their compromised immune systems, CVID patient tend to incur recurrent bacterial and viral infections, but intravenous immunoglobulin (IVIG) therapy can prevent infections and extend life. While the GPEI identified some known CVID excretors, it appears that only a small fraction of all CVID patients fails to normally clear OPV infection, because poliovirus screening studies among CVID patients very rarely detect prolonged excretors and to date never detected any chronic excretors.(Li, Ivanova et al. 2014) Estimating the survival of CVID patients in different settings remains challenging due to the need for long-term follow-up, highly variable ages of CVID onset, changing treatment options over time, and differences in hygienic conditions between countries and over time. However, some data exist to estimate survival. (Chapel, Lucas et al. 2008, Joshi, Iyer et al. 2009, Mohammadinejad, Aghamohammadi et al. 2012) Figure 1 shows the 2008 data from the most comprehensive longitudinal study,(Chapel, Lucas et al. 2008) which clearly shows decreased survival of CVID patients compared to the general population in developed countries and a trend toward improved CVID survival over time most likely reflecting improvements in treatment. Due to the finite duration of follow-up, the data remain right-censored, but some unknown maximum survival exists for CVID patients such that they cannot exceed the maximum life time for humans. The authors report that the age of onset inversely correlated with survival, but constructing statistically meaningful survival curves by age of onset would require following a larger cohort of patients than the 389 individuals included in the 2008 study survival curve.(Chapel, Lucas et al. 2008) For purposes of demonstration, we set aside these limitations and focus our analysis on the data,(Chapel, Lucas et al. 2008) although the insights from this work extend to other data sets, time periods, and countries. We also do not consider all of the other complexities associated with estimating incidence of different primary immunodeficiency diseases, delays in disease onset and diagnosis, exposure to different poliovirus serotypes, treatment with IVIG and polio antivirals, and the probability of prolonged or chronic infection by primary immunodeficiency disease.(Duintjer Tebbens, Pallansch et al. 2015)

Characterizations of survival

We consider a number of different survival characterizations, as illustrated in Figure 2 (omitting the arrows from stocks to their outflows for visual simplicity). In each characterization, CVID patients enter the CVID survival process as they develop symptoms (i.e., disease onset), and exit the process through death that may occur at different stages of CVID progression. For simplicity, the models ignore the role of the diagnostic delay with respect to CVID survival and assume that onset of CVID coincides with the time of diagnosis.(Chapel, Lucas et al. 2008) To explore the survival distribution associated with each characterization, we model a pulse of height 1 at time 0 and follow the surviving fraction of CVID patients over a period of 200 years. We use Euler integration and fix the integration step to a small value of 1/128 years to eliminate the possibility of consequential errors related to the step size. For each characterization we estimate death rates that give the best possible fit to the survival data.(Chapel, Lucas et al. 2008)

Characterization A

Characterization A (Figure 2A) reflects the standard first-order expiry process with exponentially-distributed residence times used in many SD models in which the shape of the distribution is either truly exponential or not of major importance.(Lloyd 2001, Sterman 2001) For this characterization, we calculated the average death rate from the survival data set as:

Average death rate = $-\text{Ln}(S_T)/T$,

where S_T= proportion surviving at the last survival data point (=0.58)
T = year corresponding to the last data point (=45 years)

Characterization B

Characterization B (Figure 2B) divides the survival process into n equally-wide stages with transition rates equal to the average death rate multiplied by n. To ensure maximum correspondence with the survival data set, we do not simply use the same average death rate as in Characterization A. While this would represent a reasonable standard approach when fitting to an estimated average death rate or life expectancy, the data represent a survival curve and not an average, and we found that using the same average death rates as in Characterization A results in a large distance between the model and survival curve. Instead, we fit the average rate for a survival process of n stages directly to the data by numerically solving the average death rate for each stage from the cumulative gamma distribution implied by the multi-stage process (i.e., using built-in Gamma functions and the goal seek function in MS Excel):

$G(T,n,n/ad(n))=1-S_T$

where ad(n) = average death rate for each stage in the n-stage survival process
G(x,alpha,beta) = Gamma distribution function with parameters alpha (corresponding to number of stages n) and beta (corresponding to 1 divided by the average death rate for each stage)

We initially set out to focus on the optimal number of stages in terms of the sum of squared errors (SSE) between the data and the model, but found that n=1 gave the best fit (i.e., equivalent to Characterization A). We explored potential improvements of the tail behavior despite the increased SSE by computing the results for 2, 3, or 4 stages of survival.

Characterization C

Characterization C (Figure 2C) represents an aging chain.(Sterman 2001) Conceptually, the aging chain allows us to break the survival process into any desired number of stages and use appropriate death rates as a function of time since disease onset, consistent with the reported survival data. We consider two variations of the aging chain. Characterization C1 breaks the survival process into stages corresponding to the time when the survival proportions change in the reported data in Figure 1 (i.e., 0-2, 3-5, 6-8, 9-11, 12-14, 15-17, 18-20, 21-24, 24-35, 36-38, 39-44, 45-79, and >80 years after CVID onset). While no survival data exist as far out as 80 years after CVID onset, this characterization allows us to "force" a low survival proportion beyond 80 years after CVID onset, which we set at 1% to factor in the reality of finite human survival. The choice of 80 years remains arbitrary, and the aging chain allows any alternate number of stages and values beyond the last reported data point at 45 years. In each stage s, the theoretical fit of the death rate to the data equals:

$$d(s) = -Ln(S_{t+1}/S_t)/(T_{t+1}-T_t)$$

where $d(s)$ = stage-specific death rate (between t^{th} and $t+1^{th}$ data point)
S_t = survival proportion at t^{th} data point in the survival data
T_t = number of years after CVID onset for the t^{th} data point in the survival data

For the last stage (>80 years), we assume the same d(s) as for the penultimate state. The choice of d(s) for the last stage influences the tail behavior and thus provides some flexibility to influence the tail in the absence of data.

Characterization C2 uses continuous cohorting.(Eberlein, Thompson et al. 2012) This method divides the entire survival period from 0-80 years after CVID into sub-stages of the same width as the integration time step (i.e., 10,240 stocks for our choice of a small integration step of 1/128 years). Continuous cohorting represents a hybrid approach that contains elements of discrete (deterministic) simulation but remains compatible with using rate-based flows in other parts of the SD model. The approach circumvents the implicit assumption of perfect mixing within stocks(Eberlein, Thompson et al. 2012) by transitioning the entire contents of the sub-stage to the next sub-stage at each time step, except for the fraction that dies at the given time after onset:

$$CVID(ss+1)=CVID(ss)\times(1-d(ss))$$

Where $d(ss)$ = sub-stage-specific death rate at stage ss (i.e., at ss integration steps after CVID onset)
$CVID(ss)$ = proportion of CVID patients surviving ss integration steps after CVID onset

Unlike a conventional aging chain, this approach remains consistent with how aging occurs in the real world (i.e., each day, we all get one day older, instead of a proportion of us becoming one day older). The available survival data are not granular enough to estimate different death rates at each sub-stage, but we can use the same fitting approach as for characterization C1 to the reported wider time intervals when the survival proportion changes. However, with continuous cohorting, the remaining survival proportions at different times represent the result of a discrete rather than a continuous compounding process, so that the fitted death rates for all sub-stages ss that fall with the wider data interval s equal:

$$d(s) = 1- (S_{t+1}/S_t)^{dt/(Tt+1-Tt)}$$

where dt = size of the integration time step (=1/128)

Characterization D

Characterizations A-C do not explicitly account for the age of patients because the survival data reflect time since CVID onset (Figure 1). However, arguably age significantly impacts the survival of patients, particular at older age. Unfortunately, the available data not provide patients-specific causes of death needed for a competing survival risk analysis.(Chapel, Lucas et al. 2008) They also do not provide a directly comparable age-specific survival curve for CVID patients relative to the general population because the age at onset varies widely in the CVID patient groups (between 0 and 76 years).(Chapel, Lucas et al. 2008) Derivation of the excess hazard rate would require individual patient survival data to compare each patients survival given their age of onset with the background survival rates for the general population from that age on. However, for purposes of demonstration, characterization D (Figure 2D) shows the stock-and-flow structure corresponding to a model based on the excess hazard rate. This example assumes a constant excess hazard rate by age, although sufficient data would allow estimation of age-specific excess hazard rates. To demonstrate the characterization for our data set, for simplicity we unrealistically assume that all CVID patients developed CVID onset at exactly the average onset age of 25 years. We estimate the excess hazard rate as

Excess hazard rate = $-Ln(S_T)/T$ - $-Ln(P_{70}/P_{25})/T$
Where S_T and T are as defined for Characterization A
Px is the proportion of the general population surviving to age x years (based on UK life tables)(Office for National Statistics 2015)

For comparability, we consider the same stages as for Characterization C1 based on the time points when the CVID survival data change (i.e., 0-2, 3-5, 6-8, 9-11, 12-14, 15-17, 18-20, 21-24, 24-35, 36-38, 39-44, after onset, corresponding to ages 25-27, 28-30, etc.) and further include age groups 0, 1-4, 5-14, 15-24, 70-79, 80-89,90+ to complete the aging chain. While the actual distribution of clinical CVID patients will depend on birth and death rates for pre-clinical patients, they do not factor into our focus on the survival response to a pulse of 1 CVID patient at time 0. We consider two alternative initial pulses. The first (characterization D1) follows a patient entering the clinical CVID stage at age 25. The second (characterization D2) divides the initial pulse over all age groups according to the reported distribution of the age of onset.(Chapel, Lucas et al. 2008)

Results

Figure 3 shows the behavior for the different survival characterizations compared to the data. Table 1 shows the behavior at the tail for each characterization as well as the fit to the data. The single-stage first-order expiry process (Characterization A) produces a remarkably good visual fit (Figure 3) and numerical fit (low SSE in Table 1) to the survival data. Due to estimation of the average death rate based on the last survival data point, the curve goes through this point (Figure 3). However, the single-stage survival process implies an unrealistically long tail, with 30% of modeled CVID patients expected to survive for more than 80 years after CVID onset and an impossible 23% after 120 years in the context of the late average age of onset. Thus, naïve use of Characterization A would greatly overestimate the risk associated with survival of CVID patients persistently infected with iVDPVs beyond OPV cessation.

Characterization B results in a greater SSE between the data and the model (Table 2) but more realistic behavior in the tail (Figure 3). However, for a small number of stages, the proportion surviving beyond 80 years probably remains higher than expected even for the general population, and some fraction still survives beyond any reasonably expected number of years after CVID onset (Table 3, e.g., 11% surviving beyond 120 years with 2 stages). With more stages, the tail behavior improves, but this comes at the expense of greater SSE due to poor fit to the existing data.

Characterization C1 with a conventional aging chain produces more realistic tail behavior than Characterizations A and B, but underestimates survival near the last available data points (Figure 3 and Table 1). This occurs because drainage due to mortality in each stage reduces the effective aging rate to the next stage, which effectively reduces the proportions in later stages of the survival process.(Eberlein, Thompson et al. 2012) This artifact of "cohort blending"(Eberlein, Thompson et al. 2012) represents an importation limitation of conventional aging chains to model slow processes with long tails, and in the case of the poliovirus risks analysis will lead to serious underestimation of risks. In contrast, Characterization C2 with continuous cohorting circumvents this limitation and closely mimics the survival data, yielding the lowest SSE of all characterizations (Table 1). In addition, Characterization C2 remains very flexible with respect to the tail behavior, because the modeler can specify any tail probabilities deemed realistic. However, the approach requires specification of a maximum survival time, because one can model only a finite number of sub-stages. For our application, a finite tail represents a reasonable assumption and we elected to use a maximum of 80 years after CVID onset, resulting in 0 proportion surviving beyond that point (Table 1). Additional time points after the last data point at 45 years after onset can give different shapes beyond 45 years, although these would be based on judgment rather than actual survival data. Continuous cohorting involves a large number of stocks to represent each sub-stage, which can increase multiplicatively if the model requires multiple continuous cohorting processes or stratification by other variables (e.g., sex, age, age at diagnosis, poliovirus infection with each serotype, treatment status).

Characterization D1 using the excess hazard rate with 1 initial clinical CVID patient at 25 years produces results very similar to Characterization C1. This occurs because both characterizations essentially use the same total net rates as of function time since of onset. In Characterization D1, we interpret time since onset as age and differentiate the contribution of the excess hazard rate

and the general population death rate, but the total remains similar. Assuming constant excess hazard rates versus age-specific excess hazard rates yielded minimal impact. Characterization D1 also uses slightly different age groups beyond 70 years of age than Characterization C1, with the general population death rates based on life tables rather than mere extrapolation of the CVID survival data, which accounts for the difference between the two curves. If we assume a pulse according to the actual observed distribution of the age of onset (Characterization D2), then this violates our simplifying assumption of onset at 25 years for estimating the excess hazard rate, and consequently we obtain greater errors than with Characterization D1. Cohort blending still occurs with these characterizations, but as for Characterizations C we can circumvent this using continuous cohorting.

Discussion

The choice of survival characterization matters and may result in large differences that can affect estimates of risk and risk management policies. Thus, the choice of model to characterize survival in risk analysis applications of SD models deserves careful consideration, particularly for risks involving a slow process with a long tail. Table 2 summarizes the advantages and disadvantages of the different approaches we considered for this application. The available data to estimate survival limits the choices of survival characterization, ranging from Characterization A (warranted if only an average is available and no information about the distributional form) to Characterization D (requiring individualized data). If individualized data are available, then Characterization D would provide the most realistic characterization that can account both for age and time since disease onset. In our application, the data limit our ability to use Characterization D.

For aging chains (Characterizations C and D), continuous cohorting clearly represents the most appropriate characterization for the poliovirus risk analysis application among the characterizations we considered. However, using this approach comes at the expense of the need for a very large number of stocks for multiple levels of stratification, leading to higher computational demands, more complicated implementation, and more complexity to communicate to policy makers. Stochastic formulations of continuous cohorting models, such as discrete-event simulation (DES) models, offer a more convenient approach to track time since onset and/or age and other factors, while preserving the desirable tail flexibility and behavior. Unlike the deterministic SD models described here, DES models require a large number of stochastic iterations, particularly given the importance of low probability-high consequence events. Given that risk analysis applications focus on probabilistic outcomes, the need for a large number of stochastic iterations represents a necessary requirement.

References

Alexander, J. P., Jr., H. E. Gary, Jr. and M. A. Pallansch (1997). "Duration of poliovirus excretion and its implications for acute flaccid paralysis surveillance: a review of the literature." Journal of Infectious Diseases **175**(Suppl. 1): S176-182.

Bellmunt, A., G. May, R. Zell, P. Pring-Akerblom, W. Verhagen and A. Heim (1999). "Evolution of poliovirus type I during 5.5 years of prolonged enteral replication in an immunodeficient patient." Virology **265**(2): 178-184.

Burns, C., O. Diop, R. W. Sutter and O. M. Kew (2014). "Vaccine-derived polioviruses." Journal of Infectious Diseases **210**(Suppl 1): S283-S293.
Chapel, H., M. Lucas, M. Lee, J. Bjorkander, D. Webster, B. Grimbacher, C. Fieschi, V. Thon, M. R. Abedi and L. Hammarstrom (2008). "Common variable immunodeficiency disorders: division into distinct clinical phenotypes." Blood **112**(2): 277-286.
Duintjer Tebbens, R. J., M. A. Pallansch, O. M. Kew, V. M. Cáceres, H. Jafari, S. L. Cochi, R. B. Aylward and K. M. Thompson (2006). "Risks of paralytic disease due to wild or vaccine-derived poliovirus after eradication." Risk Analysis **26**(6): 1471-1505.
Duintjer Tebbens, R. J., M. A. Pallansch, J.-H. Kim, C. C. Burns, O. M. Kew, M. S. Oberste, O. Diop, S. G. F. Wassilak, S. L. Cochi and K. M. Thompson (2013). "Review: Oral Poliovirus Vaccine Evolution and Insights Relevant to Modeling the Risks of Circulating Vaccine-Derived Polioviruses (cVDPVs)." Risk Analysis **23**(4): 680-702.
Duintjer Tebbens, R. J., M. A. Pallansch and K. M. Thompson (2015). "Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs (Under review with BMC Infect Dis-- Draft manuscript available upon request from the editor)."
Duintjer Tebbens, R. J. and K. M. Thompson (2014). "Modeling the potential role of inactivated poliovirus vaccine to manage the risks of oral poliovirus vaccine cessation." Journal of Infectious Diseases **210**(Suppl 1): S485-S497.
Eberlein, R. L., J. P. Thompson and D. B. Matchar (2012). Chronological aging in continuous time. International System Dynamics Conference, St. Gallen, Switzerland.
Gathmann, B., B. Grimbacher, J. Beaute, Y. Dudoit, N. Mahlaoui, A. Fischer, V. Knerr, G. Kindle and E. R. W. Party (2009). "The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008." Clinical and Experimental Immunology **157 Suppl 1**: 3-11.
Joshi, A. Y., V. N. Iyer, J. B. Hagan, J. L. St Sauver and T. G. Boyce (2009). "Incidence and temporal trends of primary immunodeficiency: a population-based cohort study." Mayo Clinic Proceedings **84**(1): 16-22.
Kew, O., V. Morris-Glasgow, M. Landaverde, C. Burns, J. Shaw, Z. Garib, J. Andre, E. Blackman, C. J. Freeman, J. Jorba, R. Sutter, G. Tambini, L. Venczel, C. Pedreira, F. Laender, H. Shimizu, T. Yoneyama, T. Miyamura, H. van Der Avoort, M. S. Oberste, D. Kilpatrick, S. Cochi, M. Pallansch and C. de Quadros (2002). "Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus." Science **296**(5566): 356-359.
Kew, O. M., S. L. Cochi, H. S. Jafari, S. G. Wassilak, E. E. Mast, O. M. Diop, R. H. Tangermann, G. L. Armstrong and Centers for Disease Control and Prevention (CDC) (2014). "Possible eradication of wild poliovirus type 3--worldwide, 2012." Morbidity and Mortality Weekly Report **63**(45): 1031-1033.
Li, L., O. Ivanova, N. Driss, M. Tiongco-Recto, R. de Silva, S. Shahmahmoodi, H. M. S. Sazzad, O. Mach, A.-L. Kahn and R. W. Sutter (2014). "Poliovirus excretion among persons with primary immune deficiency disorders: Summary of a seven-country study series." Journal of Infectious Diseases **210**(Suppl 1): S368-S372.
Lloyd-Smith, J. O., S. J. Schreiber, P. E. Kopp and W. M. Getz (2005). "Superspreading and the effect of individual variation on disease emergence." Nature **438**(7066): 355-359.
Lloyd, A. L. (2001). "Realistic distributions of infectious periods in epidemic models: changing patterns of persistence and dynamics." Theoretical Population Biology **60**(1): 59-71.

MacLennan, C., G. Dunn, A. P. Huissoon, D. S. Kumararatne, J. Martin, P. O'Leary, R. A. Thompson, H. Osman, P. Wood, P. Minor, D. J. Wood and D. Pillay (2004). "Failure to clear persistent vaccine-derived neurovirulent poliovirus infection in an immunodeficient man." Lancet **363**(9420): 1509-1513.
McKinlay, M. A., M. S. Collett, J. M. Hincks, M. S. Oberste, M. A. Pallansch, H. Okayasu, R. W. Sutter, J. F. Modlin and W. R. Dowdle (2014). "Progress in the development of poliovirus antiviral agents and their essential role in reducing risks that threaten eradication (*in press*)." Journal of Infectious Diseases **210**(Suppl 1): S447-453.
Mohammadinejad, P., A. Aghamohammadi, H. Abolhassani, M. S. Sadaghiani, S. Abdollahzade, B. Sadeghi, H. Soheili, M. Tavassoli, S. M. Fathi, M. Tavakol, N. Behniafard, B. Darabi, S. Pourhamdi and N. Rezaei (2012). "Pediatric patients with common variable immunodeficiency: long-term follow-up." Journal of Investigational Allergololgy and Clinical Immunology **22**(3): 208-214.
Office for National Statistics. (2015). "National Life Tables, United Kingdom, 1980-82 to 2011-13." Retrieved July 14, 2015, from http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Life+Tables#tab-data-tables.
Platt, L. R., C. F. Estivariz and R. W. Sutter (2014). "Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden." Journal of Infectious Diseases **210**(Suppl 1): S380-389.
Sandin, F. (2008). "Analyzing and modeling the relative survival rate of patients diagnosed with malignant melanoma." Retrieved July 15, 2015, from http://www2.math.uu.se/research/pub/Sandin1.pdf.
Sterman, J. (2001). Business dynamics: Systems thinking and modeling for a complex world. Boston, MA, McGraw-Hill.
Thompson, K. M. and R. J. Duintjer Tebbens (2014). "Modeling the dynamics of oral poliovirus vaccine cessation." Journal of Infectious Diseases **210**(Suppl 1): S475-S484.
World Health Organization (2001). "Transmission of wild poliovirus type 2 - Apparent global interruption." Weekly Epidemiological Record **76**: 95-97.
World Health Organization (2013). Global Polio Eradication Initiative: Polio Eradication and Endgame Strategic Plan (2013-2018). Geneva.
World Health Organization. (2015, July 7). "Global Polio Eradication Initiative -- List of wild poliovirus by country." Retrieved July 15, 2015, from http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Wildpolioviruslist.aspx.

Figure 1: Common variable immunodeficiency disease (CVID) survival data from different studies compared to the general population, as reported in (Chapel, Lucas et al. 2008)

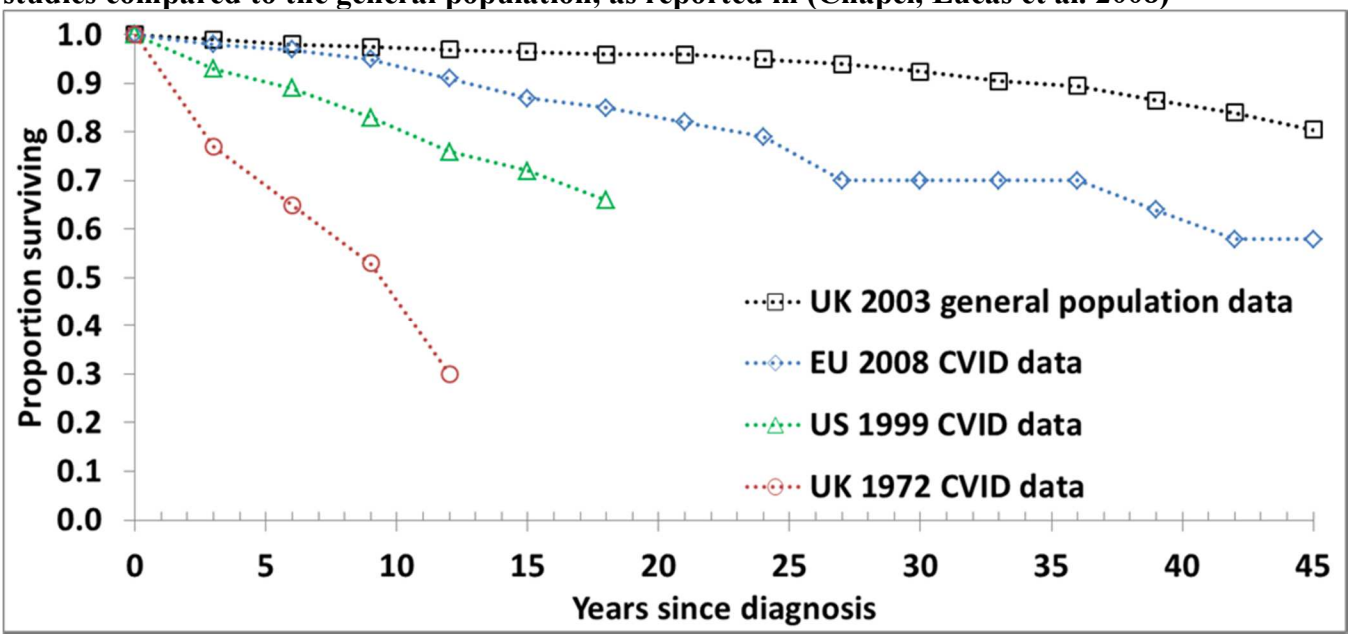
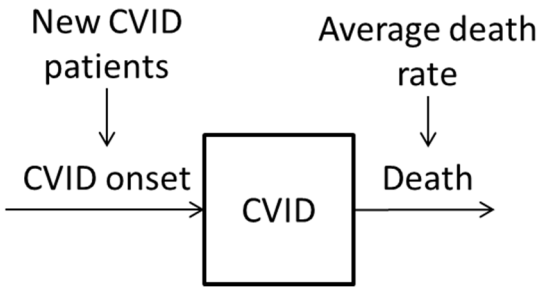
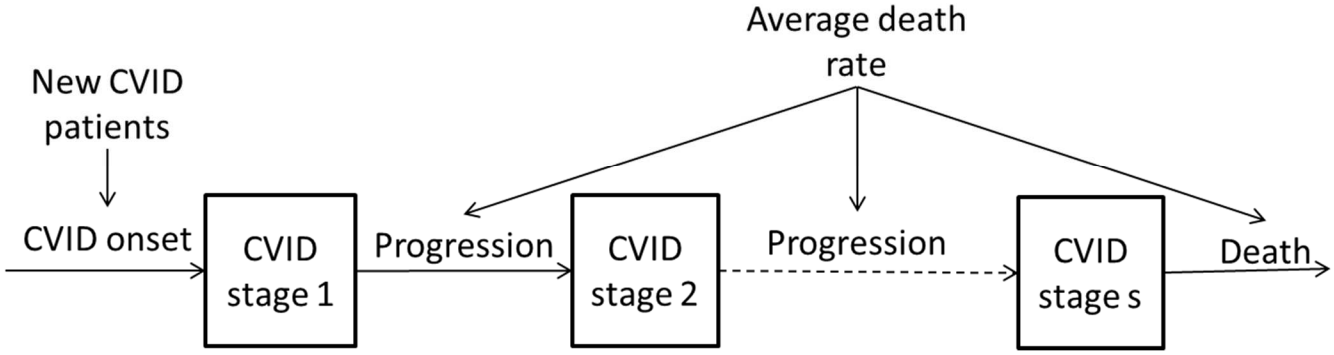


Figure 2: Stock-and-flow diagrams for the different characterizations of CVID survival

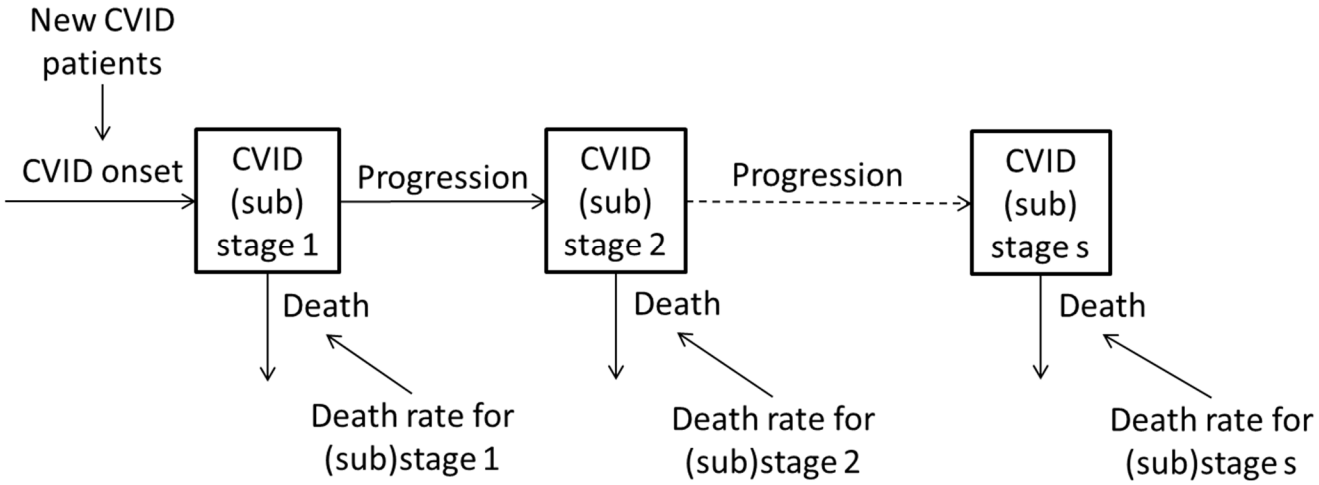
A: Single-stage process



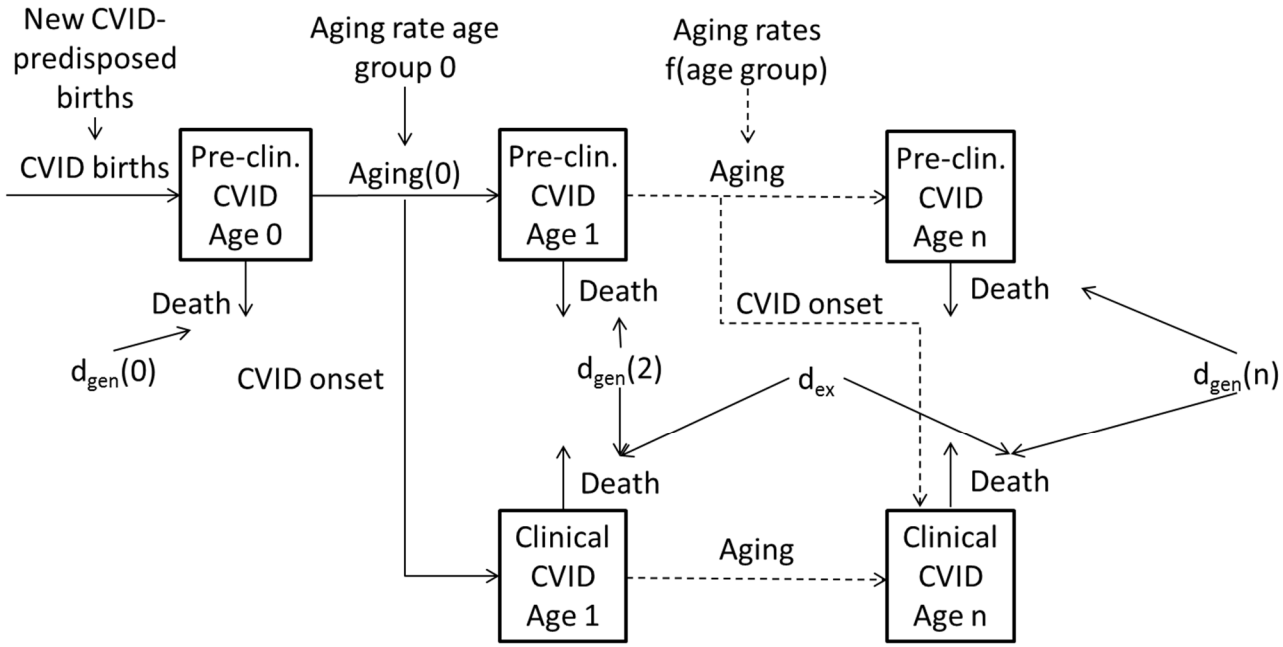
B: Multi-stage process with single average death rate



C: Aging chain with death rates that vary with time since CVID onset



D: Excess hazard rate



$d_{gen}(a)$= general population death rate for age group *a*
d_{ex} = excess death rate for CVID patients

Figure 2: Comparison of available data(Chapel, Lucas et al. 2008) to results with each survival characterization

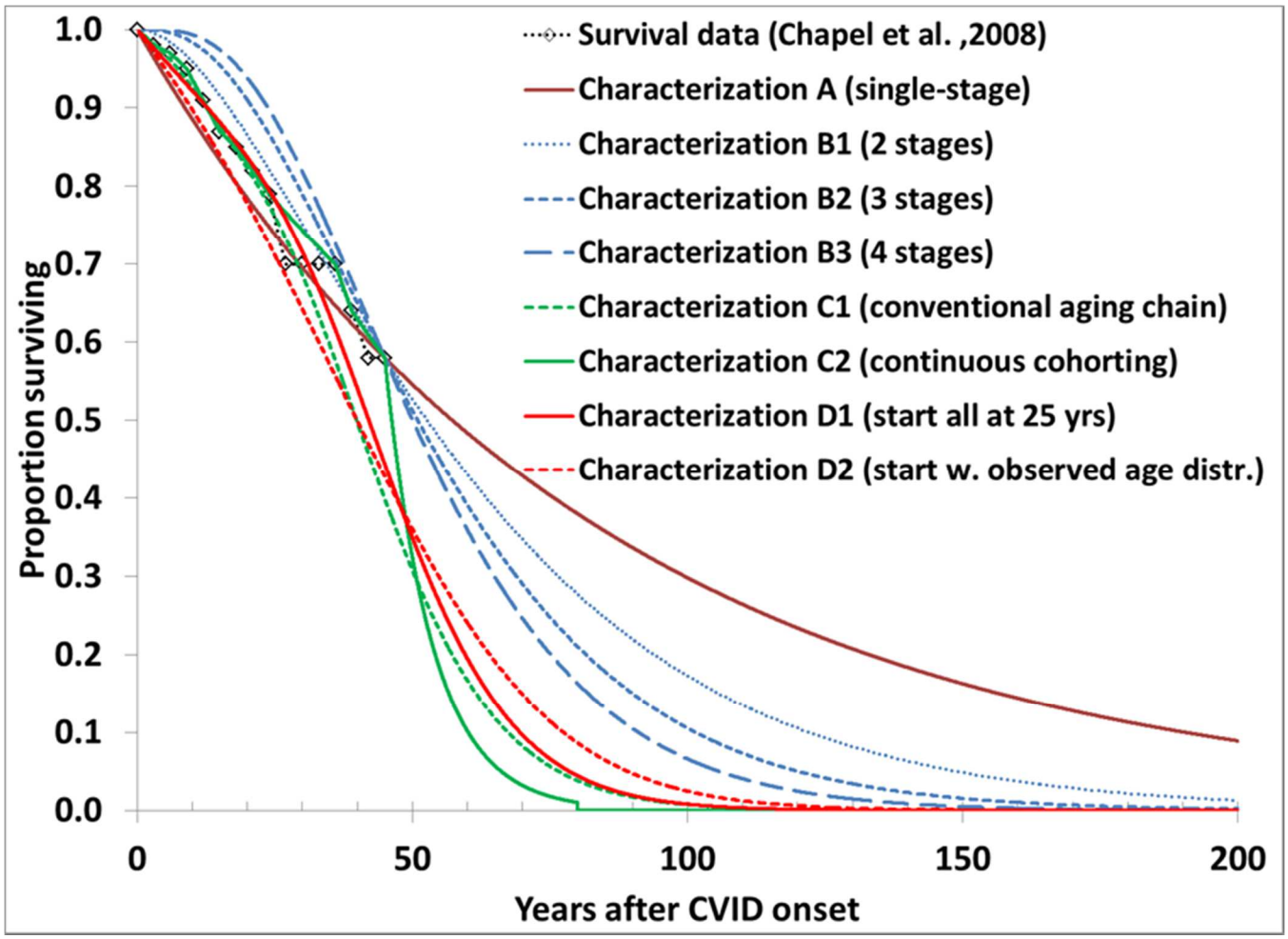


Table 1: Sum of squared errors (SSE) compared to data and tail behavior for each survival characterization

Survival characterization	SSE	Proportion surviving at			
		45 years (data: 0.58)	80 years	100 years	120 years
A	0.019	0.58	0.38	0.30	0.23
- B1 (2 stages)	0.019	0.58	0.28	0.17	0.11
- B2 (3 stages)	0.062	0.58	0.21	0.11	0.050
- B3 (4 stages)	0.105	0.58	0.16	0.066	0.024
- C1: conventional aging chain	0.084	0.40	0.038	0.0072	0.0012
- C2: continuous cohorting	0.0077	0.58	0	0	0
- D1: conventional aging chain	0.044	0.44	0.044	0.0078	0.0012
- D2: continuous cohorting	0.099	0.43	0.086	0.025	0.0058

Table 2: Pros and cons of each characterization

Survival characterization	Pros	Cons
A (single stage)	• Conceptually simple • Easiest to parametrize • Only 1 stock needed	• Only one distributional form attainable • Too many short survivors • Too many long survivors (i.e., long tail)
B (any number of stages)	• Conceptually simple • Easy to parametrize • Relatively few stocks needed	• Limited distributional forms attainable (only gamma) • Tail still too long for optimal number of stages • No better fit to data than Characterization A
C1 (conventional aging chain)	• Flexible • Ability to directly moderate tail behavior • Conceptually clear	• Poor fit to survival curve data due to cohort blending • May require many stocks to represent survival data
C2 (continuous cohorting)	• Flexible with respect to any desired realistic tail behavior • Direct fit to survival data • Realistic representation of chronological process	• Requires large number of stocks • More cumbersome to integrate with conventional rate-based processes
D (excess death rate)	• Can realistically account for both age and time since onset	• Estimates require individualized data • Cohort blending still possible (unless continuous cohorting used) • More than twice as many stocks as with Characterization C