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Origins of the problematic E in SEIR epidemic models

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ABSTRACT

During the COVID-19 pandemic, over one thousand papers were published on "Susceptible-Exposed-Infectious-Removed" (SEIR) epidemic computational models. The English word "exposed" in its vernacular and public health usage means a state of having been in contact with an infectious individual, but not necessarily infected. In contrast, the term "exposed" in SEIR modeling usage typically stands for a state of already being infected but not yet being infectious to others, a state more properly termed "latently infected." In public health language, "exposed" means *possibly infected*, yet in SEIR modeling language, "exposed" means *already infected.* This paper retraces the conceptual and mathematical origins of this terminological disconnect and concludes that epidemic modelers should consider using the "SLIR" notational short-hand (L for Latent) instead of SEIR.

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1. Introduction

During the COVID-19 pandemic public health agencies expended considerable effort to educate the public about the significance of being "exposed" to SARS-CoV-2, and what to do while waiting to find out if an exposure had resulted in an infection (**CDC, 2022**). Perplexingly, this same term "exposed' is used in a different way among modelers who work with "Susceptible-Exposed-Infectious-Removed" computational epidemic models, commonly known as "SEIR" models. Here the term "exposed" is typically defined as a person who has become infected but is not yet capable of transmitting the infection to others. SEIR models are extremely commonplace in the health literature: a PubMed search on "SEIR" AND "Model' retrieves 1339 publications, with over one thousand SEIR modeling papers published since the start of the COVID-19 pandemic. This paper retraces the origins of this terminological quirk.

2. The first SEIR paper

By following chains of reference citations, the earliest explicit SEIR model I have been able to find was in a 1965 paper by Kenneth L. Cooke of Pomona College entitled "Functional-differential equations: some models and perturbation problems." The paper was published in 1967 in a mathematics symposium collection entitled "Differential Equations and Dynamical Systems - Proceedings of an International Symposium held at the University of Puerto Rico, Mayaguez, Puerto Rico, December

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27–30, 1965" (Cooke, 1967**, pp. 27–30).** Cooke, an expert in functional-differential equations, later became the W. M. Keck Professor of Mathematics at Pomona (see Fig. 1) In his 1965 paper, at age 40, Cooke explicitly laid out an SEIR modeling framework:

We now define the following quantities.

S(t) = number of susceptible, unexposed individuals at time t,
E(t) = number of exposed but noninfectious individuals,
I(t) = number of infectious individuals,
R(t) = number of individuals recovered and not susceptible to infection,
C(t) = rate at which unexposed individuals receive first effective exposure

Interestingly, Cooke had never previously published any papers dealing with infectious diseases nor epidemics. His earlier publications are all studies of differential equations and mathematical systems dynamics. Indeed, one can read this seminal SEIR paper as being less about the behavior of epidemics than about the behavior of functional-differential equations.

3. Terminology for epidemic models

Classical epidemic models compartmentalized the infectious disease process into a series of discrete states, with state-to-state progression from susceptible to infected to removed (the removed state being achieved by either recovery of death). Epidemic growth was computed as the mass action between the number (or proportion) of susceptibles and infecteds. The labeling and abbreviating of these three compartments varied by authors but typically followed the mathematical convention of using of the terminal alphabet letters X, Y, and Z (**Anderson & May 1979**; **Bailey, 1957**; **Kermack & McKendrick, 1927**). In contrast to compartmental models, chain binomial models were used for simulating epidemics in small populations, and did not represent removed individuals. In chain binomial models the letter "S" was commonly used to represent susceptibles, and "I" was used to represent the infected. Sometimes "C" was used to designated "infectious Cases'"(**Abbey, 1952**; **En'ko, 1989**; **Soper, 1929**). I have not been able to find use of the letter "R" for the removed state, nor "E" for the exposed state, before Cooke, 1967 paper.

In 1970 two mathematicians, Frank Hoppensteadt of the Courant Institute of Mathematical Science at NYU, and Paul Waltman, a visiting member at the Courant Institute from the University of Iowa, published a theoretical paper entitled "A problem in the theory of epidemics" in the journal Mathematical Biosciences (**Hoppensteadt & Waltman, 1970**). Hoppensteadt and Waltman's goal was to study the dynamics of the epidemic spread model put forth by Cooke. They didn't take issue with his idiosyncratic definition of the Exposed state, nor did they attempt to relate their computations to any real world epidemic data. They conclude that

> "The principal result is to show that the model yields a mathematically well-posed problem"

That is, Hoppenstead and Waltman mathematically showed that the SEIR model as put forward by Cooke has a solution, the solution is unique, the solution's behavior changes continuously with the initial condition, and all the components take on

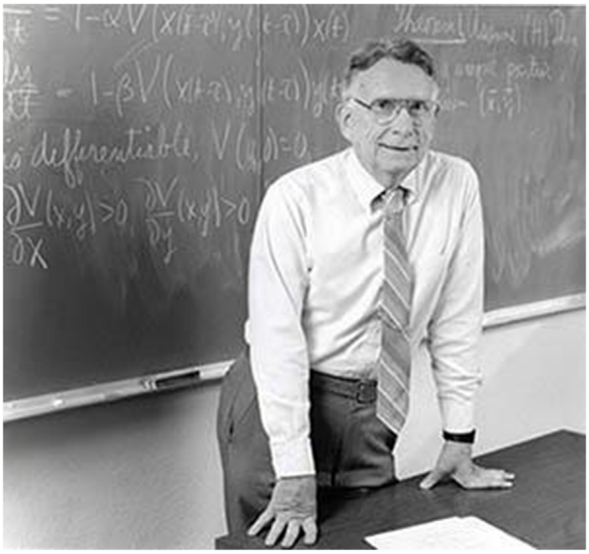

Fig. 1. Kenneth Cooke.

greater than or equal to zero values. Waltman returned to Iowa where he collaborated with his Department of Mathematics colleague Herb Hethcote to write a paper in 1973 entitled "Optimal vaccination schedules in a deterministic model" in which they employed the SIRS terminology, without including the "E" exposed state (**Hethcote & Waltman, 1973**).

In 1971 Cooke collaborated with James Yorke of the University of Maryland to publish a paper entitled "Some delay differential equations modelling population growth, economic growth, and epidemics" in the Proceedings of the National Research Laboratory Conference on Ordinary Differential Equations (**Cooke & Yorke, 1971, pp. 35–53).** Interestingly, this paper does not use the SEIR notation. Cooke and Yorke collaborated again in 1973 for a paper in Mathematical Biosciences entitled "Some equations modeling growth processes and gonorrhea epidemics" which reintroduced the SEIR terminology for a model of gonorrhea, and provided proofs for the theorems put forward in their earlier collaborative paper (**Cooke & Yorke, 1973**). Yorke was concurrently collaborating with Wayne London of the NIH to use SEI compartmental modeling to estimate contact rates for measles, chickenpox, and mumps (**London & Yorke, 1973).** Yorke later went on to become distinguished University Research Professor of Mathematics and Physics and chair of the Mathematics Department at the University of Maryland, College Park, and win the Japan Prize in Science and Technology for his work in chaotic systems. A cluster of publications that can be traced back to Cooke's 1967 SEIR publication is shown diagrammatically in Fig. 2 below (**Cooke & Yorke, 1971, 1973; Hethcote, 1973, 1976; Hoppensteadt & Waltman, 1970, 1971; London & Yorke, 1973; Smith, 1979; Wilson, 1972**). The papers are linked not only through citation chains, but through a variety of personal relationships between the authors. The 1983 paper by Ira Schwartz and Hal Smith entitled "Infinite subharmonic bifurcation in an SEIR epidemic model" is the first paper retrievable from PubMed through a search on the terms "SEIR" and "model"; none of the other earlier papers in this cluster are retrievable through PubMed (**Schwartz & Smith, 1983**). In that same year 1983 Schwartz published a separate paper in which he introduced a sensible "SLIM" notation for susceptible, latent, infectious, and immune states, respectively, but that notation never became adopted by others (**Schwartz, 1983).** Two institutions that featured prominently in the early "pre-PubMed" SEIR publication cluster are the Department of Mathematics at the University of Iowa, to which Waltman, Hethcote, and Smith belonged, and the Mathematics Department at the University of Maryland, to which Yorke and Schwartz belonged.

Hethcote's 1976 paper "Qualitative analyses of communicable disease models" was the first to use this simple coherent terminological convention to describe epidemic compartmental models as SIR, SIS, or SI models (**Hethcote, 1976).** In the body of this paper Hethcote does not review any models with a latent or exposed compartment, however, in a terminal section of this paper entitled "Other communicable disease models" he writes

> Another type of communicable disease model is the SEIR model, where E is a class of exposed individuals, who are in the latent period. Various assumptions regarding the length of the latent and infective periods lead to delay differential equations, functional differential equations, and integral equations.

Many years later in 2000, in a widely cited paper entitled "The mathematics of infectious diseases" Hethcote reviews the full panoply of acronymic names for compartmental epidemic models (Hethcote, 2000)

> The choice of which compartments to include in a model depends on the characteristics of the particular disease being modeled and the purpose of the model. The passively immune class M and the latent period class E are often omitted because they are not crucial for the susceptible-infective interaction. Acronyms for epidemiology models are often based on the flow patterns between the compartments such as MSEIR, MSEIRS, SEIR, SEIRS, SIR, SIRS, SEI, SEIS, SI, and SIS.

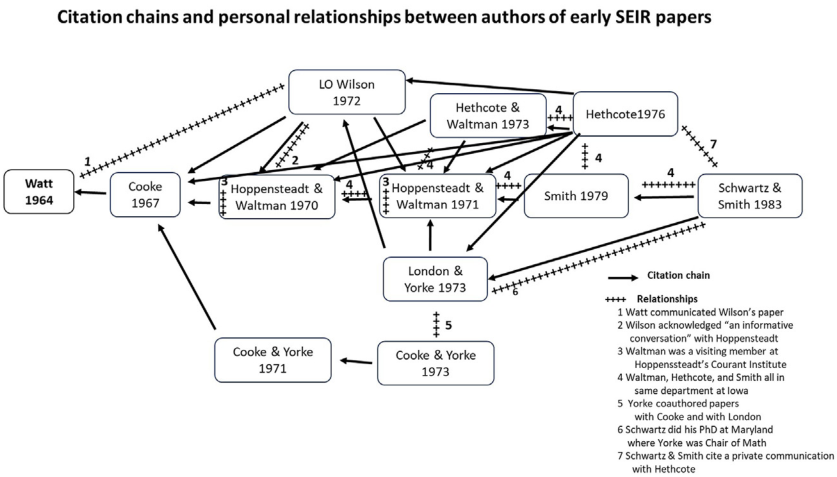

Fig. 2. Citation chains and personal relationships.

4. Conceptualization of the “exposed” or “latent” state

In their seminal paper “A contribution to the mathematical theory of epidemics,” Kermack and McKendrick do not discuss exposed or latent states, that is the possible existence of an interval from the moment that a susceptible person comes into contact with an existing case, to the time that that person becomes infectious for others (**Kermack & McKendrick, 1927**).

Soper in 1929 also does not explicitly mention an exposed nor a latent state. However in discussing the disease process he writes (**Soper, 1929**)

> We may suppose, for example, that the disease is acquired as the result of an over-accumulation of doses of infection above what can be dealt with by the resisting powers of the body, or , on the other hand, that it is acquired instantaneously.

Wilson and Burke in 1942 do discuss the concept of a latent period in a footnote comment on Soper's work, in which they propose that “the newly infected C(t)dt become infectious after a latent time Γ and remain infectious for a time σ” (**Wilson & Burk, 1942**). Theirs is a single hit process with a variable duration of latency, not a cumulative multi-hit process.

Bailey in his classic 1957 book entitled “The mathematical theory of epidemics” has a full chapter on “The measurement of latent and infectious periods” (**Bailey, 1957**) He writes

> After a susceptible individual exposed to a source of infection has actually become infected, a certain amount of biological development may be necessary before he can in turn pass the disease on to others. This interval of apparent quiescence is the latent period.

When Cooke proposed his concept of the exposed “E” state in 1965, he wrote

> We shall here outline a deterministic model somewhat similar to that of Wilson and Burke, in which however we assume that a susceptible individual, A, does not become infectious upon first exposure to an infectious individual, but only after repeated exposure to infectious individuals has broken down A’s resistance.

Cooke cites Bailey as well as Wilson and Burke for his references to epidemic modelling, but to justify his “repeated exposure” hypothesis about the mechanism of infection, he cites only Watt (**Watt, 1964**).

> *In a recent article, Watt has called attention to the importance of processes of this* kind*, pointing out that “large-scale biological mechanisms often exhibit cumulative effects, lags, and thresholds,” and illustrating with the case of insects eating perennial plants*.

It is possible that in formulating his concept of an Exposed state that Cooke was influenced by, but did not cite, Soper's speculation that “*We may suppose, for example, that the disease is acquired as the result of an over-accumulation of doses of infection.”* But the epidemic modeling papers that he does cite do not describe any kind of mutli-hit cumulative exposure process for a susceptible person to become infectious, and the only cited justification that he provides for such a mechanism is a nebulous allusion to “large scale biological mechanisms.”

Subsequently, none of the early authors in the pre-PubMed SEIR cluster of papers directly challenged Cooke's concept of a multi-hit Exposed state. LO Wilson, and Hoppensteadt and Waltman, extended their mathematical analyses directly off Cooke, 1967, pp. 27–30 paper, so they did not alter his definition of the E state (**Hoppensteadt & Waltman, 1970**; **Wilson, 1972**). When Cooke collaborated with Yorke on modelling of gonorrhea, their model “assumes that the incubation period is negligibly short” which effectively removed the mechanisms involved in the Exposed state from consideration in their calculations (**Cooke & Yorke, 1973**). And in Hoppensteadt and Waltman's second paper they modified Cooke's cumulative process for E to permit a both a multi-hit process and a single hit process that “would correspond to a fixed incubation time necessary for an exposed individual to become infectious**”** (**Hoppensteadt & Waltman, 1971**) [nb: in modern terminology this would be restated as “ .to a fixed *latent period* necessary … ”, as summarized by Dietz (**Dietiz, 1967**)]. It appears that the early authors who employed the SEIR framework used Cooke's newly introduced word “Exposed” as a generic term for a variety of mechanistic processes representing the transition from the susceptible to the infectious state. Hethcote remarked on this mathematical plasticity of the definition of Exposed in SEIR models, when he wrote in 1976 that

> “*Various assumptions regarding the length of the latent and infective periods lead to delay differential equations, functional differential equations, and integral equations.”*

5. Original mathematical rationale for the term “exposed”

In introducing his 1965 paper, Cooke explains that

> *Our models are of a somewhat novel “threshold” type and serve to draw attention to a class of equations which may prove to be of considerable importance, and which certainly are the least studied to date among what we might call the taxonomy of functional-differential equations*.

Cooke defines his Exposed state as follows:

We shall assume that once an individual has been exposed, the amount of infectious dosage is cumulative and that the does he receives in a short time h is proportional to h and to the proportion of infectious individuals in the environment. Thus an individual first exposed at time τ will at time t (t>τ) have received a total dose

where ρ(t) is a proportionality factor. Our basic assumption, the one which distinguishes our

$$\int_{\tau}^{t} \rho(x) \Big/ (x)dx$$

model, is that this individual becomes infective at the first time t at which this total dose reaches a

$$\int_{\tau}^{t} \rho(x) \Big/ (x)dx = m$$

threshold value m:

It appears that Cooke deliberately chose the word Exposed as opposed to other options like Latent or Incubating because in his conceptual model the transition from Susceptible to Infectious was not instantaneous. To describe his mathematically interesting model - one that featured a novel threshold for becoming infectious - he needed a term suitable for a repetitive, accumulating infectious process. The term Exposed easily encompasses a progressive series of exposures culminating in infection, while use of other terms like Latent or Incubating would suggest a process in which the person was infected, without having to reach a threshold.

Reflecting on this history, Hethcote remarked to me that “Many mathematicians are more interested in the mathematical aspects of models than in using the correct terminology in epidemiology … I agree that SLIR would be a better name than SEIR for these models”(**Hethcote, 2023**).

6. Cumulative or multi-hit exposure process

Although the term “exposed” is problematic when used to denote an active but latent infection, there are some epidemic circumstances for which use of the term “exposed” may be appropriate to describe an infection process that is incomplete, partial, or primed. Such interesting epidemiological processes are not reviewed in depth here but are mentioned for completeness.

- Multipartite viruses of plants are viruses that have genomes segmented in pieces enclosed in different capsids that are independently transmitted. All segments must meet in the host for complementation and completion of the viral cycle (**Lucia-Sanz & Manrubia, 2017**; **Zhang et al., 2019**).
- Viruses like dengue utilize antibody-dependent enhancement for replication and subsequent transmission. There are four dengue virus serotypes, and infection with one type primes the individual for virus greater replication and symptoms when subsequently infected with a different serotype (**Cummings et al., 2005**).
- Contagious human attitudes and behaviors are thought to require multiple and repetitive contacts and re-exposures for transmission (**Guilbeault et al., 2018**)

For these and possibly other specific epidemic circumstances, Cooke's original representation of the Exposed state as a cumulative or multi-hit process may be conceptually and computationally appropriate.

7. Conclusions

Over the years, only a small minority of modeling groups have eschewed the problematic SEIR notation in favor of the more correct SLIR notation, where the infected but not yet infectious state is denoted with the letter L (for Latent) instead of E. A few examples are provide here (**Ajelli et al., 2010**; **Arino et al., 2007**; **Brauer, 2008**; **Coutinho et al., 1999**; **Lopez & Coutinho, 2000**; **Ogut & Bishop, 2007**; **Pienaar et al., 2010**; **Van Effelterre et al., 2006**; **Woolhouse et al., 1996**). In addition to its conceptual clarity, the SLIR notation has the advantage of liberating the letter E to be available to denote a separate state to accurately represent “exposed” persons.

Most authors avoid the terminology problem altogether by simply defining the Exposed compartment as representing the latent period, that is the time between becoming infected and becoming infectious to others (**Bjornstad et al., 2020**). Many papers create sub-groups or sub-compartments of the Exposed compartment, such as in age stratified models, or models with multiple strains of transmissible agents, or models with temporarily asymptomatic and permanently asymptomatic persons.

Although referred to as sub-compartments of the Exposed compartment, such groups are actually sub-compartments of the already infected (Latent) compartment (**Abernethy & Glass, 2022**; **Berger, & HerkenhoffHuangMongey, 2022**; **Dias, & QuelrozArujo, 2022**; **Lyra et al., 2020**; **Pinky & Dobrovolny, 2022**).

Of course, the terminological and notational system has no bearing on computational results, but it does confer advantages in communicating modelling concepts and results. A basic tenet of design psychology is that a representation should fit with a concept (**Deissenboeck & Pizka, 2006**). In SEIR models, assignment of the word "exposed" to a compartment that actually means "latently infected" generates cognitive interference, especially for students and even for proficient modelers. The terminological confusion becomes especially acute when building and running models that include both latent and exposed states.

Due to an accidental "founder effect" sixty years ago, the term 'Exposed" is now almost universally used to mean "latently infected" in epidemic compartmental modeling terminology. In the initial publication, Cooke set out to build an interesting yet reasonable theoretical mathematical model of infectious disease epidemiology by positing that persons became infected only upon repeated exposures to infectious cases, and only when a cumulative threshold of exposures was exceeded. Although Cooke based this speculative mechanism on little or no scientific evidence, the acronymic appeal of his terminology led to the widespread acceptance and use of the E in SEIR modeling.

In conclusion, Cooke's problematic E was simply carried along with S, I, and R in his convenient SEIR notational short-hand for describing epidemic models.

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Donald S. Burke: Visualization, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Donald S. Burke reports a relationship with Epistemix, Inc. that includes: board membership and equity or stocks.

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