



Mechanistic mathematical models: An underused platform for HPV research



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ABSTRACT

Health economic modeling has become an invaluable methodology for the design and evaluation of clinical and public health interventions against the human papillomavirus (HPV) and associated diseases. At the same time, relatively little attention has been paid to a different yet complementary class of models, namely that of mechanistic mathematical models. The primary focus of mechanistic mathematical models is to better understand the intricate biologic mechanisms and dynamics of disease. Inspired by a long and successful history of mechanistic modeling in other biomedical fields, we highlight several areas of HPV research where mechanistic models have the potential to advance the field. We argue that by building quantitative bridges between biologic mechanism and population level data, mechanistic mathematical models provide a unique platform to enable collaborations between experimentalists who collect data at different physical scales of the HPV infection process. Through such collaborations, mechanistic mathematical models can accelerate and enhance the investigation of HPV and related diseases.

1. Introduction

The use of health economic models that integrate epidemiological and clinical data to compare different public health interventions has become an important part of health technology assessment and policy-making. Spearheaded by the work of David Eddy in the 1980s [1,2], cervical cancer was one of the first areas where models were used to inform policy recommendations, initially on optimal screening strategies. As our knowledge of the etiology and natural history of cervical cancer has grown, subsequent work has incorporated oncogenic HPV infection and HPV DNA testing [3–6].

With the introduction of HPV vaccination, health economic models have become increasingly complex, integrating human sexual behavior, virus transmission and disease progression in order to evaluate alternative intervention strategies in different socio-economic settings across the globe [7–11]. As they developed into an invaluable tool for the HPV community, these models have also set an implicit gold standard for a modeling paradigm with immediate policy impact. A different yet complementary modeling paradigm is that of mechanistic mathematical models (MMM), whose primary focus is to enhance the mechanistic understanding of HPV and associated diseases. The fact that MMMs are generally used to address basic science questions with a

less obvious impact on health policy may be a reason why the HPV community has, so far, paid relatively little attention to the potential of the mechanistic modeling paradigm.

In contrast to the HPV field, other biomedical fields have made extensive use of MMMs over the past decades. In cancer research, for instance, stochastic models of genetic mutations have been instrumental in quantifying the evolutionary dynamics of cancer initiation [12], and in understanding how cellular dynamics shape population-level cancer incidence [13]. In the clinic, mechanistic models of tumor growth help inform surgical procedures [14] and optimize radiation schedules [15]. Model-based insights into cancer evolution have motivated the concept of adaptive therapy [16], which is now being evaluated for clinical trials [17]. Similarly, in the field of HIV/AIDS research, the combination of MMMs with patient-level data led to critical insights into early infection dynamics, and model-based inference of key biologic parameters accelerated the development of therapeutic strategies [18,19]. Yet another field where MMMs enabled a breakthrough is that of epithelial stem cell research. Combining probabilistic models with in vivo lineage tracing experiments, the long-standing paradigm of epithelial stem cell dynamics has been revised [20], with critical implications for wound healing [21] and carcinogenesis [22].

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Inspired by these successes, we argue here that MMMs constitute a largely underused platform in HPV research. To motivate this perspective, we highlight three areas of HPV research where initial modeling efforts show promise to advance the field.

2. Natural history

According to the prevailing model of HPV natural history the majority of infected individuals permanently clear the virus within 1–2 years after exposure, and only a small fraction develop persistent infections with elevated cancer risk [23]. As simple and attractive as it is, there are a number of experimental findings that are inconsistent with this model [24]. For instance, longitudinal studies found that HPV types that have apparently been cleared can reappear after several negative screens [25–27], and high frequency sampling revealed stochastic loss and gain of detection on the order of days [28]. Further substantiated by animal models [29] and cohort studies in immunosuppressed individuals [30] and older women [31], these findings suggest that instead of being eradicated, HPV may enter a cycle of latent infection and detectable reactivation. An updated model of HPV natural history that incorporates latency and reactivation will require evidence synthesis from molecular, clinical and epidemiological data sources – a formidable opportunity for MMMs. In particular, we argue that mechanistic models provide a suitable methodology to expand the current natural history models, which focus on sexual behaviors as the primary determinant of HPV incidence, to biological determinants of HPV reactivation, including systemic and local immune mediators [30,32], obesity [27], sex hormones [33], vaginal microbial dysbiosis [34], obesity [27] and epithelial homeostasis [35]. Because natural history models constitute the foundation of health economic modeling [36–38], improving our understanding of natural history through mechanistic modeling efforts will have clear public health relevance [39]. Importantly, MMMs will be instrumental in identifying target pathways for novel interventions directed toward lifelong control of HPV infections in the millions of HPV-infected women who will not benefit from prophylactic vaccination. A recent modeling study on the impact of stochastic stem cell dynamics on HPV clearance [35] provides a starting point for MMMs in this arena, with much terra incognita ahead.

3. Vaccination and viral evolution

The introduction of the HPV vaccine raises a number of important questions about potential ecological and evolutionary consequences. Three recent modeling studies highlight the potential of MMMs in this field. Based on an evolutionary ecology model, a first study predicted that elimination of types targeted by the vaccine could change the evolutionary trajectory of non-vaccine types and lead to emergence of new high-risk types [40]. Another study used mechanistic in-host models to revisit the possibility of replacement of vaccine-types by non-vaccine types [41]. To date, type replacement has been deemed unlikely [42] based on the widespread assumption of type independence, which itself is based on the interpretation of co-infection patterns in the population. The authors of the modeling study [41] found a competitive model of within-host viral evolution to be compatible with observed co-infection patterns, and raised the possibility of type replacement and an increase in population prevalence of non-vaccine types. A third study found that selective pressures applied by the vaccine might increase HPV virulence by altering the transmission-recovery trade-offs [43]. It may take years to decades until the evolutionary and ecological consequences of the vaccine can be measured conclusively; in the meantime, in-depth modeling of viral evolution with MMMs can anticipate potential problems, and through close collaboration with experimentalists, aid the design of targeted experimental efforts.

4. HPV-related cancers

Infection with high-risk types of HPV is associated with cancers at multiple anatomic sites, including the cervix, anus, penis, vagina, vulva and oropharynx. There is substantial heterogeneity with respect to HPV incidence, prevalence and transmission by both gender and anatomic sites, and cancer incidence is consistent with HPV prevalence at some, but not all, sites [44]. For many of these observations, a mechanistic explanation is currently missing, providing yet another opportunity for mechanistic mathematical modeling. Initial attempts at modeling this complex multi-scale problem have been made at different scales. At the tissue-level, an ecological model has been developed to describe the interaction between tissue homeostasis, viral infection and neoplastic progression [45]. At the host level, modeling work has provided insights into the role of autoinoculation and its relevance for HPV transmission models [46]. Importantly, because relevant data stems from disparate physical scales, mechanistic multi-scale models will be critical to successfully bridge the gap between gender- and site-specific biologic mechanism and patterns of HPV prevalence and cancer incidence at the population-level. A recent study on the multi-scale dynamics of oral cancer [47] constitutes a first step towards such an integrated paradigm, opening up a wide field of opportunities for MMMs.

5. Conclusion and outlook

When evaluating a new paradigm, it is natural to make comparisons to established frameworks. Therefore, one ought to be mindful about intrinsic differences between mechanistic and health economic modeling. MMMs are usually cast within a basic science framework, and the benchmark for their quality and relevance should be chosen accordingly. More precisely, the quality of a mechanistic model is best judged in the light of the hallmarks of good basic science, such as the ability to identify gaps in knowledge, to challenge long-standing paradigms, to generate, falsify and corroborate hypotheses, and to spur new experimental research. Needless to say, such objectives are not always aligned with immediate public health impact. Another key difference between the two modeling paradigms is the desired degree of complexity. Much like when working with laboratory models, MMMs are aimed at elucidating the mechanistic essence of biological processes rather than providing concrete numerical predictions. Because overly complex models tend to obscure insight into the first principles of a process, a good MMM does not distinguish itself by an excessive degree of complexity, but rather by an economical, transparent and ultimately insightful description of the natural process.

Considering the example of integrated mathematical oncology [48], we find that successful mechanistic modeling in the biomedical sciences thrives in a multi-disciplinary and collaborative setting. Indeed, generating hypotheses and challenging prevailing theories is more likely to spur scientific progress if there is the possibility for targeted data collection and hypothesis testing. The successful application of MMMs rarely occurs in isolation, and fruitful modeling work generally builds on a close interaction with experimentalists. Unfortunately, establishment of collaborations at the interface of theory and experiment is rarely straightforward and may require significant start-up costs to overcome terminological barriers and formulate a tractable question of interest to both parties. However, once the collaboration has been successfully launched, the ensuing cross-disciplinary synergies will likely advance the research program of all participants.

As illustrated by the above examples, MMMs are often of a multi-scale nature, synthesizing data and knowledge sources across physical scales. Indeed, a multi-scale framework enables incorporation of additional and orthogonal data sets that further constrain and inform the models at the individual scales. Furthermore, by providing quantitative bridges between data from disparate physical scales,

MMMs can be used to facilitate and stimulate collaborative efforts between experimentalists working at different physical scales of the same problem. More precisely, MMMs can be used as a catalyst for multidisciplinary science between, e.g., molecular virologists and infectious disease epidemiologists, or cancer biologists and clinicians [48].

If mechanistic modeling efforts in HPV were to follow the trajectory of mathematical oncology, we would hope to see the models eventually reach the clinical setting and enable progress towards personalized approaches in HPV management. Consider, for example, a 60-year-old woman who had catch-up HPV vaccination at age 27, a combination of irregularly spaced cytology and HPV DNA tests after age 30, and a positive DNA test at age 60. As her physician, would you rather advise her based on a one-size-fits-all guideline, or apply a dynamic risk projection model that accounts for her personal history as well as knowledge about the underlying biologic mechanisms? Such is the broad objective of calls for moving away from agnostic algorithm-based cervical cancer screening and triage to a risk-based management paradigm [49] that integrates vaccination and screening into a single prevention program [50]. We argue that MMMs provide us with a unique opportunity to accelerate attaining this goal. Let us not miss this opportunity.

Potential conflicts of interest

MDR has no conflict of interest. PEG has received research reagents and travel support from Hologic, Inc. ERM has received research funding from Merck, Inc., manufacturer of Gardasil, in the past, and currently serves as a consultant to Merck on issues regarding HPV vaccination. Neither Hologic nor Merck have been involved in any way with the research described in this paper, and the results have not been presented or shared with employees or external consultants of either company.

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