Atherosclerosis: reflections on mathematical modelling, data and other matters *

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Abstract Atherosclerosis is a chronic inflammatory disease that can lead to heart attacks and strokes. Atherosclerotic plaques form in the walls of large arteries. Initially their growth is driven by modified low density lipoproteins, immune cells and inflammatory cytokines. As the plaque matures, smooth muscle cells and necrotic material become important constituents, and as it grows, the plaque starts to distort the artery wall. Modelling has started to address many of these phenomena, but is hampered by difficulties collecting, interpreting and fitting data. In this article we reflect on the enterprise of modelling atherosclerotic plaques, progress so far, what now needs to be done and its relation to cognate areas of mathematical modelling, particularly cancer and wound healing.

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1 What is Atherosclerosis? Why should we care?

Atherosclerosis is a chronic disease of the large arteries. In humans it can lead to heart attacks, strokes and peripheral vascular disease.

An atherosclerotic lesion in the artery wall is initiated when low density lipoprotein (LDL) particles that permeate the artery wall become modified and are retained in the intima, the innermost layer of the artery wall. These retained modified LDL particles (modLDL) generate an immune response which includes stimulating the production of inflammatory cytokines (cell signaling substances). In response to these inflammatory cytokines, monocytes (a type of white blood cell and immune cell) are recruited from the blood stream to the intima where they differentiate into macrophages (another type of immune cell). Macrophages ingest the modLDL particles. Since modLDL carries cholesterol and other fatty molecules, the macrophages acquire internalised stores of cholesterol from the modLDL that they ingest. Cholesterol-filled macrophages are often referred to as foam cells, since this internalised fatty material or lipids gives the cell an appearance of being filled with foam [8].

Lipid from these foam cells can be exported to high density lipoprotein particles (HDL) or the cell can leave the plaque, taking its internalised lipid with it. If neither of these things happens, when a foam cell dies, it leaves behind its load of lipid. This is either ingested by another macrophage or becomes free lipid and part of the fatty necrotic (dead) core that a mature plaque develops.

As a plaque matures, it may acquire a fibrous cap made up of collagen and smooth muscle cells from the artery wall. If this cap is strong and stable, then the material in the plaque, including the necrotic core, is safely sequestered from the bloodstream [1]. If the cap is weak then it is susceptible to rupture. When a plaque ruptures, the material from the necrotic core is released into the blood stream where it promotes the formation of blood clots. These blood clots may block the artery, causing a heart attack, if it is a cardiac artery, or a stroke, if the artery is in the brain.

This is a very simple description of the processes behind the formation of an atherosclerotic plaque. There are many finer details, some of which are critically important in determining the fate of a plaque. Some of these are captured diagrammatically in Figure 1.

Atherosclerosis is the leading cause of death worldwide, exceeding the number of deaths caused by cancer. However, whereas there are many mathematical modelling studies exploring the mechanisms underlying cancer development and progression, there are comparatively few mathematical modelling studies of the biological mechanisms underlying atherosclerotic plaque development and progression.

2 Modelling Atherosclerosis

As atherosclerotic plaque development and progression occur over a timescale of decades with cellular level processes occurring on the time scale of seconds, min-

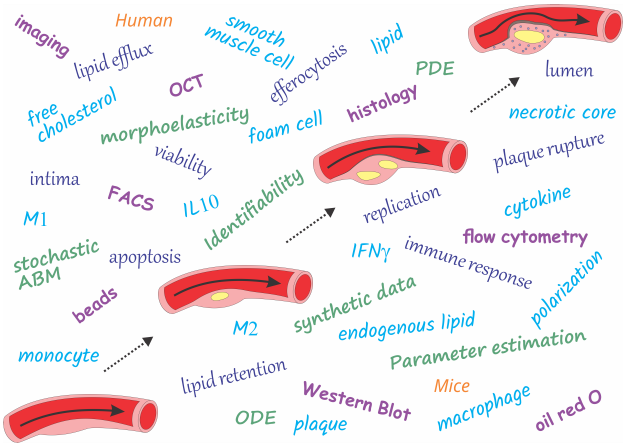

Fig. 1 A schematic diagram of the development of an atherosclerotic plaque. The plaque develops from the lower left hand corner to the upper right hand corner. The surrounding word cloud includes factors that might be incorporated into models at different stages of plaque development or techniques that might be used in modelling.

utes, and hours, most mathematical modelling studies typically focus on one stage of development or progression, typically characterised by early, mid, and late stages. Mathematical modelling studies typically take the form of a system of ordinary differential equations [10] or partial differential equations [4, 7] with, as yet, few agent-based and stochastic-type models (but see [12]). Lipids appear to be fundamental to all mathematical models, with only one model discussed during the workshop explicitly suggesting that lack of oxygen is a key driver of necrosis rather than lipids alone.

It is likely that models for immunological events in plaques will require a suite of different modelling techniques, including multi-scale and discrete models to accurately capture the complex biology of plaque formation that occurs at many scales.

Growing plaques distort the wall of the blood vessel in the latter stages of the disease. The deformation of the artery wall is an important area for classical continuum mechanics modelling, which represents the geometry and morphology of the growing plaque. Much of the current work in this domain is aimed at understanding the changing layered structure of the artery and of the late-stage developing plaque. Linking immunological events with changing plaque morphology via mathematical models is an area of active research [11].

3 Links to experimental and clinical science

Strong collaborations between experimental groups and mathematical modellers are yet to develop in modelling immune events and lipid trafficking in atherosclerosis.

There have certainly been strong collaborations in modelling blood flow and shear stress in atherosclerosis [3], and in modelling cancer and other diseases [14].

There are probably several reasons for this. Modelling the dynamics of lipids and cells in atherosclerosis is a comparatively new endeavour and the field is correspondingly small. Plaque formation, is hidden by its very nature and it is expensive and difficult to do experiments *in vivo*. And finally, it is not clear what exactly modellers can offer experimental scientists and clinicians at this stage of model development.

Most *in vivo* experiments on atherosclerosis are done in genetically modified mice. Generally speaking, mice need to be sacrificed to observe plaques and so only snapshots of plaque progression are possible. For this reason, modelling can provide a useful window into the plaque growth processes and intermediate plaque stages that connect the observed snap shots. However, modellers also need to be aware of the differences in physiology and rate of plaque development between mice (the experimental model) and humans where models, and research generally, will have potential clinical application.

However, as with other biological modelling, a lot of the usefulness of modelling to experimentalists lies in the process of modelling development. "You make me think about my work differently" or a similar statement was made by both experimentalists at the Creswick workshop.

4 Data for models, both real and synthetic

Atherosclerosis is, essentially, a disease of the whole body, so that plaques cannot be isolated and grown *in vitro* for example. Hence it is not surprising that the sort of data required by modellers is far more sparse, than in other cellular systems and cancer. The most scientifically useful models need data for validation and verification. Fitting data to an established model or creating models to fit the experimental data are common in mathematical modelling of biological processes. Extracting meaningful information from data is not merely a technical challenge but also a fundamental scientific question in model development. Modelling of atherosclerosis must address this need for fitting to data and testing against data if it is to progress.

A particular challenge in fitting atherosclerosis models to data is the difficulty in obtaining spatiotemporal *in vivo* data, with snapshot data also challenging to obtain. *In vitro* experiments have been developed to explore specific aspects of atherosclerosis, but they are not able to capture all the features observed *in vivo*. This lack of spatiotemporal data presents challenges for validating and parameterising mechanistic mathematical models, with many parameter values taken from disparate parts of the literature. Consequently, few mathematical models of atherosclerosis have been systematically connected to experimental data, as has been done in the recent cancer mathematical modelling literature. This is a great opportunity for future research.

Synthetic data, generated by simulation models, for example, may be valuable in the absence of experimental data. Such synthetic data can be used in data fitting, as long as we select and verify the data carefully [2]. Unlike real-world data,

which may be limited by factors such as sample size, noise, or missing information, synthetic data can be tailored to specific research questions, providing a more comprehensive understanding of biological phenomena. By combining the flexibility of synthetic data with the ability of stochastic models to capture uncertainty, researchers can gain a deeper understanding of complex biological processes and make more accurate predictions.

Model identifiability may be an important tool to ensure model reliability in systems where data is sparse. Structural identifiability addresses whether unique parameter values can be determined with perfect, noise-free data, and practical identifiability examines the ability to estimate parameters accurately given real-world, noisy, and limited data [9]. Understanding these concepts is particularly important in atherosclerosis modelling, where the complexity of biological processes, such as lipid uptake, inflammation, and cellular interactions within arterial plaques, requires careful model construction and validation to predict specific outcomes effectively.

5 Links to other areas of mathematical modelling

The similarities between wound healing and cancer have been made clear, leading to cancers being referred to as “wounds that do not heal” [6]. The modelling of wound healing and cancer has since been referred to as “two sides of the same coin” [5]. The biological dynamics of atherosclerosis is, in many ways, similar to both cancer and wound healing. The field of mathematical modelling of atherosclerosis can draw upon the fields of mathematical modelling in cancer and wound healing, and vice versa.

In terms of the overlaps in modelling approaches, multiphase models of cancer can (and are) being applied to atherosclerosis [13]. Both cancer growth and wound healing processes rely on angiogenesis (the formation of new blood vessels from existing vasculature). Angiogenesis has been modelled extensively in both biological contexts – this also occurs in late-stage atherosclerotic plaques and is starting to gain traction in associated modelling. A link between chronic wound healing and atherosclerosis that is an open problem for modellers, with clinical application, is the formation and treatment of arterial leg ulcers due to underlying arterial blockages due to atherosclerosis.

6 Looking into the future

Recent research has seen the development of sophisticated immunological models of plaque formation. However, these models typically do not consider the growth and morphological change of the plaque, and, moreover, they lack suitable quantitative validation against experimental data. Both of these issues must be addressed, either separately or together, if plaque formation models are to become truly reliable

and predictive. We foresee that these techniques will be adopted into our research as we look to build and validate increasingly realistic plaque models that can actively contribute to scientific efforts to reduce the burden of cardiovascular disease.

References

1. Bennett, M.R., Sinha, S. Owens, G.K. Vascular smooth muscle cells in atherosclerosis. Circulation Research (2016) 118, 692-702.
2. Bull, J.A., Byrne, H.M. Quantification of spatial and phenotypic heterogeneity in an agent-based model of tumour-macrophage interactions. PLOS Computational Biology (2023) 19, e1010994
3. Callaghan, F.M. and Grieve, S.M. Spatial resolution and velocity field improvement of 4D-flow. MRI Magnetic Resonance in Medicine (2017) 78, 1959–1968.
4. Chalmers, A.D., Bursill, C.A., Myerscough, M.R. Nonlinear dynamics of early atherosclerotic plaque formation may determine the efficacy of High Density Lipoproteins (HDL) in plaque regression. PLOS ONE (2017) 12, e0187674
5. Chaplain, M.A.J., Byrne, H.M. Mathematical modeling of wound healing and tumor growth: Two sides of the same coin. Wounds—A compendium of Clinical Research and Practice. (1996) 8, 42–48.
6. Dvorak, H.F., Flier, J., Frank, H., Tumors—Wounds that do not heal—Similarities between tumor stroma generation and wound-healing. New England Journal of Medicine (1986) 315, 1650–1659.
7. Ford, H.Z., Byrne H.M., Myerscough M.R. A lipid-structured model for macrophage populations in atherosclerotic plaques. Journal of Theoretical Biology (2019) 479, 48–63.
8. Libby P. Inflammation in atherosclerosis. Nature (2002) 420, 868-874.
9. Murphy, R.J., Maclaren, O.J., Simpson, M.J. Implementing measurement error models with mechanistic mathematical models in a likelihood-based framework for estimation, identifiability analysis and prediction in the life sciences. Journal of the Royal Society Interface (2024) 2, 20230402
10. Lui, G., Myerscough, M.R. Modelling preferential phagocytosis in atherosclerosis: delineating timescales in plaque development. Bulletin of Mathematical Biology (2021) 83, 96.
11. Mirzaei, N.M., Weintraub, W.S., Fok, P.W. An integrated approach to simulating the vulnerable atherosclerotic plaque. American Jounral of Physiology–Heart and Circulatory Physiology (2020) 319:H835–H846.
12. Pan, J.C., Cai, Y., He, H.L., Gu, N., Li, Z.Y. A multiscale modeling study of nanoparticle-based targeting therapy against atherosclerosis. Journal of Biomechanics (2024) 166, 112067.
13. Watson, M.G., Byrne, H.M., Macaskill, C., Myerscough M.R. A two-phase model of early fibrous cap formation in atherosclerosis. Journal of Theoretical Biology (2018) 456, 123-136.
14. West, J., Adler, F., Gallaher, J., Strobl, M., Brady-Nicholls, R., Brown, J. Roberson-Tessi, M., Kim, E., Noble, R., Viossat, Y., Basanta, D., Anderson, A.R.A. A survey of open questions in adaptive therapy: Bridging mathematics and clinical translation. eLife (2023) 12, e84263