Mozzie: a computationally efficient simulator for the spatio-temporal modelling of mosquitoes

1 July 2024

Note for reviewers. This paper is to be submitted to the Journal of Open Source Software (JOSS), which is different to many other academic journals. Firstly, the focus is on the software, and less on this article. Secondly, key instructions from JOSS are as follows. (A) The paper should be between 250-1000 words. Authors submitting papers significantly longer than 1000 words may be asked to reduce the length of their paper. (B) The paper needs to include a summary describing the high-level functionality and purpose of the software for a diverse, non-specialist audience. (C) The paper needs to explain the research applications of the software. (D) The paper needs to contain A Statement of Need section that clearly illustrates the research purpose of the software and places it in the context of related work.

Summary

`Mozzie` enables simulation of the lifecycle and spatial spread of mosquitoes. `Mozzie` can be used to assess risks associated with disease-control strategies at local, regional or continental scales. Most particularly, strategies involving genetic alterations of mosquitoes to eliminate malaria, are of prime interest.

More technically, `Mozzie` simulates a population-dynamics model that uses differential equations or delay differential equations (Bohner et al., 2018; El-Hachem & Beeton, 2024) to describe the spread and persistence of mosquitoes that may be genetic altered. Genetic alterations are flexibly modelled: these can involve any number of alleles; Mendelian or non-Mendelian inheritance, including gene drives; they can be self-limiting or self-sustaining; and can include the emergence of resistant alleles. The model allows simulation of N mosquito species. It incorporates mate-choice, hybridisation and intra-specific competition that occur within complexes of mosquito species (Beeton et al., 2020). This fills a gap that currently exists among similar models, allowing researchers to assess potential transfer of the genetic alterations between (sub-)species.

`Mozzie` supports spatial and temporal variations in lifecyle parameters, and local diffusion and wind-assisted, long range, advection. For example, wind patterns and the capacity of the landscape to support mosquitoes can vary spatially and temporally, reflecting daily variations, seasonality, and local conditions.

Conversely, `Mozzie` does not contain human agents, nor does it consider the effect of genetic control strategies on the prevalence of pathogens such as the malaria parasite, among human or animal populations.

`Mozzie` has been used by the authors to simulate the spread across sub-Saharan Africa of a theoretical, population-modifying, gene drive in *Anopheles gambiae s.s.* and *Anopheles coluzzii* (Beeton et al., 2022) (that paper also describes the mathematics of a particular mosquito lifecycle model that is contained in `Mozzie`). It has also been used to predict the spread of Target Malaria's Paternal Male Bias construct (Galizi et al., 2014) following a proposed field-release of genetically modified *Anopheles coluzzi* male mosquitoes in Burkina Faso (Hosack et al., 2023).

Statement of need

The numerical implementation of Mozzie is ecologically interpretable (Hosack et al., 2023) and computationally and I/O efficient. This allows rapid simulation at continental scales to investigate sensitivity to input parameters, as required in risk assessments. It is written in Cython (Behnel et al., 2011) (a mixture of Python and C), and simulations are run using Python. The test coverage of the `Mozzie` codebase is over 99%, meaning it is also suitable for risk assessments that could be subject to considerable scrutiny.

Alternatives to `Mozzie` include:

- MIT's HYDREMATS software (Bomblies et al., 2009). HYDREMATS is a coupled hydrology and entomology model that uses an agent-based approach for mosquito-human dynamics, and focuses on high-resolution village-scale understanding of malaria without genetically-modified mosquitoes.
- The well-established SkeeterBuster focuses on the *Aedes aegypti* species in order to understand insecticidal control measures such as spraying (Gunning et al., 2022; Magori et al., 2009). A stochastic, mechanistic approach is employed.
- OpenMalaria (T. Smith et al., 2006) is an open-source C++ program enabling simulation of malaria epidemiology, typically at the village scale, in order to assess the efficacy of non-genetic malaria interventions.
- IDM's EMOD software can simulate malaria epidemiology using an agent-based approach, with spatial structure based on a network (Bershteyn et al., 2018). Less emphasis is spent on genetic modifications, and a single mosquito species is the focus.
- The dynamAedes R package can be used to study the spatio-temporal

evolution of a single mosquito species, with particular attention paid to the impact of temperature heterogeneity.

- The exDE R package solves models of mosquito-borne pathogen dynamics and control (Wu et al., 2023). Attention is payed to sophisticated representations of mosquito lifecycles, including exogenous forcing by weather and vector control, as well as mosquito-malaria-human interatctions. Although a single mosquito species is the focus, the framework allows for multiple species. The code centers on traditional vector controls, rather than genetic controls.
- Berkeley's MGDrivE is an open-source framework to study gene-drives in mosquito populations (Mondal et al., 2024; Sánchez C. et al., 2019), which is written in R. With regards to lifecycle dynamics, MGDrivE has similar functionality to `Mozzie`, although MGDrivE focuses on single species, in contrast to `Mozzie` where transfer of genetic constructs between (sub-)species is of interest. MGDrivE's spatial structure is based on a network, where each node in the network could be thought of as a household, house block, or even a city. In terms of functionality, MGDrivE is the most similar to `Mozzie`, although the numerical methods employed are quite different.

If spatially explicit, these model spatial structure using a network. In contrast, `Mozzie` uses a continuous-space (diffusion-advection equation) approach, deliberately incorporating long-range dispersal in a way that is ecologically interpretable (Hosack et al., 2023). In addition, `Mozzie` does not focus on single species, but concentrates on the interaction of multiple (sub-)species. Many of the aforementioned alternatives contain human agents and the malaria parasite, which `Mozzie` does not.

In addition to the publicly available codes mentioned above, many academic articles consider the lifecycle and spatial spread of mosquitoes, for example (Bruzzone & Utgés, 2022; Dufourd & Dumont, 2013; Dye & Cain, 2024; Endo & Eltahir, 2018; Fang et al., 2020; Fernández-Carrión et al., 2018; Lutambi et al., 2013; North et al., 2013; Roques & Bonnefon, 2016; Silva et al., 2020; N. R. Smith et al., 2018; Yamashita, Takahashi, et al., 2018; Yamashita, Das, et al., 2018), but few have published their code. Most appear to rely on unpublished scripts in codes such as MATLAB (Fernández-Carrión et al., 2018; Lutambi et al., 2013; Yamashita, Das, et al., 2018), or concentrate on specialised scenarios (Bruzzone & Utgés, 2022; Roques & Bonnefon, 2016).

Example

Figure 1 shows results from `Mozzie` simulations when using 2 inter-breeding, hybridising and competing mosquito species (Beeton et al., 2022). A gene-drive is introduced into one of these species, and the modified individuals are released from one of 15 sites throughout sub-Saharan Africa.

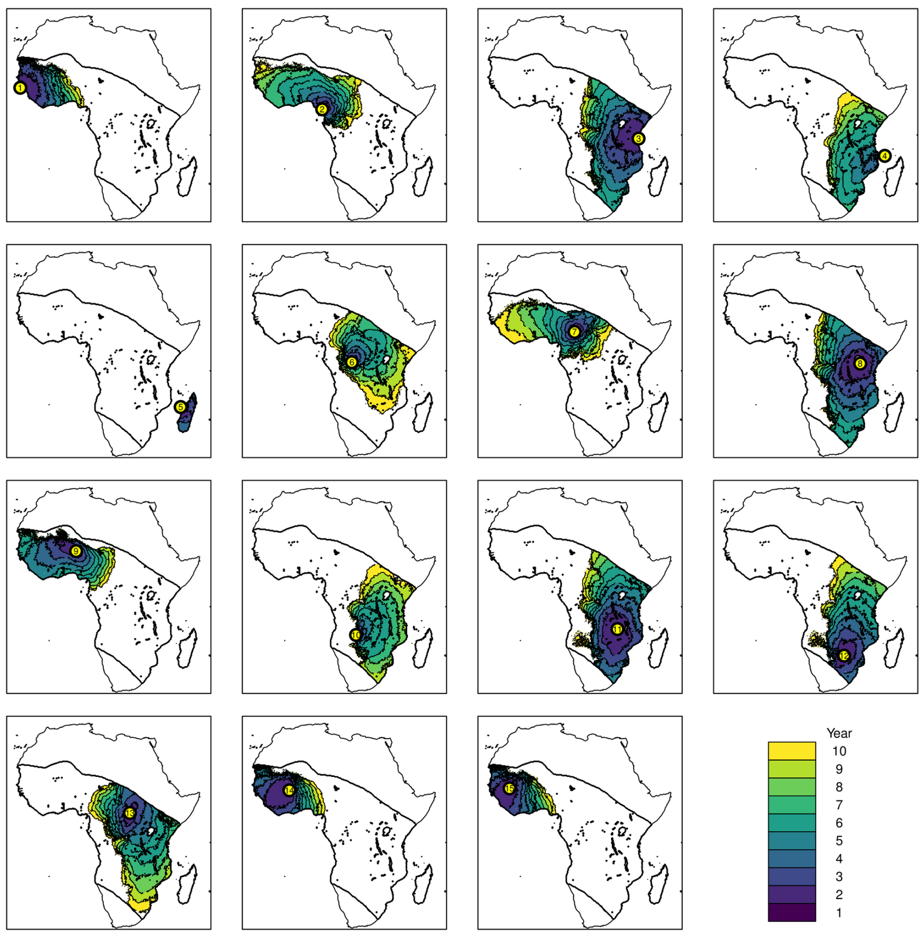

Figure 1: The invasion front of genetically-modified mosquito species from a selection of starting point, from (Beeton et al., 2022).

Acknowledgements

This work was supported, in whole or in part, by the Bill & Melinda Gates Foundation (**grant number, supplied after approval**). Under the grant conditions of the Foundation, a Creative Commons Attribution 4.0 Generic License has already been assigned to the Author Accepted Manuscript version that might arise from this submission.

References

Beeton, N. J., Hosack, G. R., Wilkins, A., Forbes, L. K., Ickowicz, A., & Hayes, K. R. (2020). Modelling competition between hybridising subspecies. *Journal of Theoretical Biology*, *486*, 110072. https://doi.org/10.1016/j.jtbi.2019.110072

Beeton, N. J., Wilkins, A., Ickowicz, A., Hayes, K. R., & Hosack, G. R. (2022). Spatial modelling for population replacement of mosquito vectors at continental scale. *PLoS Computational Biology*, *18*, e1009526. https://doi.org/10.1371/journal.pcbi.1009526

Behnel, S., Bradshaw, R., Citro, C., Dalcin, L., Seljebotn, D. S., & Smith, K. (2011). Cython: The Best of Both Worlds. *Computing in Science Engineering*, *13*(2), 31–39. https://doi.org/10.1109/MCSE.2010.118

Bershteyn, A., Gerardin, J., Bridenbecker, D., Lorton, C. W., Bloedow, J., Baker, R. S., Chabot-Couture, G., Chen, Y., Fischle, T., Frey, K., Gauld, J. S., Hu, H., Izzo, A. S., Klein, D. J., Lukacevic, D., McCarthy, K. A., Miller, J. C., Ouedraogo, A. L., Perkins, T. A., … Institute for Disease Modeling. (2018). Implementation and applications of EMOD, an individual-based multi-disease modeling platform. *Pathogens and Disease*, *76*(5), fty059. https://doi.org/10.1093/femspd/fty059

Bohner, M., Dannan, F. M., & Streipert, S. (2018). A nonautonomous Beverton–Holt equation of higher order. *Journal of Mathematical Analysis and Applications*, *457*(1), 114–133. https://doi.org/10.1016/j.jmaa.2017.07.051

Bomblies, A., Duchemin, J.-B., & Eltahir, E. A. B. (2009). A mechanistic approach for accurate simulation of village scale malaria transmission. *Malaria Journal*, *8*, 223. https://doi.org/10.1186/1475-2875-8-223

Bruzzone, O. A., & Utgés, M. E. (2022). Analysis of the invasion of a city by *Aedes aegypti* via mathematical models and Bayesian statistics. *Theoretical Ecology*, *15*, 65–80. https://doi.org/10.1007/s12080-022-00528-y

Dufourd, C., & Dumont, Y. (2013). Impact of environmental factors on mosquito dispersal in the prospect of sterile insect technique control. *Computers and Mathematics with Applications*, *66*(9), 1695–1715. https://doi.org/10.1016/j.camwa.2013.03.024

Dye, D., & Cain, J. W. (2024). Efficacy of Wolbachia-based mosquito control: Predictions of a spatially discrete mathematical model. *PLoS One*, *19*(3), e0297964. https://doi.org/10.1371/journal.pone.0297964

El-Hachem, M., & Beeton, N. J. (2024). Coexistence in two-species competition with delayed maturation. *Journal of Mathematical Biology*, *88*(1). https://doi.org/10.1007/s00285-023-02031-2

Endo, N., & Eltahir, E. A. B. (2018). Modelling and observing the role of wind in Anopheles population dynamics around a reservoir. *Malaria Journal*, *17*(1), 48. https://doi.org/10.1186/s12936-018-2197-5

Fang, J., Lai, X., & Wang, F.-B. (2020). Spatial dynamics of a dengue transmission model in time-space periodic environment. *Journal of Differential Equations*, *269*(8), 149–175. https://doi.org/10.1016/j.jde.2020.04.034

Fernández-Carrión, E., Ivorra, B., Ramos, Á. M., Martínez-López, B., Aguilar-Vega, C., & Sánchez-Vizcaíno, J. M. (2018). An advection-deposition-survival model to assess the risk of introduction of vector-borne diseases through the wind: Application to bluetongue outbreaks in Spain. *PLoS One*, *13*(3), e0194573. https://doi.org/10.1371/journal.pone.0194573

Galizi, R., Doyle, L. A., Menichelli, M., Bernardini, F., Deredec, A., Burt, A., Stoddard, B. L., Windbichler, N., & Crisanti, A. (2014). A synthetic sex ratio distortion system for the control of the human malaria mosquito. *Nature Communications*, *5*(1). https://doi.org/10.1038/ncomms4977

Gunning, C. E., Morrison, A. C., Okamoto, K. W., Scott, T. W., Astete, H., Vásquez, G. M., Gould, F., & Lloyd, A. L. (2022). A critical assessment of the detailed *Aedes aegypti* simulation model Skeeter Buster 2 using field experiments of indoor insecticidal control in Iquitos, Peru. *PLOS Neglected Tropical Diseases*, *16*(12), 1–26. https://doi.org/10.1371/journal.pntd.0010863

Hosack, G. R., Beeton, N. J., Ickowicz, A., Peel, D., Wilkins, A., Dambacher, J. M., Wickramarachchi, A., McDonald, M., Tay, W. T., Wilson, L., Bauer, D., & Hayes, K. R. (2023). *Risk assessment for controlling mosquito vectors with engineered nucleases: Paternal male bias construct*. CSIRO. https://doi.org/10.25919/2t8h-5k81

Lutambi, A. M., Penny, M. A., Smith, T., & Chitnis, N. (2013). Mathematical modelling of mosquito dispersal in a heterogeneous environment. *Mathematical Biosciences*, *241*(2), 198–216. https://doi.org/10.1016/j.mbs.2012.11.013

Magori, K., Legros, M., Puente, M. E., Focks, D. A., Scott, T. W., Lloyd, A. L., & Gould, F. (2009). Skeeter Buster: A stochastic, spatially explicit modeling tool for studying *Aedes aegypti* population replacement and population suppression strategies. *PLoS Neglected Tropical Diseases*, *3*(9), e508.

Mondal, A., Sánchez C, H. M., & Marshall, J. M. (2024). MGDrivE 3: A decoupled vector-human framework for epidemiological simulation of mosquito genetic control tools and their surveillance. *PLOS Computational Biology*, *20*(5), e1012133.

North, A., Burt, A., & Godfray, H. C. J. (2013). Modelling the spatial spread of a homing endonuclease gene in a mosquito population. *Journal of Applied Ecology*, *50*(5), 1216–1225. https://doi.org/10.1111/1365-2664.12133

Roques, L., & Bonnefon, O. (2016). Modelling Population Dynamics in Realistic Landscapes with Linear Elements: A Mechanistic-Statistical Reaction-Diffusion Approach. *PLoS ONE*, *11*(3), e0151217. https://doi.org/10.1371/journal.pone.0151217

Sánchez C., H. M., Wu, S. L., Bennett, J. B., & Marshall, J. M. (2019). MGDrivE: A modular simulation framework for the spread of gene drives through spatially-explicit mosquito populations. *Methods in Ecology and Evolution*, *11*. https://doi.org/10.1111/2041-210X.13318

Silva, M. R., Lugão, P. H. G., & Chapiro, G. (2020). Modeling and simulation of the spatial population dynamics of the *Aedes aegypti* mosquito with an insecticide application. *Parasites and Vectors*, *13*(1), 550. https://doi.org/10.1186/s13071-020-04426-2

Smith, N. R., Trauer, J. M., Gambhir, M., Richards, J. S., Maude, R. J., Keith, J. M., & Flegg, J. A. (2018). Agent-based models of malaria transmission: a systematic review. *Malaria Journal*, *17*, 299. https://doi.org/10.1186/s12936-018-2442-y

Smith, T., Killeen, G. F., Maire, N., Ross, A., Molineaux, L., Tediosi, F., Hutton, G., Utzinger, J., Dietz, K., & Tanner, M. (2006). Mathematical Modelling of the Impact of Malaria Vaccines on the Clinical Epidemiology and Natural History of Plasmodium Falciparum Malaria: Overview. *The American Journal of Tropical Medicine and Hygiene*, *75*, 1–10. https://doi.org/10.4269/ajtmh.2006.75.2_suppl.0750001

Wu, S. L., Henry, J. M., Citron, D. T., Ssebuliba, D. M., Nsumba, J. N., Sánchez C., H. M., Brady, O. J., Guerra, C. A., García, G. A., Carter, A. R., Ferguson, H. M., Afolabi, B. E., Hay, S. I., Reiner, Jr., R. C., Kiware, S., & Smith, D. L. (2023). Spatial dynamics of malaria transmission. *PLOS Computational Biology*, *19*(6), 1–42. https://doi.org/10.1371/journal.pcbi.1010684

Yamashita, W. M. S., Das, S. S., & Chapiro, G. (2018). Numerical modeling of mosquito population dynamics of *Aedes aegypti*. *Parasites and Vectors*, *11*(1), 245. https://doi.org/10.1186/s13071-018-2829-1

Yamashita, W. M. S., Takahashi, L. T., & Chapiro, G. (2018). Traveling wave solutions for the dispersive models describing population dynamics of *Aedes aegypti*. *Mathematics and Computers in Simulation*, *146*, 90–99. https://doi.org/10.1016/j.matcom.2017.10.012