

Challenges in modeling complex multi-host infectious diseases: West Nile virus spread and its dependence on climatic conditions

NORDITA – Unifying the epidemiological and evolutionary dynamics of pathogens

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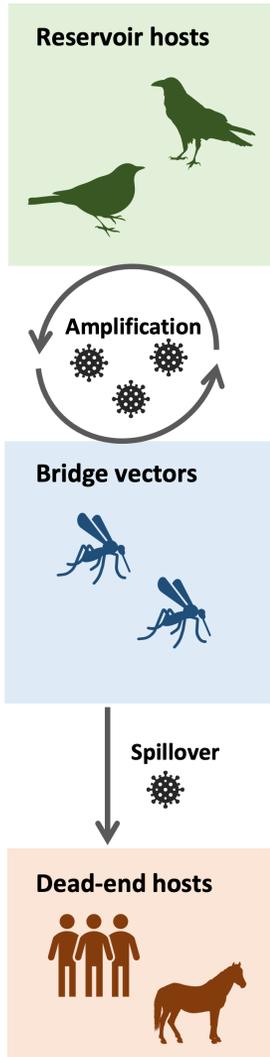
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Content

- Historic & current epidemiological WNV situation
- Dynamical models of WNV: transmission cycle & general setup
- Challenges in modeling WNV dynamics
 - Birds
 - Mosquitoes
 - Climate sensitivity
- Summary

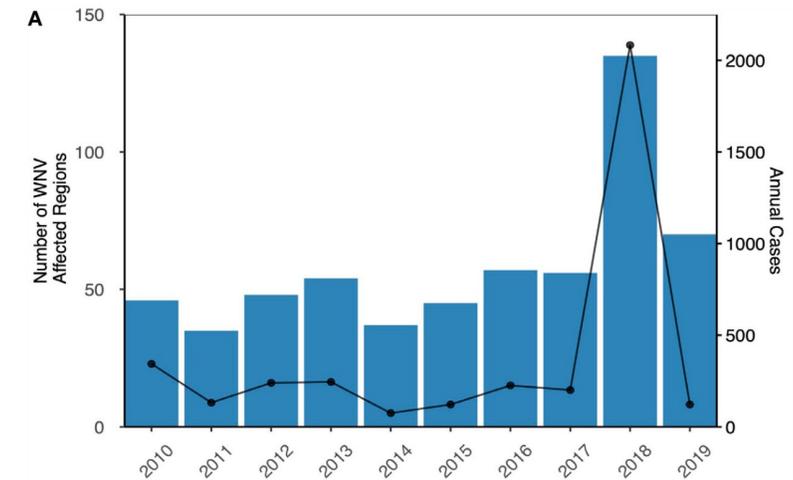


Background

- WNV is a flavivirus with an almost global distribution
- Transmitted by mosquitoes (mainly genus *Culex*)
- Birds (mainly passerines) are the reservoir hosts
- Humans, equids, other mammals are dead-end hosts
- Infection in reservoir and dead-end host can result in severe disease
 - ~25% of human infections develop into West Nile fever
 - ~1% develop neuroinvasive disease which carries 10% CFR
- No pharmaceutical prevention or treatment options for human infections

History and recent expansion of WNV

- First human case observed in West Nile district in Uganda 1937
- Until early 90s sporadic cases and outbreaks in Africa, Eurasia, and Middle East
- On the rise during recent decades:
 - Introduction to Americas in 1999
 - Expansion and intensification in Europe since late 1990s
- Strong evidence that changes in climate can create more suitable conditions driving and facilitating such processes



Source: Farooq et al. 2022

Role of models in WNV research

Process-based dynamical models

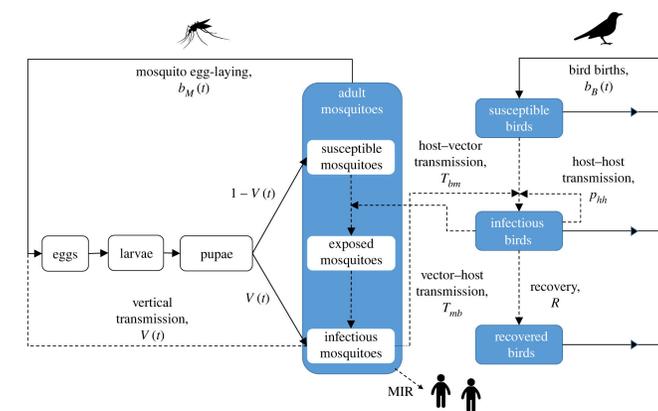
- Biological/Ecological mechanisms
- Simulation of outbreaks and seasonal patterns
- Testing of hypotheses
- Can directly incorporate interventions
- Highly interpretable but hard to build and parameterize

Data-driven statistical & machine learning models

- Build associations between predictors and disease occurrence
- Good at predicting presence/absence
- Can be hard to interpret

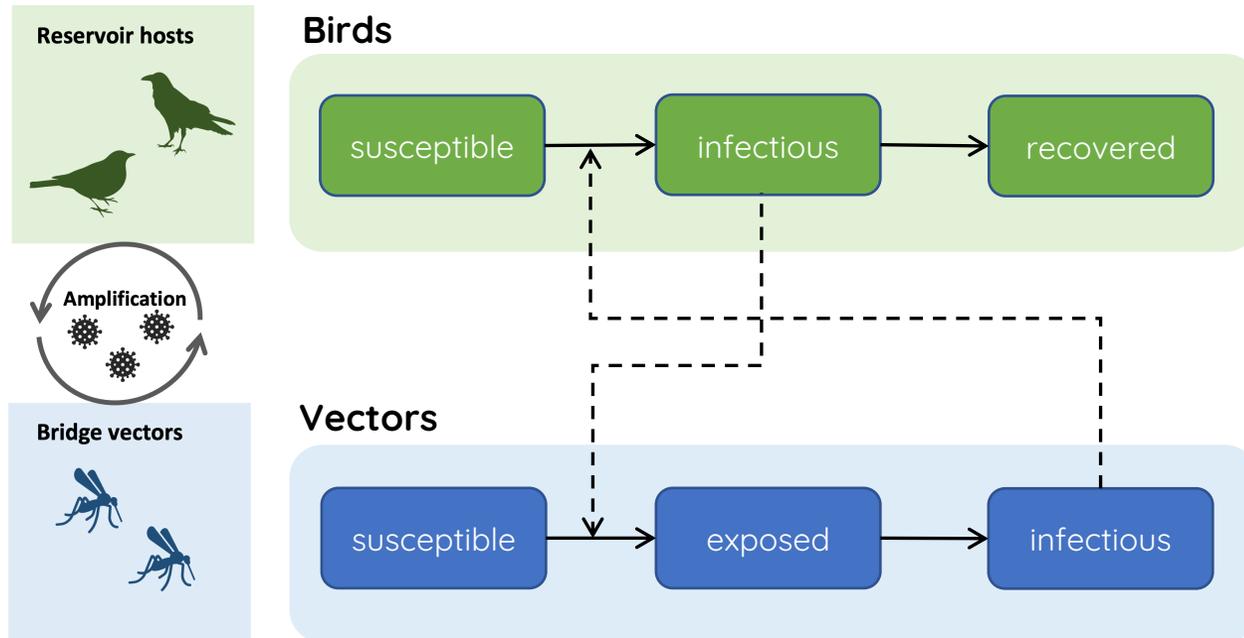
Both provide means for

- Early-warning systems
- Climate change trend estimates & projections



Source: Ewing et al. 2019

WNV transmission cycle - a first simple dynamical model



$$\dot{S}_B = \Lambda_B - a \cdot b_B \cdot I_M \cdot \frac{S_B}{N_B} - \mu_B S_B$$

$$\dot{I}_B = a \cdot b_B \cdot I_M \cdot \frac{S_B}{N_B} - \gamma_B I_B - \mu_B I_B$$

$$\dot{R}_B = \gamma_B I_B - \mu_B R_B$$

$$\dot{S}_M = \Lambda_M - a \cdot b_M \cdot p_B \cdot S_M \cdot \frac{I_B}{N_B} - \mu_M S_M$$

$$\dot{E}_M = a \cdot b_M \cdot p_B \cdot S_M \cdot \frac{I_B}{N_B} - (\alpha + \mu_M) E_M$$

$$\dot{I}_M = \alpha E_M - \mu_M I_M$$

Parameters

Λ_M : mosquito birth rate

a : biting rate

b_M : vector competence

μ_M : vector mortality rate

$1/\alpha$: extrinsic incubation period

Λ_B : host recruitment rate

p_B : host competence

b_B : host susceptibility

μ_B : host mortality rate

γ_B : host recovery rate

Basic reproduction number

Differential equation system

Hosts

$$\dot{S}_B = \Lambda_B - a \cdot b_B \cdot I_M \cdot \frac{S_B}{N_B} - \mu_B S_B$$

$$\dot{I}_B = a \cdot b_B \cdot I_M \cdot \frac{S_B}{N_B} - \gamma_B I_B - \mu_B I_B$$

$$\dot{R}_B = \gamma_B I_B - \mu_B R_B$$

Mosquitoes

$$\dot{S}_M = \Lambda_M - a \cdot b_M \cdot p_B \cdot S_M \cdot \frac{I_B}{N_B} - \mu_M S_M$$

$$\dot{E}_M = a \cdot b_M \cdot p_B \cdot S_M \cdot \frac{I_B}{N_B} - (\alpha + \mu_M) E_M$$

$$\dot{I}_M = \alpha E_M - \mu_M I_M$$

Spectral radius of K:
$$R_0 = \sqrt{\frac{a^2 b_M p_B b_B p^{EIP} \frac{N_M^*}{N_B^*}}{\mu_M (\gamma_B + \mu_B)}}$$

“New infections per generation”

Next generation matrix

$$K = \begin{bmatrix} 0 & \frac{ab_B p^{EIP}}{\mu_M} & \frac{ab_B}{\mu_M} \\ \frac{ab_M p_B \frac{N_M^*}{N_B^*}}{\gamma_B + \mu_B} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

DFE: $(N_B^*, 0, 0, N_M^*, 0, 0)$, $N_B^* = \frac{\Lambda_B}{\mu_B}$, $N_M^* = \frac{\Lambda_M}{\mu_M}$

prob. to survive latent: $p^{EIP} = \frac{\alpha}{\alpha + \mu_M}$, also common: $p^{EIP} = e^{-\mu_M \tau}$

$$R_0^2 = \frac{a^2 b_M p_B b_B p^{EIP} \frac{N_M^*}{N_B^*}}{\mu_M (\gamma_B + \mu_B)} = \frac{ab_M p_B \frac{N_M^*}{N_B^*}}{\gamma_B + \mu_B} * \frac{ab_B p^{EIP}}{\mu_M}$$

“New infections per cycle”

My project

Central incentive: Model of seasonal WNV transmission in Europe

Key goals

- Incorporate established biological mechanisms
- Include known & suspected climatic (and land cover) drivers
- Process-based model to study seasonal patterns, interventions, and climate change impacts
- Pay attention to avian hosts ecology
 - **Role of host mobility?**

Building blocks

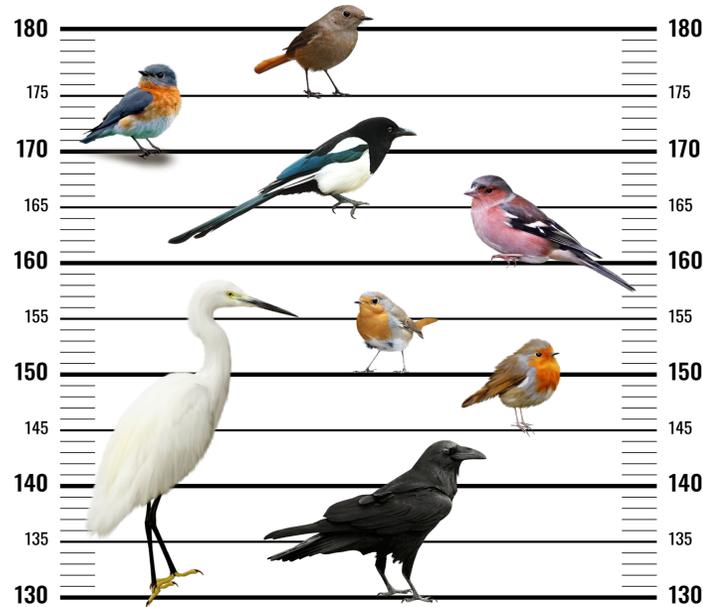
- Mosquito population model
- Bird population model
- Local transmission model
- Movement model

Challenges in modeling WNV dynamics

- Birds
- Mosquitoes
- Climate sensitivity

Challenges 1: Birds

Who is to blame?



$$R_0 = \frac{\alpha^2 b_M b_B p^{EIP} \frac{N_M^*}{N_B^*}}{\mu_M (\gamma_B + \mu_B)}$$

- early studies focused on host species abundance, host infectiousness/competence, and serology
 - later it became clear that these factors alone can be misleading
 - missing component: **mosquito host/biting preference!**
- Preferred species can act as sink or source of transmission depending on their host competence
- information about the decisive factors: abundance, competence, and mosquito biting preference only available for few species and locations

The problem with host competence

- It is common practice to calculate host competence from species' viraemia profile and generalized viraemia-infectiousness relationships

EMERGING INFECTIOUS DISEASES® ISSN: 1080-6059

EID Journal > Volume 9 > Number 3—March 2003 > Main Article

Volume 9, Number 3—March 2003

Research

Experimental Infection of North American Birds with the New York 1999 Strain of West Nile Virus

Nicholas Komar*, Stanley Langevin*, Steven Hinten*, Nicole M. Nemeth*†, Eric Edwards*†, Danielle L. Hettler*†, Brent S. Davis*, Richard A. Bowen†, and Michel L. Bunning*‡

Author affiliations: *Centers for Disease Control and Prevention, Fort Collins, Colorado, USA; †Colorado State University, Fort Collins, Colorado, USA; ‡Office of the Surgeon General, United States Air Force, Bolling Air Force Base, Washington, D.C., USA

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- Based on these host competence indices phylogenetic imputation has been used to predict community competence

RESEARCH Open Access

Predicting West Nile virus transmission in North American bird communities using phylogenetic mixed effects models and eBird citizen science data

Morgan P. Kain¹ and Benjamin M. Bolker^{1,2}



- Unfortunately

PLOS **NEGLECTED TROPICAL DISEASES**

RESEARCH ARTICLE

Bird species define the relationship between West Nile viremia and infectiousness to *Culex pipiens* mosquitoes

Jefferson A. Vaughan^{1*}, Robert A. Newman¹, Michael J. Turell^{2*}

¹ Department of Biology, University of North Dakota, Grand Forks, North Dakota, United States of America, ² Virology Division, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland, United States of America

General model with preferred host species

Avian host species 1

$$\dot{S}_{B_M} = \Lambda_{B_M} - a \cdot b_{B_M} \cdot I_M \cdot \frac{\sigma_{B_M} S_{B_M}}{\sigma_{B_M} N_{B_M} + N_{B_R}} - \mu_{B_M} S_{B_M}$$

$$\dot{I}_{B_M} = a \cdot b_{B_M} \cdot I_M \cdot \frac{\sigma_{B_M} S_{B_M}}{\sigma_{B_M} N_{B_M} + N_{B_R}} - (\gamma_{B_M} + \mu_{B_M}) I_{B_M}$$

$$\dot{R}_{B_M} = \gamma_{B_M} I_{B_M} - \mu_{B_M} R_{B_M}$$

Avian host species 2

$$\dot{S}_{B_R} = \Lambda_{B_R} - a \cdot b_{B_R} \cdot I_M \cdot \frac{S_{B_R}}{\sigma_{B_M} N_{B_M} + N_{B_R}} - \mu_{B_R} S_{B_R}$$

$$\dot{I}_{B_R} = a \cdot b_{B_R} \cdot I_M \cdot \frac{S_{B_R}}{\sigma_{B_M} N_{B_M} + N_{B_R}} - (\gamma_{B_R} + \mu_{B_R}) I_{B_R}$$

$$\dot{R}_{B_R} = \gamma_{B_R} I_{B_R} - \mu_{B_R} R_{B_R}$$

Mosquitoes

$$\dot{S}_M = \Lambda_M - a \cdot b_M \cdot S_M \cdot \frac{p_{B_M} \sigma_{B_M} I_{B_M} + p_{B_R} I_{B_R}}{\sigma_{B_M} N_{B_M} + N_{B_R}} - \mu_M S_M$$

$$\dot{E}_M = a \cdot b_M \cdot S_M \cdot \frac{p_{B_M} \sigma_{B_M} I_{B_M} + p_{B_R} I_{B_R}}{\sigma_{B_M} N_{B_M} + N_{B_R}} - (\alpha + \mu_M) E_M$$

$$\dot{I}_M = \alpha E_M - \mu_M I_M$$

$\sigma_{B_M} > 1 \rightarrow$ Species 1 preferred by mosquitoes

$\sigma_{B_M} < 1 \rightarrow$ Species 2 preferred by mosquitoes

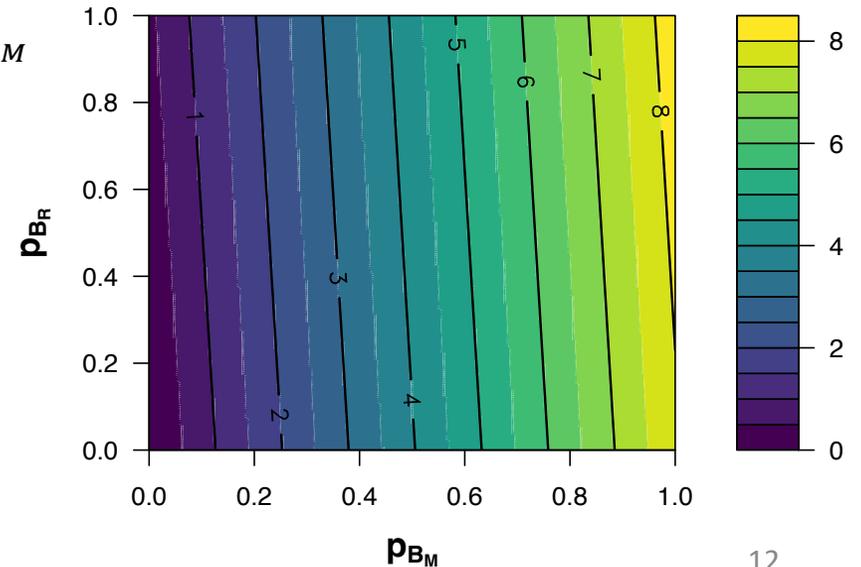
Basic reproduction number

$$R_0 = \frac{ab_M p_{B_M} \frac{\sigma_{B_M} N_M^*}{\sigma_{B_M} N_{B_M}^* + N_{B_R}^*} ab_{B_M} \frac{\sigma_{B_M} N_{B_M}^*}{\sigma_{B_M} N_{B_M}^* + N_{B_R}^*} p^{EIP}}{\gamma_{B_M} + \mu_{B_M} \mu_M} + \frac{ab_M p_{B_R} \frac{N_M^*}{\sigma_{B_M} N_{B_M}^* + N_{B_R}^*} ab_{B_R} \frac{N_{B_R}^*}{\sigma_{B_M} N_{B_M}^* + N_{B_R}^*} p^{EIP}}{\gamma_{B_R} + \mu_{B_R} \mu_M}$$

$$\sigma_{B_M} = 10$$

$$N_{B_R}^* = 5N_{B_M}^*$$

R0 in relation to host competence



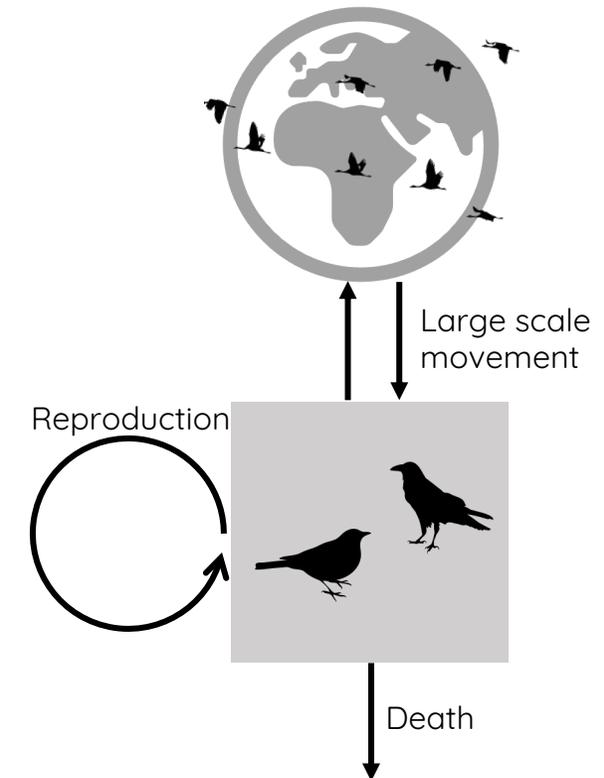
Host ecology - model host population

$$\dot{N}_{BR} = \beta_{BR}(t)N_{BR} - (d_{BR} + h_{BR}(t, N_B))N_{BR}$$

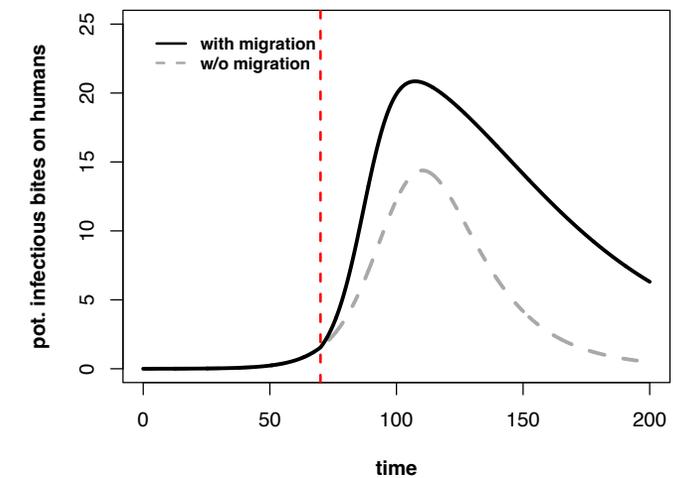
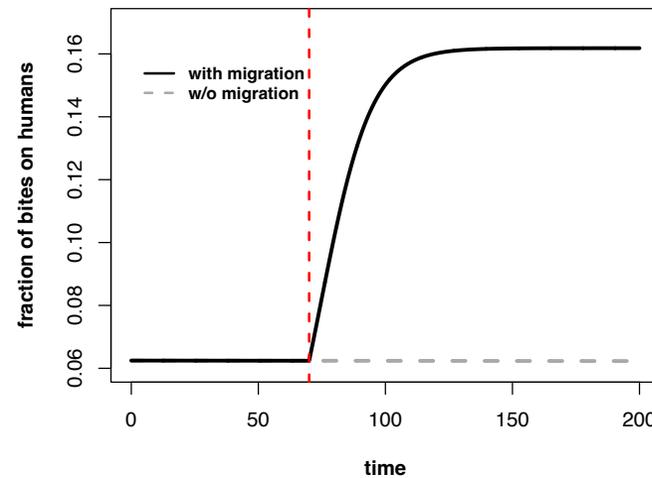
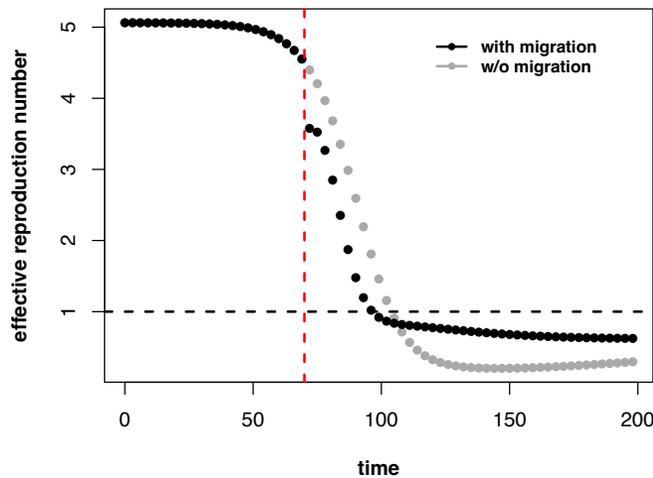
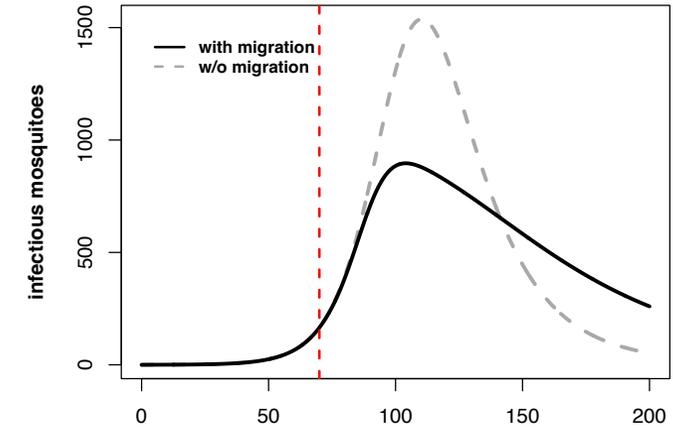
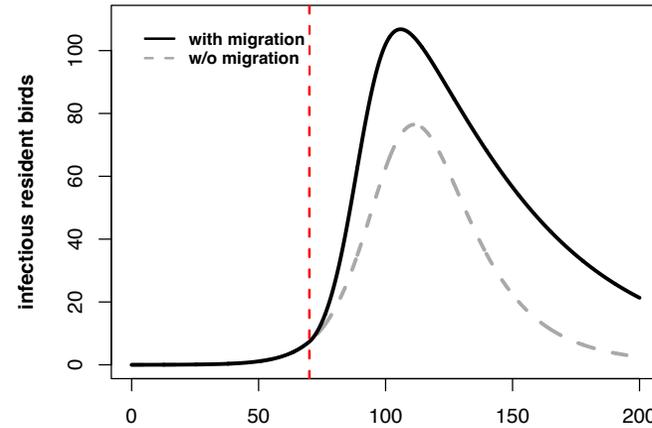
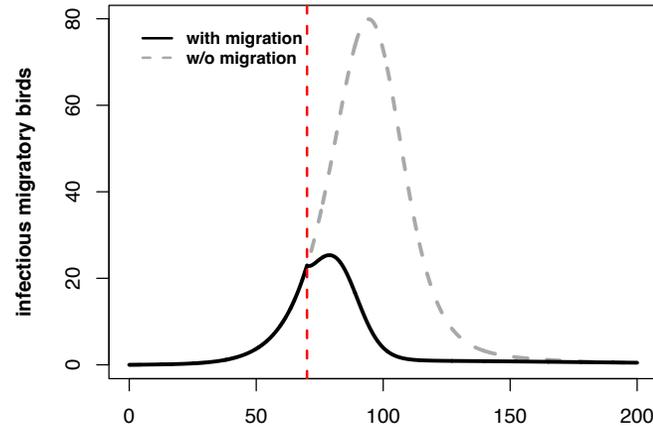
$$\dot{N}_{BM} = \Omega_I(t) + \beta_{BM}(t)N_{BM} - (d_{BM} + h_{BM}(t, N_B))N_{BM} - \Omega_E(t)N_{BM}$$

$$N_B(t) = N_{BR}(t) + N_{BM}(t)$$

- Differentiate resident N_{BR} & migratory N_{BM} populations
- Birds in temperate regions only breed in spring and summer
→ $\beta_X(t)$ should capture seasonal birth pulse
- $h_X(\cdot)$ describe density-dependent mortality
→ usually highest during breeding season
→ likely depends on local resource avail. (land cover etc.)
- $\Omega_I(t), \Omega_E(t)$ are immigration and emigration, resp.
→ represent seasonal migration (pulse in spring/fall)
- Local movements (where do species really co-occur)?



Simulation of hypothetical scenario: Migration of preferred bird species slows down outbreak and shifts mosquito bites



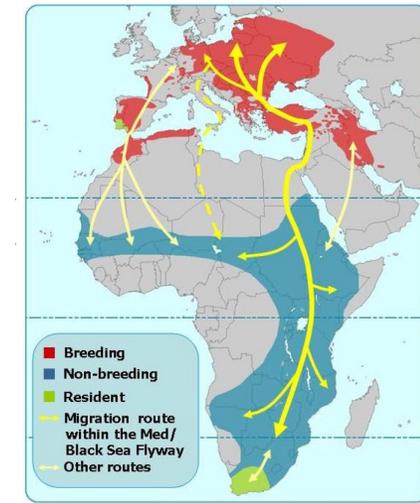
Bigger picture - Large scale seasonal migrations of birds

- Twice a year millions of birds migrate in response to biological needs
- Provides mechanism to spread pathogens along migration routes
- Shifts to species distribution and abundance can impact local transmission

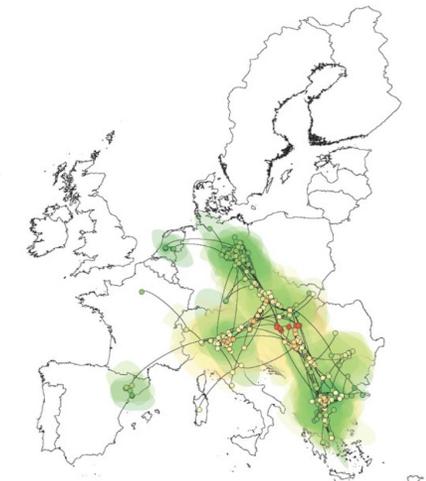
Impact on WNV?

It is unclear... but:

- Reintroductions of WNV to temperate regions likely not needed for seasonal transmission
- Impacts on local transmission have been observed
- Phylogenetic studies show rapid “long”-distance movements
- Likely played a role in rapid dissemination of WNV in North America and might act in synergy with climate change in Europe



Source: BirdLife International



Source: Lu et al. 2023

Modeling bird migrations

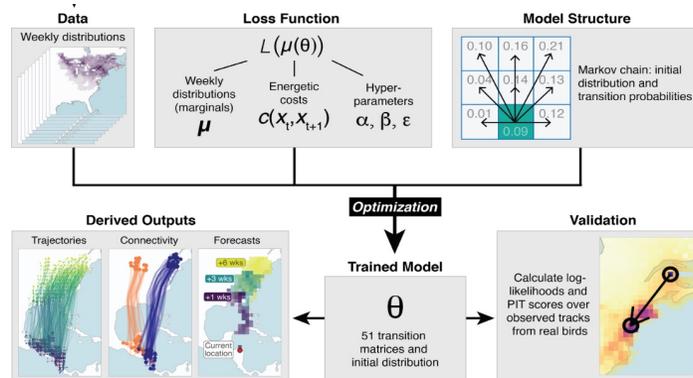
Received: 31 March 2022 | Accepted: 9 November 2022
DOI: 10.1111/2041-210X.14052

RESEARCH ARTICLE

Methods in Ecology and Evolution

BirdFlow: Learning seasonal bird movements from eBird data

Miguel Fuentes¹ | Benjamin M. Van Doren² | Daniel Fink² | Daniel Sheldon¹



Markov model derived from species-specific abundance data

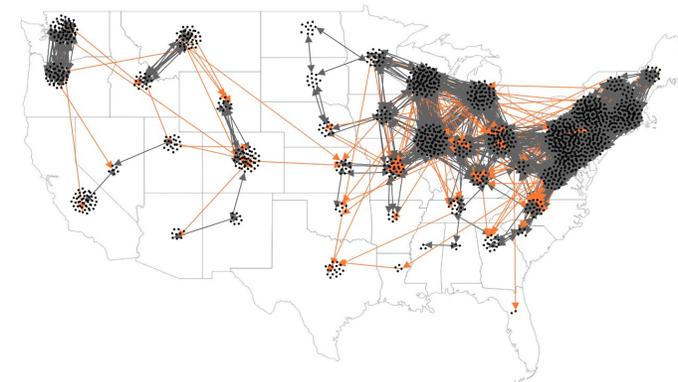
RESEARCH ARTICLE

A spatio-temporal individual-based network framework for West Nile virus in the USA: Spreading pattern of West Nile virus

Sifat A. Moon¹, Lee W. Cohnstaedt^{2*}, D. Scott McVey², Caterina M. Scoglio¹

¹ Department of Electrical & Computer Engineering, Kansas State University, Manhattan, Kansas, United States of America, ² Arthropod-Borne Animal Diseases Research Unit, Center for Grain and Animal Health Research, USDA ARS, Manhattan, Kansas, United States of America

* Lee.Cohnstaedt@ARS.USDA.GOV

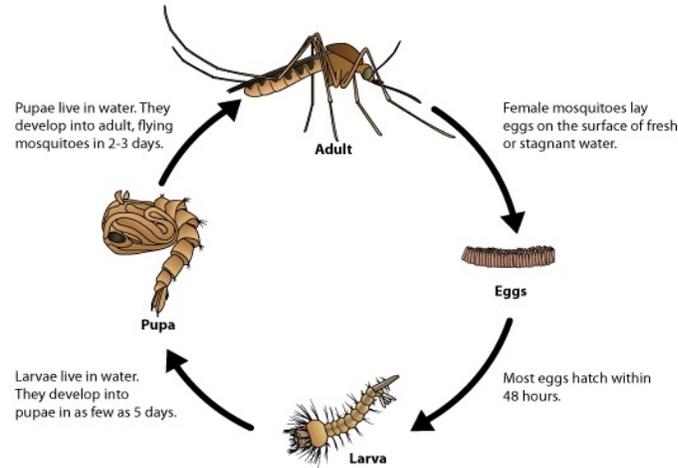


Network model based on dispersal kernel and knowledge about location of migration routes

Challenges 2: Mosquitoes

- Various mosquito species identified as competent to transmit WNV including species from genus *Aedes* and *Culex*
 - Only *Culex* considered primary vectors of WNV due to mammalophilic biting of *Aedes* species
 - Despite predominantly ornithophilic *Culex* also considered main bridge vectors
 - Within *Culex* genus species differ in their characteristics and behavior (e.g., habitat, diapause, biting)
 - Even within intraspecific differences can be significant (e.g., *Culex pipiens* biotype *pipiens* vs biotype *molestus*)
 - Hybrid populations can develop their very own characteristics as well
- Such heterogeneities often neglected in models

Life Cycle of *Culex* species



Source: CDC Factsheet

- Mosquito life cycle divided into life stages characterized by different environments and biological needs
- Juvenile stages aquatic, Adult stages flying
- Larva compete for space and resources
- Adults can enter dormancy

Typical age-structured ODE-model

$$\begin{aligned}\dot{E} &= \beta (M + M_{pd}) - \mu_E E - \delta_E E \\ \dot{L} &= \delta_E E - \mu_L L - f(L)L - \delta_L L \\ \dot{P} &= \delta_L L - \mu_P P - \delta_P P \\ \dot{M} &= \omega \delta_P P - \mu_M M - \phi M \\ \dot{M}_d &= \phi M - \sigma M_d \\ \dot{M}_{pd} &= \sigma M_d - \mu_{M_{pd}} M_{pd}\end{aligned}$$

- Life-history parameters often derived from lab studies
 - Mismatch between lab and field
 - Density-dependent effects often not accounted
- Density in juvenile stage also impacts development rates, adult size, adult fecundity ...
- In real settings very hard to describe due to variations in land cover, nutrients, breeding site availability, species
 - Very sensitive to environmental fluctuations

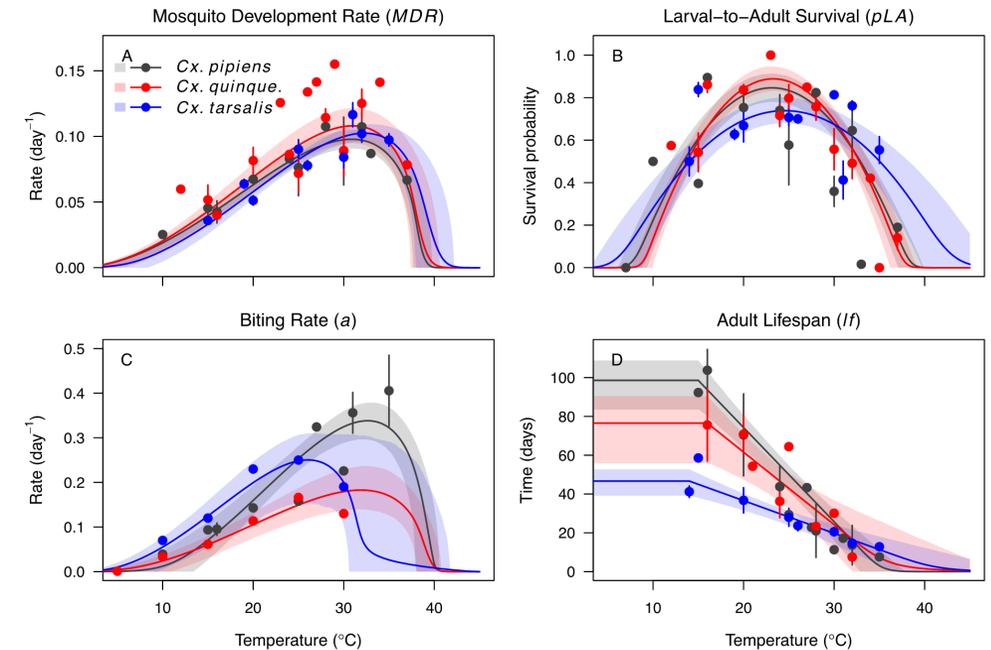
Challenges 3: Climate sensitivity

Vectors & pathogen - Temperature

- Mosquitoes are ectotherms
→ Temperature directly impacts life-history traits
- Species-specific!
- Temperature also modulates replication of virus inside mosquitoes
→ Extrinsic incubation period and vector competence

Humidity

- Known to impact vector lifespan and biting rate
- When considered often treated as independent of temperature but response to high temperatures likely depends on desiccation (wet vs dry heat)



Source: Shocket et al. 2020

PERSPECTIVE

ECOLOGY LETTERS WILEY

Humidity – The overlooked variable in the thermal biology of mosquito-borne disease

Joel J. Brown¹ | Mercedes Pascual² | Michael C. Wimberly³ | Leah R. Johnson⁴ | Courtney C. Murdock¹

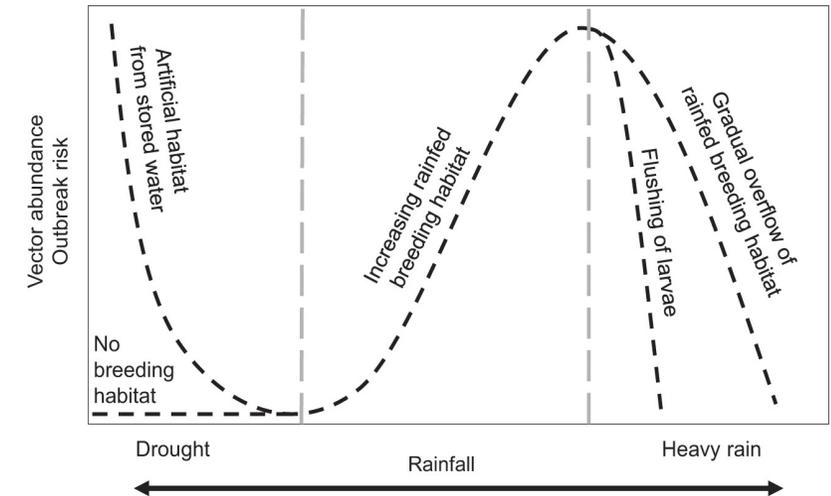
Water body availability

- Mosquitoes depend on aquatic breeding sites for egg laying & juvenile development
- Human water storing behavior complicates the picture
- Negative impacts of heavy rainfall
- Precipitation can impact vector-host contact rates
- Drought can benefit larval development by disrupting food-web structures and concentrate nutrients in remaining water pools

Sunlight hours

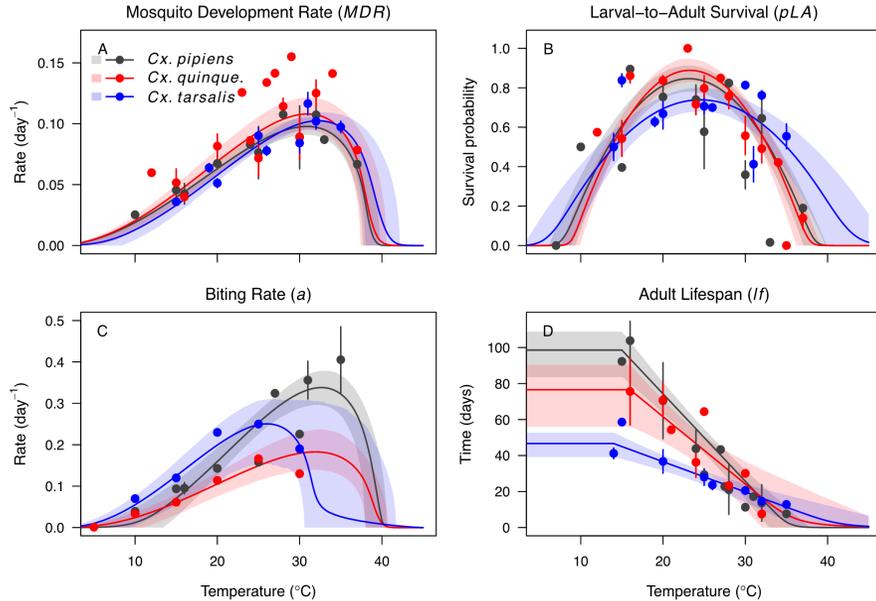
- Regulates proportion of adult mosquitoes in diapause

Further impacts of windspeed ...



Source: Caldwell et al. 2021

Incorporate response of parameters in the model (diapause neglected)



Source: Shocket et al. 2020

Mosquito population

$$\begin{aligned}\dot{E} &= \beta(T)(A + A_{pd}) - \mu_E(T)E - \delta_E(T)E \\ \dot{L} &= \delta_E(T)E - \mu_L(T)L - f(L, W)L - \delta_L(T)L \\ \dot{P} &= \delta_L(T)L - \mu_P(T)P - \delta_P(T)P \\ \dot{M} &= \omega\delta_P(T)P - \mu_M(T, H)M\end{aligned}$$

Disease transmission

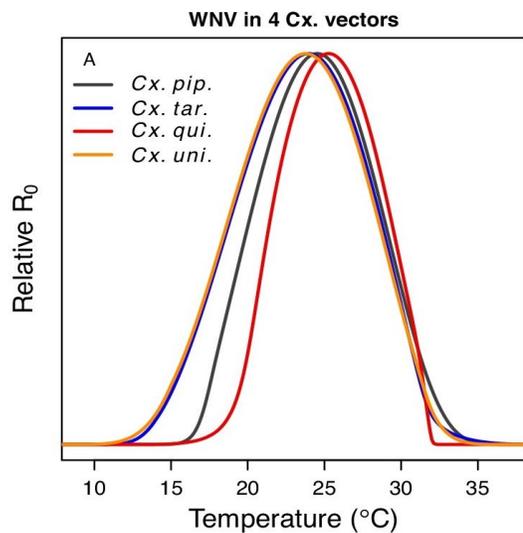
$$\begin{aligned}\dot{S}_B &= \Lambda_B - a(T, H) \cdot b_B \cdot I_M \cdot \frac{S_B}{N_B} - \mu_B S_B \\ \dot{I}_B &= a(T, H) \cdot b_B \cdot I_M \cdot \frac{S_B}{N_B} - \gamma_B I_B - \mu_B I_B \\ \dot{R}_B &= \gamma_B I_B - \mu_B R_B \\ \dot{S}_M &= \omega\delta_P(T)P - a(T, H) \cdot b_M(T) \cdot S_M \cdot \frac{I_B}{N_B} - \mu_M(T, H)S_M \\ \dot{E}_M &= a(T, H) \cdot b_M(T) \cdot S_M \cdot \frac{I_B}{N_B} - (\alpha(T) + \mu_M(T, H))E_M \\ \dot{I}_M &= \alpha E_M - \mu_M(T, H)I_M \\ M &= S_M + E_M + I_M\end{aligned}$$

T: Temperature, W: Water avail., H: Humidity

Application examples

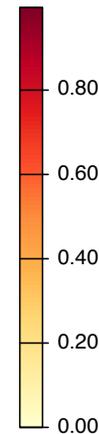
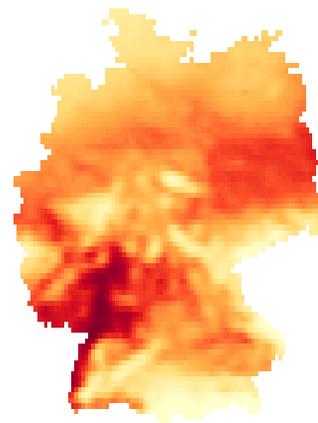
- Seasonal dynamics of vector populations and impact on transmission
- Incorporate response of parameters into R_0
→ climatic/environmental transmission suitability measure

$$R_0(T) = \frac{a(T)^2 b_M(T) b_B p^{EIP}(T) \frac{N_M^*(T)}{N_B^*}}{\mu_M(T) (\gamma_B + \mu_B)}$$

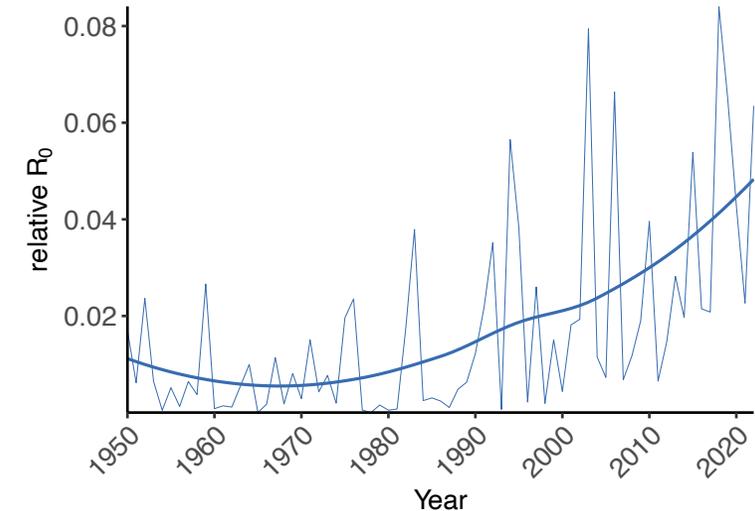


Source: Shocket et al. 2020

average relative R_0 August 2022 Germany



Yearly average relative R_0 Germany



Avian hosts & climate

- Climatic changes known to impact
 - Migratory behavior, timing and routes
 - Bird populations composition and species abundance ...
- To best of my knowledge these impacts are currently only incorporated phenomenologically in WNV models

Summary of main challenges

- Host heterogeneity + lacking knowledge on their role in amplification
 - Impact of (species-specific) host ecology on transmission very hard to study
- Vector diversity further complicates parameterization of models
- Climate sensitivity beyond the temperature-vector-pathogen relationship not understood in depth
 - Many aspects are understood phenomenologically but not mechanistically and not quantified!

Is West Nile unpredictable?

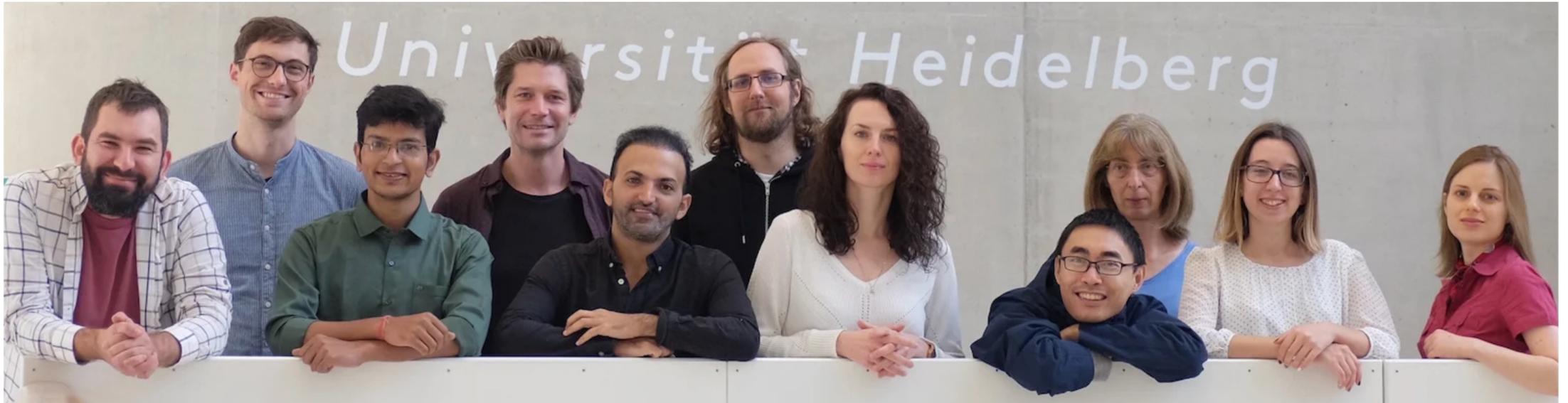
Maybe not if we truly account for the multi-disciplinarity of the problem

- Better data and collaboration is needed
- Human-centered approach likely not sufficient

Thank you!



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