

WBIO2019 Workshop Project Descriptions-IPAM

Project 1

Title: Mathematical Modeling of Inherited Retinal Degeneration.

Leader: Erika Camacho (Arizona State University) and Co-Leader: Anca Radulescu (SUNY-New Paltz)

The retina plays a central role in our vision. A great deal of laboratory studies examine healthy retinas and also diseased retinas with hopes of gaining insight into how to prevent blindness. While many causes of blindness are curable, those involving degeneration of the photoreceptors have no cure.

Current areas of laboratory research in these areas involve trying to gain an understanding of various mechanisms that cause photoreceptor degeneration. These areas of interest include understanding the roles of different cell death pathways and cell stresses, identifying unique aspects of photoreceptor metabolism and their key interactions with other retinal cell types (in particular with Muller cells, microglia, and retinal pigment epithelium cells), and determining the mechanisms affected during disease progression (such as Age-related Macular Degeneration and Retinitis Pigmentosa), and many others.

In this project, we aim to develop a mathematical model to better understand key photoreceptor interactions and the role of various molecular mechanisms in maintaining healthy photoreceptors. We will build upon recent biological and mathematical work that examines various aspects of retinal degeneration. With the model, we will mathematically examine some current hypotheses and will explore long-term behavior with techniques from dynamical systems as well as perform a global sensitivity analysis in order to determine the implications of variation of parameters. This project aims to contribute to the understanding of key aspects of photoreceptor health and death.

This project will use methods from dynamical systems, statistics as it relates to sensitivity analysis and inverse problem methodology, and numerical simulation.

Suggested Readings

Banks HT, Davidian M, Samuels JR, Sutton KL. An inverse problem statistical methodology summary. In *Mathematical and statistical estimation approaches in epidemiology 2009* (pp. 249-302). Springer, Dordrecht.

Camacho ET, Leveillard T, Sahel JA, Wirkus S. Mathematical Model of the Role of RdCVF in the Coexistence of Rods and Cones in a Healthy Eye. *Bulletin of Mathematical Biology*. 2016;78(7):1394–1409.

Camacho ET, Radulescu A, Wirkus S. Bifurcation analysis of a photoreceptor interaction model for retinitis pigmentosa. *Communications in Nonlinear Science and Numerical Simulation*. 2016 Sep 1;38:267-76

Duncan JL, Pierce EA, Laster AM, Daiger SP, Birch DG, Ash JD, Iannaccone A, Flannery JG, Sahel JA, Zack DJ, Zarbin MA. Inherited Retinal Degenerations: Current Landscape and Knowledge Gaps. *Translational vision science & technology*. 2018 Jul 1;7(4):6-.

Leveillard T, Sahel JA. Metabolic and redox signaling in the retina. *Cellular and Molecular Life Sciences*. 2016;p. 1–17

Marino S, Hogue IB, Ray CJ, Kirschner DE. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *Journal of Theoretical Biology*. 2008; 254:178–196.

Roberts PA, Gaffney EA, Luthert PJ, Foss AJ, Byrne HM. Mathematical and computational models of the retina in health, development and disease. *Progress in retinal and eye research*. 2016 Jul 1;53:48-69.

Project 2

Title: Connecting Biopolymer Dynamics Across Multiple Scales.

Leader: Adriana Dawes (Ohio State University) and Co-Leader: Calina Copos (New York University)

Cells rely on a network of biopolymers, including actin, microtubules and intermediate filaments, to provide structural support and scaffolding for biochemical reactions [1]. The polymers are interconnected by specific proteins to form higher order structures, such as branched meshworks, or bundles that can reach a long distance, as well as transient patterns like vortices and asters [2,3]. The polymers are highly dynamic and constantly remodeling both themselves and the meshwork they form. Stochastic individual based models (eg. the simulation software MEDYAN [4]) have provided valuable information about small scale dynamics of these polymers, but it is not clear how to translate this information to higher scales such as the level of a whole cell, a tissue and ultimately, a whole organism. Using stochastic and continuum techniques, we will address the following broad questions:

- How can we meaningfully approximate small scale stochastic behavior to preserve its essential dynamics and interactions for use in macroscale cell or tissue level models?

- Are there measures, such as from topological data analysis, that we can use with both micro and macroscale models, allowing us to translate large scale dynamics (such as experimental observations) to small scale local dynamics?

One potential starting point is investigating how to derive a meaningful integral kernel for a model such as the one in [2,3] based on information from stochastic simulations using MEDYAN [4].

References:

[1] Florian Huber, Adeline Boire, Magdalena Preciado Lopez, and Gijsje H Koenderink. Cytoskeletal crosstalk: when three different personalities team up. *Current Opinion in Cell Biology*, 32:39--47, 2015

[2] Diana White, Gerda de Vries, and Adriana Dawes. Microtubule patterning in the presence of stationary motor distributions. *Bulletin of Mathematical Biology*, 76(8):1917--1940, 2014

[3] Diana White, Gerda de Vries, Jonathan Martin, and Adriana Dawes. Microtubule patterning in the presence of moving motor proteins. *Journal of theoretical biology*, 382:81--90, 2015

[4] Konstantin Popov, James Komianos, and Garegin A Papoian. MEDYAN: Mechanochemical Simulations of Contraction and Polarity Alignment in Actomyosin Networks. *PLoS computational biology*, 12(4):e10004877, 2016

Project 3

Title: Identifying the structure of nucleic acids: shadows, braids and crossing changes.

Leader: Mariel Vazquez (University of California, Davis) and Co-Leader: Nataša Jonoska (University of South Florida)

Background

DNA and RNA play essential roles in the life of any organism. They often occur as long biopolymers subjected to high levels of confinement. They are substrates or products of a variety of important enzymatic processes such as DNA replication and transcription. Double-stranded DNA molecules often form topologically closed loops and are thus subjected to supercoiling, knotting and interlinking. Single-stranded DNA and RNA molecules also adopt interesting secondary structure with the formation of hairpins and cruciforms. The objective of this research team is to design mathematical methods, rooted in combinatorics and low-dimensional topology, for addressing two biological questions: (1) Link type identification based on shadows obtained from electron micrographs of circular DNA molecules; (2) Characterization of post-transcriptional entanglement in R-loops, a type of DNA-RNA hybrid.

Objectives:

(1) Topology identification from link shadows

Linked DNA molecules provide valuable information to understand the molecular mechanisms that produce them (note: a knot is a link with one component). Proper identification of the link type of circular DNA molecules is essential. We model a DNA link as one or more circles embedded in 3-dimensional space, i.e. a mathematical link with one or more components. With traditional electron microscopy (EM) it is possible to obtain planar projections of individual DNA links with the limitation that the over/crossing information at each crossing is not identified. The electron micrographs correspond to planar projections of the DNA curves where every multiple point is a double point. We model these as link shadows, i.e. 4-regular planar graphs. The notion of ‘shadow graph’ is related to that of ‘assembly graphs’ used in the studies of DNA recombinant processes, except that assembly graphs may be non-planar.

We first aim to further develop unpublished work from the Vazquez group, as well as the notion of common subshadow introduced in [Medina et al. 2017] and the work on assembly graphs from [Burns et al, 2013]. The goal is to establish a framework to systematically identify all topologies sharing a shadow and, combined with biological information, determine the minimum information needed to uniquely determine the link type. We will also consider the case of weighted shadows, which arise naturally in the modeling of DNA circles as self-avoiding polygons in the simple cubic lattice [Ishihara et al. 2012, 2017]. One can identify necessary conditions for a weighted lattice graph to be the weighted shadow of some knot. A harder problem is to give a characterization that can be used to test this property efficiently. It is not even clear that such a good characterization exists. Weighted assembly graphs have not been considered; hence, results from these studies may affect DNA recombinant models.

(2) Post-transcriptional entanglement in R-loops.

R-loops are three-stranded hybrid structures consisting of a DNA:RNA duplex, and a displaced single strand of DNA. R-loops have been shown to occur as a product of transcription with surprising regularity

at highly conserved hotspots throughout mammalian genomes. Using DRIP-seq, the Chedin lab at UC Davis showed that R-loops are the most abundant non-B DNA structures to date, constituting up to 5% of the human and mouse genomes (reviewed in Chedin, 2016). However, little is known about their function, their mechanism of formation, or their geometry and topology.

With evidence connecting them to a range of physiological and pathological cellular processes, understanding what drives R-loop formation and stability is of great importance. One key feature of R-loops that could contribute to their stability is the topological entanglement of the displaced DNA strand with the DNA:RNA hybrid. Furthermore, secondary and tertiary structure in the free DNA strand and the uninvolved mRNA could potentially impede disentanglement. If this entanglement occurs, enzymes that alter the local topology of the DNA may be needed to resolve them through strand passage, "unzipping" or by other methods.

A duplex molecule is often modeled as a ribbon graph (or a thickened graph) that is an oriented manifold with boundaries whose deformation retract is the graph itself (Jonoska et al. 2009). The formation of the RNA-DNA duplex imposes 'unwinding' of the DNA-DNA duplex (representing changes within the ribbon graph). The topological model that describes an R-loop has not been proposed nor studied before. In addition, crossings of multiple strands (as would appear in the R-loop) can be modeled as elements (represented with words) of a 3-string braid group, hence the annealing and branch migration can be seen as walks between the elements in the group. We propose to describe a graph of the 3-string braid group whose vertices are elements of the group and the edges connecting two vertices represent possible topological changes during the formation of the complex.

References

- J. Burns, E. Dolzhenko, N. Jonoska, T. Muche, M. Saito (2013) Four-regular Graphs with Rigid Vertices Associated to DNA Recombination. *Discrete and Applied Math* 161(10-11): 1378--1394. DOI: 10.1016/j.dam.2013.01.003
- F. Chedin (2016) Nascent connections: R-loops and chromatin patterning. *Trends Genet.* 32 (12): 828-838. doi: 10.1016/j.tig.2016.10.002
- K. Ishihara, R. Scharein, Y. Diao, J. Arsuaga, M. Vazquez, and K. Shimokawa (2012) Bounds for the minimum step number of knots confined to slabs in the simple cubic lattice, *J. Phys. A: Math. Theor.* 45 (6):065003.
- K. Ishihara, M. Pouokam, A. Suzuki, R. Scharein, M. Vazquez, J. Arsuaga, K. Shimokawa (2017) Bounds for minimum step number of knots confined to tubes in the simple cubic lattice, *J. Phys. A: Math. Theor.* 50 (21):215601.
- N. Jonoska, G. Wu, and N.C. Seeman (2009) Existence of single-stranded reporters in {DNA}-based graph structures. *Theoretical Computer Science* 410:1448--1460.
- C. Medina, J. Ramírez-Alfonsín, and G. Salazar (2017) On the number of unknot diagrams, ArXiv e-prints, available at 1710.06470.

Project 4

Title: Discrete mathematical biology: new approaches to ensemble analysis.

Leader: Christine Heitsch (Georgia Institute of Technology) and Co-Leader: Blair Sullivan (North Carolina State University)

Many important questions in molecular biology revolve around understanding the sequence/structure/function of nucleic acids, and are amenable to combinatorial modeling and analysis. Applications of discrete mathematics in DNA sequence analysis are long-standing and widespread, including DNA fragment assembly, sequence alignment and comparison, motif discovery, optical mapping, word design, and chromosome rearrangements. In many cases, related results exist for RNA sequences, including RNA comparative sequence analysis, secondary structure prediction, inverse folding, and three-dimensional alignment and comparison.

This project will take a new look at two foundational problems: DNA sequence alignment and RNA secondary structure prediction. Traditionally, these are each approached as a discrete optimization problem, where an optimal solution under the given objective function can be computed efficiently via dynamic programming. Often, though, there is significant biological interest in suboptimal solutions which may be "close" to having the optimal score but are structurally distinct.

We will explore the extent to which the ensemble of suboptimal configurations can be realized efficiently by encoding the optimization as a suitable graph. For instance, can the dynamic programming process be augmented to enable efficient sampling of structures farther from equilibrium? What do we gain by viewing these problems through the lenses of structural graph theory and parameterized complexity? Theoretical explorations will be complemented by computational experiments as we experience the productive interplay between combinatorics, algorithms, and optimization in modern molecular biology research.

Project 5**Topic: Mathematical modeling of multidrug-resistant organisms.****Leader: Mary-Ann Horn (Case Western Reserve University) and Co-Leader: Qimin Huang (University of Miami)**

Multidrug-resistant organisms (MDRO) continue to spread in hospitals globally, but the population-level impact of recommended preventive strategies and the relative benefit of individual strategies targeting all MDRO in the hospital setting remain unclear. Exploring the dynamics of MDRO transmission in the hospital involves extending data from clinical individual-level studies to quantify the impact of hand hygiene, contact precautions, reducing antimicrobial exposure and screening surveillance cultures in decreasing the prevalence of MDRO colonization and infection. In addition, environmental aspects can play a significant role in the spread of antibiotic resistant bacteria. Effects of increases in the influx of patients colonized with MDRO into the hospital setting continues to be a challenge that needs to be addressed. Many recommended strategies have impact in decreasing the prevalence of MDRO over time. However, screening for asymptomatic MDRO colonization among patients who are not receiving antimicrobials is often of minimal value in reducing the spread of MDRO.

Various scenarios can be considered and a variety of models, analysis, and numerical approaches can be used.

Project 6

Title: Modelling tumour growth and treatment responses for decision-making in the clinic.

Leader: Helen Byrne (University of Oxford) and Co-Leader: Angela M Reynolds (Virginia Commonwealth University)

Advances in technology mean that it is now possible to collect detailed information about tumours (e.g., their size, spatial composition, mutational status, vascularity and degree of immune infiltration). Even so, decisions about treatment options (eg surgery, radiotherapy, chemotherapy and immunotherapy), and assessments about treatment responses are often based on sparse data for a small number of metrics. The aim of this project is to investigate how existing mathematical models can help clinicians to decide between alternative treatment options and to establish whether additional data could improve their decision-making.

Project outline

Depending on participants' backgrounds, there are many ways in which this project could develop. One possible plan is outlined below.

1. Choose 2 different models of solid tumour growth (ODE, PDE, CA, deterministic, stochastic) and select a treatment option (eg radiotherapy).

[ideally one of the models will be more detailed than the other]

2. Use the selected models to generate synthetic data describing tumour growth pre-, during and after treatment

3. Separately fit the models to (their) synthetic data and aim do determine what data are needed to recover the original parameter values.

4. By adding noise to the synthetic data, determine also how noise levels affect your ability accurately to estimate the parameter values. Determine also how well each model can fit the same data – in particular, is it possible to determine which model generated which data?

References

1. H Enderling, MAJ Chaplain and P Hahnfeldt (2010). Quantitative modelling of tumour dynamics and radiotherapy. *Acta Biotheoretica* 58(4): 341-353.
2. J Collis, AJ Connor, M Paczkowski, P Kannan, J Pitt-Francis, HM Byrne, ME Hubbard (2017). Bayesian calibration, validation and uncertainty quantification for predictive modelling of tumour growth: a tutorial. *Bull Math Biol* 79(4): 939-974.
3. AV Ponce Bobadilla, P Maini and H Byrne (2017). A stochastic model for tumour control probability that accounts for repair from sublethal damage. *Math Med Biol* (DOI: <https://doi.org/10.1093/imammb/dqw024>).
4. TD Lewin, H Enderling, EG Moros, PK Maini and HM Byrne (2018). The legacy of hypoxia on tumour responses to fractionated radiotherapy. *Bull Math Biol.* 80(5): 1207-1235

Project 7

Title: Infectious diseases, geospatial modeling and geostatistics - focusing on malaria.

Leader: Sally Blower (University of California, Los Angeles) and Co-Leader: Suzanne Sindi (University of California, Merced)

Background:

The importance of geographic heterogeneity in the study of infectious disease has been apparent to modelers of malaria for over 50 years (1), and more recently has begun to be considered in studies of Tuberculosis, Ebola, and HIV. In this workshop, we will mainly focus on malaria due to the rich history of modeling in this field. Two main approaches are used to study the importance of geographic heterogeneity: geospatial transmission models (1-3) and geostatistical models (4-6). In this workshop, we will explore both approaches.

To develop useful models for resource-constrained countries where malaria is endemic, it is necessary to consider the rural-urban divide and population mobility/migration. These are critical factors in determining the spread, and control, of malaria in Africa; recent studies have shown that they are also crucial factors to consider in the spread, and control, of HIV (7,8). The majority of individuals in Africa live in rural areas: e.g., in Lesotho and Malawi ~75% live in rural communities. Notably, populations in African countries are highly mobile. Mobility/migration patterns link rural-rural settlements, urban-urban centers, or rural settlements-urban centers. Short-term migration can be either circular (due to employment) or unidirectional (due to urbanization). Notably, population mobility has been identified as a substantial obstacle in global attempts to eliminate malaria (9, 10). In the modeling that we will conduct in the workshop, we will develop models that are designed to include the rural-urban divide and that incorporate population mobility/migration.

Objectives:

- 1) To develop, and analyze, geostatistical models in order to identify drivers of disease transmission when there is geographic variation in transmission intensity.
- 2) To develop, and use, transmission models to determine how to mitigate the potential detrimental impact of high levels of population mobility on the effectiveness of the geographically targeted elimination strategies.

References:

1. Reiner RC Jr, et al., A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970-2010. *J R Soc Interface*. 2013 Feb 13;10(81):20120921.
2. Smith DL, et al. Recasting the theory of mosquito-borne pathogen transmission dynamics and control. *Trans R Soc Trop Med Hyg*. 2014 Apr;108(4):185-97.
3. Ruktanonchai NW, Smith DL, De Leenheer P. Parasite sources and sinks in a patched Ross-Macdonald malaria model with human and mosquito movement: Implications for control. *Math Biosci*. 2016 Sep;279:90-101.

4. Gething PW, et al. Mapping Plasmodium falciparum Mortality in Africa between 1990 and 2015. *N Engl J Med* 2016 Dec 22;375(25):2435-2445.
5. Kang SY et al. Spatio-temporal mapping of Madagascar's Malaria Indicator Survey results to assess Plasmodium falciparum endemicity trends between 2011 and 2016. *BMC Med.* 2018 May 23;16(1):71.
6. Cohen JM et al., Mapping multiple components of malaria risk for improved targeting of elimination interventions. *Malar J.* 2017 Nov 13;16(1):459.
7. Dobra A, et al., Space-time migration patterns and risk of HIV acquisition in rural South Africa. *AIDS* 2017 31(1) 137-145.
8. Coburn BJ, Okano JT, Blower S. Using geospatial mapping to design HIV elimination strategies for sub-Saharan Africa. *Sci Transl Med* 2017 9.
9. Newby G et al., The path to eradication: a progress report on the malaria-eliminating countries. *Lancet* 2016387: 1775-1784
10. Rabinovich RN et al., malERA: An updated research agenda for malaria elimination and eradication. *PLoS Med.* 2017 Nov 30;14(11):e1002456.