Delay differential models and transmission dynamics of infectious diseases – in the shadow of the Saguaro

Gergely Röst

Delay differential equations are one of our most powerful mathematical modeling tools and they appear in various applications from life sciences to engineering and physics, whenever temporal delays are important. They describe dynamical systems, when their evolution depends on prior times. A large class of epidemiological models can be formulated as a system of differential equations, frequently involving spatial structure and time lags. I had the privilege to work on such topics with some of the world’s leading experts at Arizona State University. Arizona is a very special and (from a Hungarian perspective) exotic place, so besides my research, in this report I write also about the everyday life and travels of my family in the land of canyons and saguaros.
1. Mathematics

1.1. Time delays in dynamics

Differential equations arise in many areas of science and technology. When a deterministic rule is known or postulated about the rate of change of some important variables of a system, we can formulate an abstract model to mathematically describe the dynamics of the given system and predict the behavior of solutions. Delay differential equations, or functional differential equations describe physical and biological systems when their evolution depends on the solution at prior times. Not only a powerful mathematical modeling tool which is relevant for applications, but an important class of infinite dimensional dynamical systems and the subject of theoretical investigations as well. Time delays are known to cause instabilities and oscillations, which we can observe even in our everyday life, if we think about reaction times or delayed responses. The proper mathematical description and analysis of systems with delayed feedback can be rather challenging.

1.2. Mathematical epidemiology

We can mathematically model the progress of most communicable diseases to discover the likely outcome of an epidemic or to help manage them by vaccination and other control measures. Mathematical epidemiology has a long history (starting with Bernoulli’s investigation on smallpox in 1766), but in recent decades researchers in this area have developed more complex and biologically relevant models that have become important for influencing public health decisions and the design of control programs. Some of these new models have been developed for new diseases, such as severe acute respiratory syndrome (SARS), the vector-borne West Nile virus in North America, or prion diseases (like the Creutzfeldt-Jacob disease). The thorough analysis of such models requires advanced mathematical skills. We always need new models to face new challenges and follow recent changes in epidemiology: to include new treatments (e.g., antiviral drugs for influenza), to involve evolutionary aspects (drift of influenza A virus, emergence of resistant strains), to understand the possible population-wide emergence of (multi)resistance, to consider new migration trends, changing social behavior and travel patterns, and also the appearance of diseases in new geographical areas due to global climate change.

1.3. Interface: infectious diseases and time delays

A large class of epidemiological models can be formulated as a system of differential equations, frequently involving spatial structure and time lags. Time lags arise due to delayed feedback: this can be delay in treatment, constant or distributed sojourn time in certain compartments (for example latency), travel delay, waning immunity, memory effects, etc. and certain age structured models (here age might refer to age of infection, or age of treatment as well) are also equivalent with delay differential systems. To make models more realistic, we need to take into account such effects.

One of the key concepts in epidemiology is the basic reproduction number (R0), which expresses the expected number of generated secondary infections by an initial infected individual. One of the most urgent tasks in a case of an epidemic is to estimate this number. One can learn about this even in Hollywood: R0 was explained by Kate Winslet in the recent movie Contagion.

Even if my reader did not watch the movie, there are a number of significant questions that comes to everyone’s mind when we talk about disease modeling: Can a disease invade the population? When will be the peak time? What will be the peak size? What will be the total number of infections (final size)? How can we control the disease? Which are the optimal intervention strategies (treatment, vaccination, quarantine, social distancing, school closures etc.) for controlling the epidemic or mitigation? If we consider a longer, demographic time scale: will the disease persist in a population or will be eradicated?

2. ASU – the host institution

Arizona State University is located in the Phoenix Metropolitan Area. According to wikipedia, with a 2011 enrollment of 72,254, it is the largest university in the United States by enrollment. The main campus is in Tempe, Arizona, and it is the largest campus in US by enrollment (59,794 in 2011, the second is University of Central Florida, the third is Ohio State University). The ASU campus is indeed huge, but very nice and pleasant with its palm and orange tree walkays. I was hosted by Professor Horst R. Thieme at the ASU School of Mathematical and Statistical Sciences. The group in mathematical biology here is one of the world’s leading places where rigorous mathematics is applied to study problems arisen in biology. Besides Horst Thieme, many well-known mathematicians work here in the biomath field including Hal L Smith, Yang Kuang, Carlos Castillo-Chávez, Karl Hadeler, Fabio Milner, Yun Kang, Haiyan Wang and others. It was a great experience to interact with these scientists, and to participate in the regular
seminars and other activities. The School of Mathematics is very well prepared for hosting visitors. Immediately after my arrival I received my keys to the visitor’s office where I did my work, a computer was already set up for me, such as a mailbox at the department’s secretariat.

3. My research at ASU

3.1 Phages on a plate

Bacteriophage is a virus that infects bacteria. Phages are among the most common biological entities. If we spread liquid agar containing a very small quantity of virus together with susceptible host bacteria on a plate of solid agar, after some time we observe a number of plaques (disk-shaped regions), growing with a well-characterized speed, each initiated from a single virus that infected a host cell. This process has the following key components: a free virus diffuses in the agar, and when attached to a host cell, injects its genetic material into the cell. After a latent period, during which the machinery of the host cell is used to produce new virus particles, the host cell lyses and releases a large number of newly made virus.

To describe this phenomenon, a mathematical model can be formulated as a system of reaction-diffusion equations with time delay. As the length of the latent period appears to be remarkably fixed with very small variation, we can take this into account explicitly as a constant time delay, more realistically than in some previous literature where exponentially distributed latent period was assumed. Thus we can predict the asymptotic spreading speed more accurately. The related paper Jones DA, Smith HL, Thieme HR, Röst G, On spread of phage infection of bacteria in a Petri dish has recently been accepted for publication in SIAM Journal of Applied Mathematics. In this paper an interval of possible spreading speeds for virus infection is established in a mathematically rigorous way and traveling wave solutions are shown to exist. Linear determinacy of spreading speed breaks down for some parameter values.

3.2 Persistence of bluetongue disease

Bluetongue is a viral infection of ruminants, including cattle and sheep, spread by biting midges of the Culicoides family. The bluetongue virus tends to cause abortion, congenital anomalies, and death in sheep, but mild cases usually recover rapidly and completely. In cattle, bluetongue generally does not cause death. Previously a model was presented for bluetongue dynamics that includes midges with a general incubation period as vectors and cattle and sheep as hosts, by S. Gourley, H. Thieme and P. van den Driessche, where they established fundamental properties of the model, such as existence and uniqueness of solutions and their positivity and boundedness, and also necessary and sufficient conditions for local stability of the disease free equilibrium (with all host species present) and for uniform weak disease persistence in the midges. However, the question of strong uniform persistence remained open. The purpose of our research was to answer this question. The disease persists uniformly if the disease prevalence is bounded away from 0 with the lower bound being independent of initial data for sufficiently large times. The disease persists uniformly weakly if its prevalence keeps dropping to arbitrarily low values but always returns to a certain level that does not depend on initial data. Obviously, the mathematically more desirable property of uniform persistence implies uniform weak persistence. In the case of the bluetongue model we
consider, the mathematical transition from uniform weak to uniform persistence is difficult because bluetongue affects the livelihood of the two host species very differently: The cattle’s livelihood is affected hardly at all while the sheep’s mortality is increased and their fertility decreased. Cattle may even play the role of a reservoir based on which bluetongue can eradicate the sheep without dying out itself. A further technical difficulty is that the distribution of the midge latency period is not known, hence we used a rather general formulation which resulted in a system with infinite delays, which is mathematically rather challenging. We showed that uniform disease persistence occurs if the basic reproduction number $R_0 > 1$, in two different scenarios, which require different mathematical treatment. In one case, bluetongue can persist even though it may eradicate the sheep. In the other case, bluetongue persists with simultaneous persistence of sheep. The manuscript containing our related results is soon to be submitted for publication. The description above is mostly taken from the introduction of the paper.

4. Chaotic arrival to Phoenix

For various reasons we could go to the US Embassy in Budapest to apply for our visa in the last minute, and they issued the visa only a few days before our departure. The delivery company failed to bring us the visa in time, so just in the afternoon before the day of our travel I had to drive to their central storage facility to get the visa. On the next day, we left Hungary in a freezing January morning. It was nice to leave our coats and boots behind, when we took off with our plane, knowing that we would need them in the hot Phoenix area. We prepared ourselves for the worse—traveling with children is never easy — but the journey wasn’t that bad at all. My daughter was 2 and a half, and my son half years old when we traveled. The day-long travel wasn’t unbearable, they even enjoyed it and made some friends on the planes. We managed to catch all our connecting flights, although our luggage could not make it to the connecting flight in Frankfurt, and we made the terrible mistake not to eat all of our apples on the plane before arriving to Dallas: one piece left unnoticed in the bottom of my daughter’s backpack. My daughter was very delighted when a nice dog approached her at Dallas Airport, but it turned out that the dog’s motivation was not playing with my daughter: he worked as a detector dog for the U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and being well trained for this job, sniffed the apple in her bag. We were sent for special inspection and our apple was confiscated. We were a little worried in advance what we would do in the two and half hours we needed to wait for our connection to Phoenix, but this dilemma was resolved as the special inspection took nearly two hours. My host professor Horst Thieme was waiting for us at Phoenix airport, where we arrived late at night. Not only our baggage has not arrived, but one wheel of our stroller broke out during the transportation, so we had to carry our sleeping children in our arms. The lack of our luggage had the advantage that we could all fit in to my host’s car. Horst and his wife Adelheid were truly amazing, they brought us in our new home from the airport, they put air mattresses, blankets, pillows etc. into our apartment in advance, and even prepared some dinner for us (thank you for the delicious stew, Adelheid), and we could borrow some clothes from them to spend the night and the next day in, since we did not have anything with us afterall. Luckily our baggage arrived the next night, and after that everything was just fine.

![Bluetongue Model Equations](image)

Model equations of the bluetongue model and how I celebrated after proving the persistence.
5. Everyday life in Tempe

We rent a two-bedroom apartment at the Rancho Murrietta complex. The reservation was made with the help of Horst before our arrival, and it was not easy at all to find a place with a short term lease. There are plenty apartment complexes in the neighborhood of the university: most of them have a pool what is considered a basic accessory in Phoenix. The apartment was unfurnished, but Adelheid helped us. We went to the U-Haul to rent a truck for one afternoon, then I was driving the truck to a thriftstore nearby (I think in Hungary I am not allowed to drive such a truck with my license, but it did not seem to be a problem there). We bought there very cheap furniture (dining table with chairs, desk, office chair, mattresses, lamps, ironer, vacuum cleaner etc.), and carried them back to the apartment by the truck. We furnished our apartment from less than 400 $! In the following days, I bought a cell phone and have the internet installed so we could communicate with the world. Later on we went to several thriftstores and bought wonderful toys and books to the children. I can suggest this method to those who relocate in the US, to set up quickly, easily and cheaply some basic living conditions. When my scholarship ended, we donated the furniture back to the store, and they came to the apartment and took back everything without a transport fee.

The public transportation in Phoenix (and Tempe) is relatively well-developed by US standards. There is a free shuttle service that collects students form the university neighborhood and takes them to the campus. From the campus one can go easily to Phoenix by a light rail. There are bus lines servicing the main avenues. What we specially liked are the bike racks on every bus, so it was easy for people to combine their means of transportation. Nevertheless, to go to farther places in the city with the children, and to travel around Arizona, we needed a car. I found on craigslist a ’96 Plymouth Voyager minivan with 290K miles. I bought it for 1600$, and I could sell it within two days (on craigslist) for 1200$, after putting 10K more miles into it in a couple months, such that meanwhile the compressor of the air condition failed (which is bad news in early summer in Arizona). Once we had a car, we could travel easily with my family. The minivan was huge, my children could run up and down inside (of course not while I was driving). We almost never used the car on weekdays, except when the weather became unbearably hot, so that long walks on daylight became a torture.

My wife took the children regularly to the Tempe Public Library and to the playground. They particularly enjoyed the water playgrounds which were a great fun. Our daughter just couldn’t play enough. You could run through water spraying arches, shoot each other with huge water pistols, or get a big splash of water from slinging buckets above. With kids, you need a pediatrician. It was not easy to find one that is contracted with our insurance provider, but the child care was excellent, the kids loved to go there. If something is not covered by your insurance though that costs a fortune even if it is only a simple blood test. My wife became a great fan of tex-mex cuisine, she still misses guacamole made from fresh avocados, cilantro (parsley-like vegetable), burritos with jalapeno sauce, quesadillas etc. I joined Tempe Pickup Soccer on meetup.com and every Saturday we went to play. In January we started the games at 10 AM, but as the weather became hotter, we shifted the starting time to 9 AM and then to 8 AM, and as I heard after I left they started to play from 7 AM. I joined another meetup group, the Phoenix Skeptics in the Pub for the 10:23 campaign. Skeptics are those who are highly critical of various pseudoscientific claims, such as astrology and many alternative medicine, and try to educate the public about the dangers of dubious practices. The purpose of the 10:23 campaign was to call attention to the fact that homeopathic remedies do not contain anything but sugar and they are utterly useless, therefore people should not spend money on this stuff. In this campaign hundreds of skeptical groups gathered at pharmacies around the world for a mass-overdose and swallowed large amount of homeopathic medicines. The event in Tempe was covered on TV channel CBS5 Phoenix in the evening news, I also appeared on television overdosing myself.

6. Cultural experiences

The greatest cultural experiences I had are related to the marvelous ASU Origins Project, which brings together an interdisciplinary group of great thinkers to discuss the “big questions”. Where did humans come from? Where did life come from? Where did the universe come from? One special event was The Great Debate: What is Life?, with a discussion panel including evolutionary biologist Richard Dawkins, human genome sequencer J. Craig Venter, Nobel Laureate molecular biologist Sidney Altman, NASA astrobiologist Chris McKay, renowned physicist Paul Davies, and Nobel Laureate biologist Lee Hartwell. The event was held at the ASU Gammage Auditorium, which has the capacity around 3000 seats, and it was almost completely full though they charged an entry fee. I am a fan of Richard Dawkins and Craig Venter, so I enjoyed this discussion about the definition, characterization and recognition of biological such as artificial life very much. One other great Origins event was the night when Gustav Holst’s ”The Planets” music masterpiece was performed by the ASU symphony orchestra and chorus, with scientific multimedia presentations, HD pictures from various NASA missions and Hubble telescope. Once we heard a music piece about one planet of the solar system, then we could watch a breathtaking presentation about the same planet with
amazing pictures and the narration of Lawrence Krauss, who explained what science can tell us about that planet. It was followed by Stephen Hawking’s lecture on the history of his life (he has a great sense of humor) and the history of our universe. This night was again a sold out show in Gammage. It was truly amazing to see that thousands of people were going to such events about science (especially that the tickets were not cheap at all).

Besides those, I attended AC Grayling British humanist philosopher’s introduction of his recent work the Good Book. My children enjoyed very much the Arizona Science Center in Phoenix, such as the Japanese Cultural Festival, a classic American car show, the Phoenix Zoo and the McCormick-Stillman Railroad Park.

7. Professional travels

I started my stay at ASU by giving a presentation at the mathematical biology seminar. Later, I gave talks at other places as well, for example at the Modeling and Computation Seminar of the University of Arizona in Tucson. I could use this occasion to meet an old friend of mine, with whom we lived together in a university residence in Szegez as students, who is just finishing his PhD in astronomy in Tucson. It was quite remarkable that after seven years we met again in Arizona, we could never guess back in our student days that this would ever happen.

Rongsong Liu is assistant professor of mathematics and ecology at the University of Wyoming in Laramie. In 2006, we worked together at the same department in the group of Jianhong Wu at York University, Toronto. We are still in contact since then, and she invited me for a visit in Wyoming. I was flying in March from Mesa to Fort Collins, Colorado. I remember when the current temperature was announced on the plane (it was much-much colder than in Phoenix), the passengers were so shocked that I fear a mutiny on board.

The Wyoming landscape was very different from Arizona, and the weather indeed was also quite refreshing. I had some difficulties, because I did not have any warm clothes at all (who needs that in Phoenix?), but some good oat beers in the historical pubs of Laramie (it has a crazy history, I suggest to look it up) made me forget about the cold. I also gave a seminar talk in Wyoming, and we started some new research projects. Besides, we organized a special session on the SIAM Conference on the Application of Dynamical Systems in Snowbird, Utah in May 2011, entitled Infinite Dimensional Models in Mathematical Epidemiology, with invited speakers Zhisheng Shuai (U. Victoria, BC Canada), Chuncheng Wang (Harbin Institute of Technology, China) and Lydia Bourouiba (Massachusetts Institute of Technology, USA). You can read more about this travel to Utah in the next section of my report.

8. Travel, travel and more travel

Arizona is known as “The Grand Canyon State”, but the Grand Canyon is just one of the countless natural wonders the state can offer. We traveled around as much as we could, so we could get a bit of a taste of everything. To discover Arizona, one really needs a lifetime. This is a country, where places like the breathtaking beauty of the Horseshoe Bend is just a stop at the side of the highway, and the amazing Chiricahua National Park is a place, where even Arizona residents seldom travel. At most places we found well maintained trails and pathways, so hiking was easy even with kids.

It is impossible to describe everything we have seen, so below I just give a brief list of four travels. To participate at the SIAM conference in Snowbird, Utah, we decided to drive to Salt Lake City from Phoenix (700 miles) so that
we can visit some of the most beautiful national parks on the way in Arizona and in Utah. We chose a western way to Salt Lake, and an eastern way for the return trip, these are listed in Travel 4 and 5. Each travel took 2-4 days. So here is the list:

**Travel 1:** mining town Globe, Rio Salado Canyon, Painted Desert, staying in the Wigwam Motel in Holbrook, Petrified Forest, the world’s best preserved meteor crater near Winslow

**Travel 2:** western town Tombstone and the Boothill Graveyard, mining town Bisbee and the Lavender Pit, Douglas at the Mexican border, Chiricahua National Park, Saguaro National Park, Tucson, Sonora Desert Museum

**Travel 3:** Sunset Crater Volcano and lava flow, Wupatki National Monument, Horseshoe Bend on the Colorado River, Page and Glen Canyon Dam at lake Powell, Bryce Canyon National Park and the Navajo Trail, Scenic route 89, Provo

**Travel 4:** Snowbird in the Rockies, Salt Lake City, Arches National Park (Moab), Monument Valley (this travel has been shortened because we had some troubles with the car, we skipped for example Natural Bridge)

**Travel 5:** Montezuma Castle National Monument, Walnut Canyon, Grand Canyon, Flagstaff, Museum of Northern Arizona, Grand Canyon, Deer Farm near Williams, Red Rock Country (Scenic route Road 89A), Oak Creek Canyon, Sedona

### 9. Aftermath

After returning to Hungary, I am still being in contact with my colleagues at ASU, and we have ongoing research projects. It was great to meet several of them as old friends at the International Congress of Industrial and Applied Mathematics in Vancouver. Haiyan Wang has attended the 9th Colloquium on Qualitative Theory of Differential Equations, a traditional conference series we organize in Szeged (being the first speaker from ASU ever on this meeting). Rongsong Liu, whom I visited in Wyoming during my Fulbright scholarship, will come to Szeged as a visiting professor this May. When I am typing this, we are arranging the forthcoming visits of Hal Smith and Horst Thieme to Szeged. What I have experienced at ASU is strongly influenced the way I do teaching and research in Hungary. I taught a graduate course based on the new book of Hal Smith. I have incorporated and applied persistence theory in my research motivated by the works of Horst Thieme. I firmly believe that mathematical biology (and disease modeling in particular) will have growing
importance in the future in Hungary. By the European Research Council’s Starting Investigator Grant, I have established a new international research group in Szeged, at the interface of mathematical epidemiology and functional differential equations. In many aspects, the mathematical biology group at the School of Mathematics of ASU served as a role model on how to organize and run this new team. Overall, this semester was an amazing experience for me both professionally and personally. I am very grateful for the staff of ASU and the Fulbright Commission that made this visit possible. It will have a long lasting impact on my career. Finally, I’d like to express my gratitude to my host professor, Horst Thieme and his wife Adelheid, who were incredibly helpful to my family.