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What do we do: modeling the evolution and immunology of pathogens

Pathogens evolve rapidly to circumvent drug treatments and immune surveillance, which dramatically impacts public health. Research and treatment are complicated by high genetic diversity of some viruses within and across infected individuals, as well as their complex evolutionary mechanisms, including selection, random genetic drift, and temporal variation in a host environment. Moreover, many pathogens have a large number of linked sites approximately $10^2 -10^3$ for HIV and hepatitis C virus (HCV) that evolve simultaneously and inter-dependently through two different effects, "epistasis" due to interaction between proteins and signaling network, and co-inheritance linkage ("clonal interference"). Our research is focused on developing mathematical tools that predict evolution of pathogens with strong linkage effects, including analytic and computational methods and estimators of evolutionary parameters from sequence data.

Motivation

The last decade has seen explosive progress in mathematical modeling of microbial populations and high-fidelity sequencing. Taking advantage of these developments, my team will address evolution of microbes (yeast, bacteria) and viruses (HIV, influenza, polio, CHIKV, Dengue, HCV). Launching from my previous mathematical and applied studies, we are applying existing methods and models to study the viral evolution under time-dependent conditions, develop new mathematical techniques and improve existing phylogenetic tools, and identify some key
Our multi-disciplinary team fuses the recent mathematical discoveries with multi-scale modeling and software tools. We are especially interested in the evolutionary effects of epistasis, recombination, and the theory of phylogenetic relationships in the presence of selection and the other factors. The project is designed to create significant clinical impact by fostering research into novel classes of drugs to control viral adaptation rate and achieve viral containment. Our software will facilitate personalized medicine and vaccine design against the pathogens escaping treatment and immune responses. The results are published and diffused in higher education and public presentations.

**An example of a recent work**

![Diagram](image)

**High-fidelity detection method of epistasis from DNA sequence samples**

Pedruzzi & Rouzine, PLOS Pathogens 2021

**A.** The computer model of asexual evolution includes the factors of random mutation, selection, epistasis, and random genetic drift. Pairwise haplotype frequencies are averaged over an ensemble of independent simulation runs (populations). The strength of interactions, $UE_{ij}$, is calculated. The indirect links and the residual stochastic linkage disequilibrium are excluded by using triple-site haplotype frequencies, $UE_{ij0}$. **B.** Pre-set epistatic network for 50 sites. Real epistatic links are shown by green lines. The resulting indirect links are red lines. Some examples of stochastic linkage bonds are shown by blue lines. **C-D.** The network of strong ($UE > 0.5$) candidate epistatic interactions predicted (C) from a single population and (D) after averaging over 200 populations. **E.** Scatter plot of 3-locus haplotype min($UE_{ij0}$) shown against $UE_{ij}$ for the pairs identified in (D). Dashed sector (green): Predicted direct interactions. **F.** Predicted network accurately recapitulates the pre-set epistatic network. Parameters: initial allele frequency 0.45, mutation rate per genome $U_{b} = 0.07$, fixed selection coefficient $s = 0.1$, epistatic strength $E = 0.75$.

**Biography**

Before 1995, Igor Rouzine worked in Condensed Matter Theoretical Physics, where he published 27 papers. Then he moved to the theory of evolution, application to viruses, and immunology of pathogens. Combining the
methods of theoretical physics, population genetics, and epidemiology, he models mathematically the evolution, dynamics, and immunology of viruses. The aim is to understand and predict, with a mathematical precision, the systemic interaction between factors shaping evolution and dynamics of a pathogen. The modeling-style, commonly referred to as "biology-driven" or "bottom-up" approach, is designed to answer the questions "Why", "How", and "How much", rather than merely describing data. PI worked on evolution and immunology of HIV, influenza virus, polio virus, vesicular stomatitis virus, and LCMV, and Plasmodium. The work was conducted in collaboration with virology and immunology laboratories in the USA (John Coffin at Tufts University, Boston, Leor Weinberger at the Gladstone Institute of Virology and Immunology, San Francisco, Raul Andino at UCSF, San Francisco, Rafi Ahmed at Georgia State University, Atlanta).

In 1999-2001, Igor published several papers, which detailed the basic mechanism of the rapid evolution of HIV in untreated patients and argued that it is due to the compensatory mutations of early CTL escape mutants, which prediction has been confirmed later. At the same time, he determined the relative role of stochastic effects and natural selection in HIV evolution. Later, he developed the first accurate theory of asexual evolution taking into account strong linkage effects existing between many evolving sites. Later, he showed that even rare recombination, which is the case for HIV, can accelerate evolution. His team then estimated the most important average parameters of HIV evolution, such as the average selection coefficient, the effective populations size, and the recombination rate.

Recently, Igor has proposed a model of primary HIV infection explaining the early formation of the latent HIV reservoir and proposing an evolutionary role for latency. He also investigated the stability and evolution of a virus in the presence of Defective Interference Particles and helped Leor Weinberger (Gladstone Institute) and Raul Andino (UCSF) to get NIH and DARPA grants on this topic. For all these tasks, Igor developed his own, custom-made mathematical approaches. In 2018, PI’s team published a paper explaining data on the evolution of influenza in the host population driven by immune response. They also developed a high-fidelity method of measuring the fitness landscape from viral sequence data, which is the most essential parameter for predicting viral adaptation.

Diplomas

1985  M.S., Theor. Semicond. Physics, Electrical Engineering Institute, St. Petersburg, Russia
1988  Ph.D., Theor. Semic. Physics, Ioffe Physico-Technical Institute, St. Petersburg, Russia

Academic appointments

2017-2021  Group Leader, Sorbonne Université (Pierre et Marie Curie), Laboratory of Computational and Quantitative Biology, Paris
2015-2017  Specialist, Microbiology, University of California, San Francisco
2012-2015  Staff Scientist, The Gladstone Institute of Virology and Immunology, San Francisco
2007-2011  Research Associate Professor, Department of Molecular Biology and Microbiology, Tufts University, Boston
2001-2007  Research Assistant Professor, Department of Molecular Biology and Microbiology, Tufts University, Boston
1996-2000  Research Associate, Department of Molecular Biology and Microbiology, Tufts University, Boston
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1993-1995  Postdoctoral (Research) Associate, Department of Physics, University of California, Los Angeles

1990-1993  Postdoctoral (Research) Associate, Theoretical Physics Institute, University of Minnesota, Minneapolis

1985-1990  Researcher, Theoretical Department, A.F. Ioffe Physical Technical Institute, St. Petersburg, Russia

Languages

English: fluent
Russian: native
French: advanced
German: intermediate
Italian: elementary

Visiting positions

May 2016: Pekin University, Center for Quantitative Biology, Beijing, China.
Oct-Nov 2015: UPMC, Laboratory of Computational and Quantitative Biology, UMR 7238 CNRS-UPM, Paris, France
Oct-Dec 2011: University of Cologne, Department of Physics, Germany
Aug-Sep 2011: The Gladstone Institute of Virology and Immunology, San Francisco
June-July, 2011: University of California at San Diego, Department of Chemistry and Biochemistry, La Jolla, CA, USA
Feb 2011: Workshop on Microbial Evolution, KITP, University of California at Barbara, CA, USA
Mar, Jun-Aug 1995: Harvard University, Department of Physics, Boston, USA
Apr-May, 1995: Leiden University, Department of Physics, Leiden, Netherlands

Research areas

Computational and theoretical biology
Dynamics and evolution of viruses
Semiconductor Physics

Associations and service
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2021-2022  Organization Committee “QLife WS Quantitative Viral Dynamics Across Scales, March 21-25, 2022”

2021-now  Topic Editorial Board of Microorganisms

2018-2019  Guest Editor of Pathogens

2006-2009  Associate Editor of the Journal of Mathematical Analysis and Applications

2015-2017  Member of the Society for Mathematical Biology

2013-2016  Member of the American Mathematical Society

1990-1995  Member of the American Physical Society

**Teaching**

2017-2019  Instructor in Evolution Modeling for third-year students of Sorbonne-Polytech, Paris

2013  Adjunct Professor in Astronomy for business majors, University of San Francisco

1995  Lecturer in Electricity and Magnetism for CS and EE majors, University of California at Los Angeles

2018-2020  Public lectures at la Fête de la Science, Sorbonne Université Campus Pierre et Marie Curie, Paris, [https://www.sorbonne-universite.fr/les-lois-de-la-selection-naturelle](https://www.sorbonne-universite.fr/les-lois-de-la-selection-naturelle)

**Reviewer for international journals**

AIDS Research Retroviruses  Journal of Theoretical Biology
American Naturalist  Journal of Virology
BMC Evolution  Lancet Microbe
BMC Microbiology  Nucleic Acid Research
Bulletin of Mathematical Biology  Pathogens
Cell  Proceed. of Nat. Acad. Sciences of USA
Critical Reviews of Microbiology  PLoS Computational Biology
EMBO  PLoS Pathogens
Genetics  PLoS Genetics
Genes  PLoS ONE
Evolutionary Applications  Physical Review Letters
Frontiers of Immunology  Physical Review B
Inter. Journal of Molecular Sciences  Theoretical Population Biology
Journal of Statistical Mechanics  Viruses
Reviewer for grants

2020: Vici grant proposal, Hague, Netherlands
2011: NIH research grant proposal (R01)
2012: NIH research grant proposal (R01)
2012: Vienna Research Group grant proposal for Young Investigators

Grants received

2017-2021: ANR grant "Hosting high-level researchers", $600,000 direct expenses
Title: "The fusion of modeling and data analysis to study the evolution of pathogens"
Host organization: UPMC, Paris
Role: Principal Investigator

2016-2020: Grant DARPA-BAA-16-35--INTERCEPT, USA, $273 000
Role: Co-PI (with Raul Andino, University of California San Francisco)

2014-2016: grant R21AI109611 from National Institutes of Health, $500,000 total
Title: "Experiment & theory to test an evolutionary fitness role for lentiviral latency"
Role: Co-Principal Investigator (with Leor Weinberger, Gladstone Institutes)

2006-2010: grant R01AI063926 from National Institutes of Health, USA, $1000,000 total
Title: “Working models of HIV persistence and evolution”.
Role: Principal Investigator

2001-2005: grant K25AI01811 from National Institutes of Health, USA, $600,000 total
Title: “Search for working models of HIV persistence and evolution”.
Role: Principal Investigator

Invited talks at seminars and conferences (28 total)

2021: Seminar "Progression to AIDS and HIV controllers", IAME, University de Paris, INSERM
2021: Seminar "Progression to AIDS and HIV controllers", University of Heidelberg, Germany
2020: Seminar "Progression to AIDS and HIV controllers", University of Montpelier, France
2018: 3d IFOM Symposium "Evolution, Resistance, and Cancer", IFOM, Milan, Italy.
2015: 5th Interdisciplinary Symposium "Genomics and Microbial Communities", Institut de Biologie Paris-Seine, UPMC, Paris

2015: Two seminars on the evolutionary role of HIV latency: Groupe de Travail math / bio, UPMC, Paris; Biophysique, Institut Curie, Paris

2015: Seminar on the evolutionary role of HIV latency, IBM, Almaden Research Center, San Jose, CA

2014: Seminar on modeling HIV evolution caused by the host immune response, IBM, Almaden, CA

2014: Program "Evolution of Drug Resistance", Kavli Institute of Theoretical Physics, University of California at Santa Barbara, CA

2014: "Workshop on From Within-Host Dynamics to the Epidemiology of Infectious Disease", Institute of Mathematical Biosciences, Columbus, Ohio

2014: Seminar on therapeutic interference particles, Institute of Biology, Paris Seine, UPMC, 2012: Workshop on Discrete and Topological Models in Molecular Biology and AMS special session on Discrete Models in Molecular Biology, University of Florida, Tampa, FL, USA

2011: Seminar on modeling immune response against influenza, Department of Physics, University of Exeter, Exeter, UK

2011: Workshop on Microbial Evolution, Kavli Institute for Theoretical Physics, University of California at Santa Barbara, Santa Barbara, CA, USA

2010: Seminar on evolution theory, The National Evolutionary Synthesis Center, Duke University, Durham, NC, USA

2009: International 3rd Eastern European and Central Asia AIDS Conference, Moscow, Russia

2007: Workshop on Theoretical Immunology, University of Leuven, Belgium

2006: Workshop on Mathematical Population Genetics, Edinburgh, UK

2006: Seminar on evolution theory, Department of Evolution and Ecology, University of California at Davis, CA, USA

2006: Two seminars on evolution theory and modeling HIV immunology, Department of Physics, University of California at San Diego, CA, USA

2005: Seminar on modeling HIV immunology, Centre for Non-Linear Dynamics, Department of Physiology, McGill University, Montreal, Canada

2004: Seminar on asexual evolution, Department of Biostatistics, University of California at Los Angeles, CA, USA

2004: Seminar on evolution and dynamics of HIV at A.F. Ioffe Physical Technical Institute, St. Petersburg, Russia

2003: Seminar in Genomics Center, Harvard University, Cambridge, MA, USA

2002: Seminar on evolution theory of asexual populations, Department of Applied Mathematics, Massachusetts Technological Institute, Cambridge, MA, USA

2002: Seminar on evolution theory of asexual populations, Department of Physics, Harvard University, Cambridge, MA, USA

1998: Meeting on HIV Dynamics and Evolution, organized by University of California at San Diego
1995: Seminar on antigenic escape of HIV from the immune response, Department of Microbiology, University of California, CA, USA

Other presentations at conferences

2021: EEID Agropolis International (Université de Montpellier)
2021: WIP ANRS AC41 (ANRS, Paris)
2021: Alphy: Genomique evolutive (Université de Montpelier, Lyon, Grenoble)
2020: Approche Interdisciplinaire de l’Evolution Moleculaire, Annual Meeting (CNRS INEE)
2012-2013: 4 informal seminars and 6 talks at the University of California at San Francisco
2012: 20+ conferences including annual series:
Meeting on HIV evolution and dynamics (organized by UCSD, La Jolla, CA, USA)
Retroviruses (Cold Spring Harbor, NY)
Conference on Retroviruses and Opportunistic Infections
Keystone meetings at Keystone, Colorado, and Banff, Alberta, Canada

1990-1995:
8-9 conferences including annual series:
Meeting of American Physical Society
Aspen Workshop on Condensed Matter Theory, Aspen, Colorado

Instruction of graduate and postdoctoral students

2020: Luis Pereira, postdoctoral associate, Sorbonne Université Campus Pierre et Marie Curie, Paris
2018: Ayuna Barlukova, postdoctoral associate, Sorbonne Université Campus Pierre et Marie Curie, Paris
2017-2019: Gabriele Pedruzzi, postdoctoral associate, Sorbonne Université Campus Pierre et Marie Curie, Paris
2014-2015: Ariel Weinberger, collaborator and postdoctoral fellow at Harvard University
2013-2015: Luke Rast, intern, Gladstone Institute of Virology and Immunology, University of California, San Francisco
2012: Lisa Bishop, postdoctoral associate, Gladstone Institute of Virology and Immunology, University of California at San Francisco
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2008-2012: Rebecca Batorsky, graduate student, Department of Physics at Tufts University, Boston.

2006-2009: Rinat Sergeev, postdoctoral associate, Department of Molecular Biology and Microbiology, Tufts University. (Current employment: Institute for Quantitative Social Science, Harvard University)

2007-2008: Elena Gubankova, postdoctoral associate, Department of Molecular Biology and Microbiology, Tufts University

2003-2005: Speranta Gheorghiu, postdoctoral associate, Department of Molecular Biology and Microbiology, Tufts University

Collaboration with experimental teams

Raul Andino lab, Department of Microbiology and Immunology, University of California at San Francisco
Weinberger lab of Synthetic and Quantitative Virology, Gladstone Institute of Virology and Immunology, San Francisco
Coffin lab of Retrovirology, Department of Molecular Biology and Microbiology, Tufts University, Boston
John Coffin, Director (now Special Consultant), the HIV Drug Resistance Program at National Cancer Institute, NIH, Frederick, DC, USA
Novella lab of RNA virus evolution, College of Medicine, University of Toledo, Toledo, OH, USA
Rafi Ahmed, Director, Emory Vaccine Center, Atlanta, GA, USA
Results beyond the state-of-art


The first accurate mathematical analysis predicting the evolution rate of a population with a large number of linked loci in the absence of recombination.


An evolutionary role for HIV latency is a Trojan horse effect during transmission.


The classical stochastic theory of evolution 1930-1970 is reviewed and adapted for virology.

IM Rouzine (2020) An evolutionary model of progression to AIDS. Microorganisms 8, 1714

The first closed model of progression to AIDS is proposed based on gradual adaptation of HIV to a host is proposed.


The traveling wave theory is generalized for the arbitrary distribution of mutational fitness effects.


A model of genetic evolution of a virus in a host population accumulating the immune memory connects epidemiology to immunology and the modern evolution theory. The predicted parameters are tested against data for influenza A.


The effective population size and the effective recombination rate of HIV are estimated correctly for the first time.
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Recombination is incorporated in the modern multi-locus evolution theory


The high diversity of HIV within and between infected individuals is explained as a result of compensatory mutations for the early escape mutations in CD8 T cell epitopes. The average value of the effective selection coefficient for HIV patient is estimated.


Chaotic oscillations of parasitemia in malaria are predicted as a result of communication between different parasites in different phases of cell replication.

Books


Book chapters

* Auteur correspondant


https://www.worldscientific.com/doi/abs/10.1142/9789814434447_0017
Peer-reviewed publications (64 total)

*Computational and theoretical biology*


**Rouzine IM** (2020) An evolutionary model of progression to AIDS. *Microorganisms* 8, 1714 IF 4.2


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Rouzine* IM, Coffin JM (1999) T cell turnover in SIV infection [comment]. Science 284: 555b IF 37.2

Theoretical physics
(Note spelling of name “Rouzine” as “Ruzin” from Cyrillic original name “Рузин”)


Cooper* NR, Halperin BI, Ruzin IM Thermoelectric response of an interacting two-dimensional electron gas in quantizing magnetic field. Phys Rev B 1997; 55: 2344-

Ruzin* IM, Cooper N, Halperin BI Non-universal behavior of finite quantum Hall systems as a result of weak macroscopic inhomogeneities. Phys Rev B 1996; 53: 1558-


Glazman* LI, Ruzin IM Metal-to-insulator crossover in mesoscopic wires [review]. Physica Scripta 1992; T42: 122-


Raikh ME, Ruzin IM Fluctuations of the hopping conductance of one-dimensional systems. Sov Phys JETP 1989; 68: 642-647


Levin EI, Ruzin IM, Shklovskii BI Transverse hopping conductivity of amorphous films in strong electric fields. Sov Phys Semicond 1988; 22: 401-408


Raikh ME, Ruzin IM Temperature dependence of fluctuation excess currents flowing across a metal-semiconductor contact. Sov Phys Semicond 1987; 21: 283-285

Raikh ME, Ruzin IM Mesoscopic behavior of the temperature dependence of the transverse hopping conductivity of an amorphous film. JETP Lett 1986; 43: 563-565


Raikh* ME, Ruzin IM Fluctuation mechanism of excess tunnel currents in reverse-biased p-n- junctions. Sov Phys Semicond 1985; 19: 745-750