Understanding the human innate immune system

In-silico studies

Presbitero, L.A.

Publication date
2019

Document Version
Other version

License
Other

A

Addenda

Acknowledgments

Journal Publications

Conference Proceedings

Prepared Manuscripts

Addenda

What do you see when you turn out the light?
I can't tell you, but I know it's mine.

Oh, I get by with a little help from my friends

~ The Beatles

Acknowledgments

I moved to Saint Petersburg, Russia in the heart of winter back in December 2015.

I remember having a full-course dinner at a café called "*The Idiot*" to celebrate my birthday, an empty seat in front of me. I remember looking out the window, mesmerized as I see, for the first time, snow, which I fondly call a slow-motion version of rain, lazily piling on the river embankment. I have not gotten used to the lack of sunshine yet, still confused at how swiftly the city gets devoured by darkness.

I've come a long way from home to pursue a PhD that, looking back from now, I was not even prepared for.

This is the corner in my thesis where I can fully express my deepest gratitude to the people who have shaped me as a researcher. I've come a long way, and I still have a long way to go. Indeed, it's not always about the destination.

To **Professor Dr. Peter M.A. Sloot** who has been an excellent mentor, who provided me the necessary guidance I needed, and the motivation to keep going and digging deeper into the fascinating realm of the innate immune response, a field that I've grown to love over the years. To **Dr. Valeria V. Krzhizhanovskaya**, my daily supervisor in Russia, who always has a smile for everyone, and with whom I exchange ideas with over tea, coffee and chocolates, and that person who always has my back when it comes to battling with bureaucracy. To **Dr. Emiliano Mancini** and **Dr. Rick Quax** who both have given me a concrete lesson on being a researcher, and for giving me valuable feedback that immensely improved my work. To **Dr. Ruud Brands**, the token immunologist in the team, whom I converse with regarding the amazing biology behind the system I am working on. To the **ITMO university personalities** for giving me "*the*" Russian environment I called my second home.

To my **family**, to **Mommy**, **Ariel**, **Ate, JJ** and **Kuya**, who constantly reminded me to continue the struggle each day. To my **barkada**, **Che** and **Miguel**, who are always a click away, and kept me sane throughout my PhD. To **Neen** for the lovely layout of my cover page. To **Vlad** for being my confidante in every aspect. And to **spider**, for making me appreciate the small things in life (pun intended).

Journal Publications

Presbitero, A., Mancini, E., Brands, R., Krzhizhanovskaya, V. V., & Sloot, P. M. A. (2018). Supplemented Alkaline Phosphatase Supports the Immune Response in Patients Undergoing Cardiac Surgery: Clinical and Computational Evidence. Frontiers in Immunology, 9, 2342. https://doi.org/10.3389/fimmu.2018.02342

All authors have contributed substantially to the conception and design of the work. All authors have drafted and revised the work for intellectual content. All authors have equally provided the approval for plausible publication of the content. All authors have agreed to be accountable for all aspects of the work, which includes ensuring the accuracy and integrity of all parts of the work.

Presbitero, A., Mancini, E., Castiglione, F., Krzhizhanovskaya, V. V., & Quax, R. (2019). Game of Neutrophils: Modeling the Balance Between Apoptosis and Necrosis. BMC Bioinformatics. (*manuscript accepted for publication*)

A.P. conceived the idea. All authors contributed to developing the model. A.P. designed the coding work and performed the computational experiments. R.Q. and V.V.K. supervised the findings of this work. All authors have contributed to the writing of the article. All authors have read and approved the final version of the manuscript.

Presbitero, A., & Monterola, C. (2018). Challenging the evolution of social cooperation in a community governed by central control. Physica A: Statistical Mechanics and Its Applications. https://doi.org/10.1016/j.physa.2018.08.008

A.P. developed the model. A.P. designed the coding work and performed the computational experiments. C.P. supervised the findings of this work. All authors have contributed to the writing of the article.

Conference Proceedings

Presbitero, Alva, Mancini, E., Castiglione, F., Krzhizhanovskaya, V. V., & Quax, R. (2018). Evolutionary Game Theory Can Explain the Choice Between Apoptotic and Necrotic Pathways in Neutrophils. In 2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM) (pp. 1401–1405). IEEE. https://doi.org/10.1109/BIBM.2018.8621127

Presbitero, A., Quax, R., Krzhizhanovskaya, V., & Sloot, P. (2017). Anomaly Detection in Clinical Data of Patients Undergoing Heart Surgery. In Procedia Computer Science (Vol. 108). https://doi.org/10.1016/j.procs.2017.05.002

Presbitero, A., Krzhizhanovskaya, V., Mancini, E., Brands, R., & Sloot, P. (2016). Immune System Model Calibration by Genetic Algorithm. In Procedia Computer Science (Vol. 101). https://doi.org/10.1016/j.procs.2016.11.020

Presbitero, Alva, Krzhizhanovskaya, V., & Sloot, P. (2016). Reproducibility of Three Innate Immune System Models. Lecture Notes in Computer Science, in print.

Prepared Manuscript

Presbitero, A., Quax, R., Mancini, E., Brands, R., Krzhizhanovskaya, V. V. & Sloot, P. M. A. Detecting Critical Transitions in the Human Innate Immune System Post-Cardiac Surgery

A.P. designed the coding work and performed the computational experiments. R.B. provided consultation for the biology behind the model assumptions. E.M. provided feedback on the manuscript. P.M.A.S. and V.V.K. supervised the findings of this work. All authors have contributed to the writing of the article.

References

1. Gordon, S. Elie Metchnikoff: Father of natural immunity. *European Journal of Immunology* (2008). doi:10.1002/eji.200838855
2. Yatim, K. M. & Lakkis, F. G. A brief journey through the immune system. *Clin. J. Am. Soc. Nephrol.* (2015). doi:10.2215/CJN.10031014
3. Janeway, C. A. & Medzhitov, R. Innate Immune Recognition. *Annu. Rev. Immunol.* (2002).
4. Chaplin, D. D. Overview of the immune response. *J. Allergy Clin. Immunol.* (2010). doi:10.1016/j.jaci.2009.12.980
5. Netea, M. G., Latz, E., Mills, K. H. G. & O'Neill, L. A. J. Innate immune memory: A paradigm shift in understanding host defense. in *Nature Immunology* (2015). doi:10.1038/ni.3178
6. Turvey, S. E. & Broide, D. H. Innate immunity. *J. Allergy Clin. Immunol.* **125**, (2010).
7. Presbitero, A., Mancini, E., Brands, R., Krzhizhanovskaya, V. V. & Sloot, P. M. A. Supplemented Alkaline Phosphatase Supports the Immune Response in Patients Undergoing Cardiac Surgery: Clinical and Computational Evidence. *Front. Immunol.* **9**, 2342 (2018).
8. Van Veen, S. Q. *et al.* Bovine intestinal alkaline phosphatase attenuates the inflammatory response in secondary peritonitis in mice. *Infect. Immun.* **73**, 4309–4314 (2005).
9. Kats, S. *et al.* Prophylactic treatment with alkaline phosphatase in cardiac surgery induces endogenous alkaline phosphatase release. *Int. J. Artif. Organs* **35**, 144–151 (2012).
10. Von Neumann, J. & Morgenstern, O. Theory of Games and Economic Behavior. *Princet. Univ. Press* 625 (1944). doi:10.1177/1468795X06065810
11. Helbing, D. & Yu, W. The outbreak of cooperation among success-driven individuals under noisy conditions. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 3680–5 (2009).
12. Presbitero, A. & Monterola, C. Challenging the evolution of social cooperation in a community governed by central control. *Phys. A Stat. Mech. its Appl.* (2018). doi:10.1016/j.physa.2018.08.008
13. Torres-Dueñas, D., Benjamim, C. F., Ferreira, S. H. & Cunha, F. Q. Failure of neutrophil migration to infectious focus and cardiovascular changes on sepsis in rats: Effects of the inhibition of nitric oxide production, removal of infectious focus, and antimicrobial treatment. *Shock* (2006). doi:10.1097/01.shk.0000208804.34292.38
14. Benjamim, C. F., Ferreira, S. H. & Cunha, F. d. Q. Role of Nitric Oxide in the Failure of Neutrophil Migration in Sepsis. *J. Infect. Dis.* (2002). doi:10.1086/315682
15. Dakos, V. *et al.* Methods for detecting early warnings of critical transitions in time series illustrated using simulated ecological data. *PLoS One* **7**, (2012).
16. Tettey, M. *et al.* Predictors of post operative bleeding and blood transfusion in cardiac surgery. *Ghana Med. J.* (2011). doi:10.4314/gmj.v43i2.55316
17. Shander, A. Financial and clinical outcomes associated with surgical bleeding complications. *Surgery* (2007). doi:10.1016/j.surg.2007.06.025
18. Zbrozek, A. & Magee, G. Cost of Bleeding in Trauma and Complex Cardiac Surgery.

Clin. Ther. (2015). doi:10.1016/j.clinthera.2015.06.007
19. Spahn, D. R. *et al.* Management of bleeding and coagulopathy following major trauma: An updated European guideline. *Crit. Care* (2013). doi:10.1186/cc12685
20. Robison, R. The Possible Significance of Hexosephosphoric Esters in Ossification. *Biochem. J.* 17, 286–93 (1923).
21. Poelstra, K., Bakker, W. W., Klok, P. A., Hardonk, M. J. & Meijer, D. K. A physiologic function for alkaline phosphatase: endotoxin detoxification. *Lab Invest* 76, 319–327 (1997).
22. Poelstra, K. *et al.* Dephosphorylation of endotoxin by alkaline phosphatase in vivo. *Am. J. Pathol.* 151, 1163–1169 (1997).
23. Koyama, I., Matsunaga, T., Harada, T., Hokari, S. & Komoda, T. Alkaline phosphatases reduce toxicity of lipopolysaccharides in vivo and in vitro through dephosphorylation. *Clin. Biochem.* 35, 455–461 (2002).
24. Bentala, H. *et al.* Removal of phosphate from lipid A as a strategy to detoxify lipopolysaccharide. *Shock* 18, 561–566 (2002).
25. Beumer, C. *et al.* Calf intestinal alkaline phosphatase, a novel therapeutic drug for lipopolysaccharide (LPS)-mediated diseases, attenuates LPS toxicity in mice and piglets. *J. Pharmacol. Exp. Ther.* 307, 737–744 (2003).
26. Van Veen, S. Q., Dinant, S., Van Vliet, A. K. & Van Gulik, T. M. Alkaline phosphatase reduces hepatic and pulmonary injury in liver ischaemia-reperfusion combined with partial resection. *Br. J. Surg.* 93, 448–456 (2006).
27. Goldberg, R. F. *et al.* Intestinal alkaline phosphatase is a gut mucosal defense factor maintained by enteral nutrition. *Proc. Natl. Acad. Sci.* 105, 3551–3556 (2008).
28. Kats, S. *et al.* Anti-inflammatory effects of alkaline phosphatase in coronary artery bypass surgery with cardiopulmonary bypass. *Recent Pat Inflamm Allergy Drug Discov* 3, 214–220 (2009).
29. Kaliannan, K. *et al.* Intestinal alkaline phosphatase prevents metabolic syndrome in mice. *Proc. Natl. Acad. Sci. U. S. A.* 110, 7003–8 (2013).
30. Huizinga, R. *et al.* Endotoxin- and ATP-neutralizing activity of alkaline phosphatase as a strategy to limit neuroinflammation. *J. Neuroinflammation* 9, 754 (2012).
31. Moss, A. K. *et al.* Intestinal alkaline phosphatase inhibits the proinflammatory nucleotide uridine diphosphate. *AJP Gastrointest. Liver Physiol.* 304, G597–G604 (2013).
32. Malo, M. S. *et al.* Intestinal alkaline phosphatase preserves the normal homeostasis of gut microbiota. *Gut* 59, 1476–84 (2010).
33. Poelstra, K., Bakker, W. W., Klok, P. A., Hardonk, M. J. & Meijer, D. K. A physiologic function for alkaline phosphatase: endotoxin detoxification. *Lab. Invest.* 76, 319–27 (1997).
34. Geddes, K., Philpott, D. J., Kuhlman, J. & al., et. A new role for intestinal alkaline phosphatase in gut barrier maintenance. *Gastroenterology* 135, 8–12 (2008).
35. Matzinger, P. An innate sense of danger The signals that initiate immune responses. *Semin. IMMU Nol.* 10, 399–415 (1998).
36. Miller, S. I., Ernst, R. K. & Bader, M. W. LPS, TLR4 and infectious disease diversity. *Nat. Rev. Microbiol.* 3, 36–46 (2005).
37. Riggle, K. M. *et al.* Intestinal alkaline phosphatase prevents the systemic inflammatory response associated with necrotizing enterocolitis. *J. Surg. Res.* 180, 21–6 (2013).
38. Pickkers, P. *et al.* Clinical pharmacology of exogenously administered alkaline phosphatase. *Eur. J. Clin. Pharmacol.* 65, 393–402 (2009).

39. Heemskerk, S. *et al.* Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients. *Crit. Care Med.* 37, 417–23, e1 (2009).
40. Head, S. J., Kieser, T. M., Falk, V., Huysmans, H. A. & Kappetein, A. P. Coronary artery bypass grafting: Part 1 - the evolution over the first 50 years. *European Heart Journal* 34, 2862–2872 (2013).
41. D'Agostino, R. S. *et al.* The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2017 Update on Outcomes and Quality. *Ann. Thorac. Surg.* 103, 18–24 (2017).
42. Laffey, J. G., Boylan, J. F. & Cheng, D. C. H. The systemic inflammatory response to cardiac surgery. *Anesthesiology* 97, 215–252 (2002).
43. Lauffenburger, D. & Keller, K. H. Effects of leukocyte random motility and chemotaxis in tissue inflammatory response. *J. Theor. Biol.* 81, 475–503 (1979).
44. Lauffenburger, D., Aris, R. & Keller, K. Effects of cell motility and chemotaxis on microbial population growth. *Biophys. J.* 40, 209–219 (1982).
45. Lauffenburger, D. A. & Kennedy, C. R. Localized bacterial infection in a distributed model for tissue inflammation. *J. Math. Biol.* 16, 141–163 (1983).
46. Reynolds, A. *et al.* A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation. *J. Theor. Biol.* 242, 220–236 (2006).
47. Kumar, R., Clermont, G., Vodovotz, Y. & Chow, C. C. The dynamics of acute inflammation. *J. Theor. Biol.* 230, 145–155 (2004).
48. Dunster, J. L., Byrne, H. M. & King, J. R. The resolution of inflammation: a mathematical model of neutrophil and macrophage interactions. *Bull. Math. Biol.* 76, 1953–1980 (2014).
49. Su, B., Zhou, W., Dorman, K. S. & Jones, D. E. Mathematical Modelling of Immune Response in Tissues. *Comput. Math. Methods Med.* 10, 9–38
50. Pigozzo, A. B., Macedo, G. C., Santos, R. W. dos & Lobosco, M. On the computational modeling of the innate immune system. *BMC Bioinformatics* 14 Suppl 6, S7 (2013).
51. Andrew, S. M., Baker, C. T. H. & Bocharov, G. A. Rival approaches to mathematical modelling in immunology. *J. Comput. Appl. Math.* 205, 669–686 (2007).
52. Janeway, C. A., Travers, P., Walport, M. & Shlomchik, M. *Immunobiology: The Immune System In Health And Disease*. *Immuno Biology 5* (2001). doi:10.1111/j.1467-2494.1995.tb00120.x
53. Damas, P. *et al.* Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg* 215, 356–362 (1992).
54. Flögel, U., Willker, W. & Leibfritz, D. Determination of de novo synthesized amino acids in cellular proteins revisited by 13C NMR spectroscopy. *NMR Biomed.* 10, 50–58 (1997).
55. Yoshikawa, M., Yamauchi, K. & Masago, H. De Novo Messenger RNA and Protein Synthesis Are Required for Phytoalexin-mediated Disease Resistance in Soybean Hypocotyls. *Plant Physiol.* 61, 314–7 (1978).
56. van der Graaf, P. H. & Benson, N. Systems Pharmacology: Bridging Systems Biology and Pharmacokinetics-Pharmacodynamics (PKPD) in Drug Discovery and Development. *Pharm. Res.* 28, 1460–1464 (2011).
57. Helmlinger, G. *et al.* Drug-disease modeling in the pharmaceutical industry - where mechanistic systems pharmacology and statistical pharmacometrics meet. *European Journal of Pharmaceutical Sciences* 109, S39–S46 (2017).
58. Gadkar, K., Kirouac, D. C., Mager, D. E., Van Der Graaf, P. H. & Ramanujan, S. A six-stage

workflow for robust application of systems pharmacology. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 235–249 (2016).
59. Watanabe, T. *et al.* The role of HMGB-1 on the development of necrosis during hepatic ischemia and hepatic ischemia/reperfusion injury in mice. *J. Surg. Res.* **124**, 59–66 (2005).
60. Baumann, A. *et al.* RECCAS -REmoval of Cytokines during CArdiac Surgery: study protocol for a randomised controlled trial. *Trials* 1–8 (2016). doi:10.1186/s13063-016-1265-9
61. Tibi, L., Chhabra, S. C., Sweeting, V. M., Winney, R. J. & Smith, A. F. Multiple forms of alkaline phosphatase in plasma of hemodialysis patients. *Clin. Chem.* **37**, (1991).
62. Su, B., Zhou, W., Dorman, K. S. & Jones, D. E. Mathematical Modelling of Immune Response in Tissues. *Comput. Math. Methods Med.* **10**, 9–38 (2009).
63. Price, C. P. Multiple Forms of Human Serum Alkaline Phosphatase: Detection and Quantitation. *Ann. Clin. Biochem.* **30**, 355–372 (1993).
64. Kiffer-Moreira, T. *et al.* Catalytic signature of a heat-stable, chimeric human alkaline phosphatase with therapeutic potential. *PLoS One* **9**, (2014).
65. Kawai, S. *et al.* The Role of Interleukin-10 in Systemic Inflammatory Response Syndrome with Sepsis. *J. Infect. Chemother.* **4**, 121–127 (1998).
66. Starr, C. & Taggart, R. *Biology: The Unity and Diversity of Life*. *Diversity* (2009).
67. Nocedal, J. & Wright, S. J. *Numerical optimization*. *Springer series in operations research* (2006). doi:10.1007/978-0-387-40065-5
68. Kawai, S. *et al.* The role of interleukin-10 in systemic inflammatory response syndrome with sepsis. *J. Infect. Chemother.* **4**, 121–127 (1998).
69. Li, Y., Karlin, A., Loike, J. D. & Silverstein, S. C. A critical concentration of neutrophils is required for effective bacterial killing in suspension. *Proc. Natl. Acad. Sci. U. S. A.* **99**, 8289–8294 (2002).
70. Swameye, I., Muller, T. G., Timmer, J., Sandra, O. & Klingmuller, U. Identification of nucleocytoplasmic cycling as a remote sensor in cellular signaling by databased modeling. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 1028–1033 (2003).
71. Raue, A. *et al.* Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics* **25**, 1923–1929 (2009).
72. Saltelli, A., Chan, K. & Scott, E. M. *Sensitivity Analysis*. *Wiley series in probability and statistics* (2000).
73. Schaibly, J. H. & Shuler, K. E. Study of the sensitivity of coupled reaction systems to uncertainties in rate coefficients. II Applications. *J. Chem. Phys.* **59**, 3879–3888 (1973).
74. Cukier, R. I., Schaibly, J. H. & Shuler, K. E. Study of the sensitivity of coupled reaction systems to uncertainties in rate coefficients. III. Analysis of the approximations. *J. Chem. Phys.* **63**, 1140–1149 (1975).
75. Cukier, R. I., Fortuin, C. M., Shuler, K. E., Petschek, A. G. & Schaibly, J. H. Study of the sensitivity of coupled reaction systems to uncertainties in rate coefficients. I Theory. *J. Chem. Phys.* **59**, 3873–3878 (1973).
76. Cukier, R. I., Levine, H. B. & Shuler, K. E. Nonlinear sensitivity analysis of multiparameter model systems. in *Journal of Physical Chemistry* **81**, 2365–2366 (1977).
77. Savill, J. S. *et al.* Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. *J. Clin. Invest.* (1989). doi:10.1172/JCI113970

78. Kruger, P. *et al*. Neutrophils: Between Host Defence, Immune Modulation, and Tissue Injury. *PLoS Pathogens* (2015). doi:10.1371/journal.ppat.1004651
79. Barton, G. M. A calculated response: Control of inflammation by the innate immune system. *Journal of Clinical Investigation* (2008). doi:10.1172/JCI34431
80. Cartwright, G., Athens, J. & Wintrobe, M. The kinetics of granulopoiesis in normal man. *Blood* (1964). doi:http://dx.doi.org.proxy.library.uu.nl/
81. Coxon, A. *et al.* A novel role for the β2 integrin CD11b/CD18 in neutrophil apoptosis: A homeostatic mechanism in inflammation. *Immunity* (1996). doi:10.1016/S1074-7613(00)80278-2
82. Ulevitch, R. J. & Tobias, P. S. Recognition of Gram-negative bacteria and endotoxin by the innate immune system. *Current Opinion in Immunology* (1999). doi:10.1016/S0952-7915(99)80004-1
83. Fox, S., Leitch, A. E., Duffin, R., Haslett, C. & Rossi, A. G. Neutrophil apoptosis: Relevance to the innate immune response and inflammatory disease. *Journal of Innate Immunity* (2010). doi:10.1159/000284367
84. Turina, M., Miller, F. N., McHugh, P. P., Cheadle, W. G. & Polk, H. C. Endotoxin inhibits apoptosis but induces primary necrosis in neutrophils. *Inflammation* **29**, 55–63 (2005).
85. McClenahan, D. *et al*. Effects of lipopolysaccharide and Mannheimia haemolytica leukotoxin on bovine lung microvascular endothelial cells and alveolar epithelial cells. *Clin. Vaccine Immunol.* (2008). doi:10.1128/CVI.00344-07
86. Jones, H. R., Robb, C. T., Perretti, M. & Rossi, A. G. The role of neutrophils in inflammation resolution. *Seminars in Immunology* (2016). doi:10.1016/j.smim.2016.03.007
87. Fisher, D., Wicks, P. & Babar, Z. U. D. Medicine and the future of health: Reflecting on the past to forge ahead. *BMC Medicine* (2016). doi:10.1186/s12916-016-0717-0
88. Okin, D. & Medzhitov, R. Evolution of inflammatory diseases. *Current Biology* (2012). doi:10.1016/j.cub.2012.07.029
89. Presbitero, A., Mancini, E., Castiglione, F., Krzhizhanovskaya, V. V. & Quax, R. Evolutionary Game Theory Can Explain the Choice Between Apoptotic and Necrotic Pathways in Neutrophils. in *2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)* 1401–1405 (IEEE, 2018). doi:10.1109/BIBM.2018.8621127
90. Chiacchio, F., Pennisi, M., Russo, G., Motta, S. & Pappalardo, F. Agent-based modeling of the immune system: NetLogo, a promising framework. *Biomed Res. Int.* **2014**, (2014).
91. Celada, F. & Seiden, P. E. A computer model of cellular interactions in the immune system. *Immunol. Today* **13**, 56–62 (1992).
92. Halling-Brown, M. *et al.* Immunogrid: Towards agent-based simulations of the human immune system at a natural scale. *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.* (2010). doi:10.1098/rsta.2010.0067
93. Weibull, J. W. *Evolutionary game theory*. *The MIT Press* (1986). doi:10.1016/0167-2789(86)90232-0
94. Hofbauer, J. & Sigmund, K. *The theory of evolution and dynamical systems: mathematical aspects of selection*. *London Mathematical Society student texts* (1988). doi:10.1007/BF00049131
95. Maynard Smith, J. The theory of games and the evolution of animal conflicts. *J. Theor. Biol.* (1974). doi:10.1016/0022-5193(74)90110-6
96. Nash, J. F. Equilibrium points in n-person games. *Proc. Natl. Acad. Sci.* (1950).

doi:10.1073/pnas.36.1.48

97. Francis, K. & Palsson, B. O. Effective intercellular communication distances are determined by the relative time constants for cyto/chemokine secretion and diffusion. *Proc. Natl. Acad. Sci. U. S. A.* **94**, 12258–62 (1997).

98. Wolfram, S. Stephen Wolfram: A New Kind of Science. *Wolfram Media* (2002).

99. Williams, M. R., Azcutia, V., Newton, G., Alcaide, P. & Luscinskas, F. W. Emerging mechanisms of neutrophil recruitment across endothelium. *Trends in Immunology* (2011). doi:10.1016/j.it.2011.06.009

100. Sadik, C. D., Kim, N. D. & Luster, A. D. Neutrophils cascading their way to inflammation. *Trends in Immunology* (2011). doi:10.1016/j.it.2011.06.008

101. Mócsai, A., Walzog, B. & Lowell, C. A. Intracellular signalling during neutrophil recruitment. *Cardiovascular Research* (2015). doi:10.1093/cvr/cvv159

102. Presbitero, A. & Monterola, C. Challenging the evolution of social cooperation in a community governed by central control. *Phys. A Stat. Mech. its Appl.* **511**, (2018).

103. Axelrod, R. & Hamilton, W. D. The Evolution of Cooperation. *Science* **211**, 1390–6 (1981).

104. Dawkins, R. *The Selfish Gene : 30th Anniversary edition*. *Oxford University Press* (2006). doi:0195673441

105. Keller, L. & Chapuisat, M. Cooperation Among Selfish Individuals In Insect Societies. *Bioscience* **49**, 899–909 (1999).

106. Jiang, L. L., Wang, W. X., Lai, Y. C. & Wang, B. H. Role of adaptive migration in promoting cooperation in spatial games. *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* **81**, (2010).

107. Challet, D. & Zhang, Y.-C. Emergence of cooperation and organization in an evolutionary game. *Phys. A Stat. Mech. its Appl.* **246**, 407–418 (1997).

108. Axelrod, R. The Emergence of Cooperation among Egoists. *Am. Polit. Sci. Rev.* **75**, 306–318 (1981).

109. Nowak, M. A., Sasaki, A., Taylor, C. & Fudenberg, D. Emergence of cooperation and evolutionary stability in finite populations. *Nature* **428**, 646–650 (2004).

110. Xie, F., Cui, W. & Lin, J. Prisoner's dilemma game on adaptive networks under limited foresight. *Complexity* **18**, 38–47 (2013).

111. Nowak, M. A. & May, R. M. Evolutionary games and spatial chaos. *Nature* **359**, 826–829 (1992).

112. Szolnoki, A. & Perc, M. Reward and cooperation in the spatial public goods game. *EPL (Europhysics Lett.* **92**, 38003 (2010).

113. Szolnoki, A. & Perc, M. Evolutionary advantages of adaptive rewarding. *New J. Phys.* **14**, 93016 (2012).

114. Hauert, C., Traulsen, A., Brandt, H., Nowak, M. A. & Sigmund, K. Via Freedom to Coercion: The Emergence of Costly Punishment. *Science (80-.).* **316**, 1905–1907 (2007).

115. Ohtsuki, H., Iwasa, Y. & Nowak, M. A. Indirect reciprocity provides only a narrow margin of efficiency for costly punishment. *Nature* **457**, 79–82 (2009).

116. Helbing, D., Szolnoki, A., Perc, M. & Szabó, G. Evolutionary establishment of moral and double moral standards through spatial interactions. *PLoS Comput. Biol.* **6**, 1–9 (2010).

117. Wang, Z., Xia, C.-Y., Meloni, S., Zhou, C.-S. & Moreno, Y. Impact of Social Punishment on Cooperative Behavior in Complex Networks. *Sci. Rep.* **3**, 3055 (2013).

118. Szolnoki, A., Szabó, G. & Perc, M. Phase diagrams for the spatial public goods game

with pool punishment. *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* **83**, 36101 (2011).
119. Szolnoki, A. & Perc, M. Second-order free-riding on antisocial punishment restores the effectiveness of prosocial punishment. *Phys. Rev. X* **7**, (2017).
120. Vainstein, M. H., T.C. Silva, A. & Arenzon, J. J. Does mobility decrease cooperation? *J. Theor. Biol.* **244**, 722–728 (2007).
121. Meloni, S. *et al.* Effects of mobility in a population of prisoner's dilemma players. *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* **79**, 67101 (2009).
122. Chen, Z., Gao, J., Cai, Y. & Xu, X. Evolution of cooperation among mobile agents. *Physica A* **390**, 1615–1622 (2011).
123. Wang, Z., Chen, T., Wang, X., Jin, J. & Li, M. Evolution of co-operation among mobile agents with different influence. *Phys. A Stat. Mech. its Appl.* **392**, 4655–4662 (2013).
124. Santos, F. C., Santos, M. D. & Pacheco, J. M. Social diversity promotes the emergence of cooperation in public goods games. *Nature* **454**, 213–216 (2008).
125. Perc, M. Chaos promotes cooperation in the spatial prisoner's dilemma game. *Europhys. Lett.* **75**, 841–846 (2006).
126. Perc, M. *et al.* Coherence resonance in a spatial prisoner's dilemma game. *New J. Phys* **8**, 1367–2630 (2006).
127. Perc, M. Transition from Gaussian to Levy distributions of stochastic payoff variations in the spatial prisoner's dilemma game. *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* **75**, 22101 (2007).
128. Perc, M. & Szolnoki, A. Coevolutionary games-A mini review. *BioSystems* **99**, 109–125 (2010).
129. Perc, M. *et al.* Statistical physics of human cooperation. *Physics Reports* **687**, 1–51 (2017).
130. Bonner, J. T. *The social amoebae : the biology of cellular slime molds*. (Princeton University Press, 2009).
131. Naeger, N. L., Peso, M., Even, N., Barron, A. B. & Robinson, G. E. Altruistic behavior by egg-laying worker honeybees. *Curr. Biol.* **23**, 1574–1578 (2013).
132. Bartal, I. B.-A., Decety, J. & Mason, P. Empathy and Pro-Social Behavior in Rats. *Science (80-.).* **334**, 1427–1430 (2011).
133. Capraro, V. The emergence of hyper-altruistic behaviour in conflictual situations. *Sci. Rep.* **4**, 9916 (2015).
134. Crockett, M. J., Kurth--Nelson, Z., Siegel, J. Z., Dayan, P. & Dolan, R. J. Harm to Others Outweighs Harm to Self in Moral Decision Making. *PNAS* **111**, 17320–17325 (2014).
135. Lotem, A., Fishman, M. A. & Stone, L. Evolution of cooperation between individuals. *Nature* **400**, 226–227 (1999).
136. Hauser, O. P., Nowak, M. A. & Rand, D. G. Punishment does not promote cooperation under exploration dynamics when anti-social punishment is possible. *J. Theor. Biol.* (2014). doi:10.1016/j.jtbi.2014.06.041
137. Yamamoto, H. & Okada, I. How to keep punishment to maintain cooperation: Introducing social vaccine. *Phys. A Stat. Mech. its Appl.* **443**, 526–536 (2015).
138. Perc, M. Double resonance in cooperation induced by noise and network variation for an evolutionary prisoner's dilemma. *New J. Phys.* **8**, (2006).
139. Perc, M. & Szolnoki, A. Social diversity and promotion of cooperation in the spatial prisoner's dilemma game. *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* **77**, (2008).
140. NOWAK, M. A. & MAY, R. M. THE SPATIAL DILEMMAS OF EVOLUTION. *Int. J. Bifurc. Chaos* (2004). doi:10.1142/s0218127493000040

141. Perc, M. Coherence resonance in a spatial prisoner's dilemma game. *New J. Phys.* **8**, (2006).
142. Valenzuela, J. F. B. & Monterola, C. P. Convective flow-induced short timescale segregation in a dilute bidisperse particle suspension. *Int. J. Mod. Phys. C* **19**, 1829–1845 (2008).
143. DECRAENE, J., MONTEROLA, C., LEE, G. K. K. & HUNG, T. G. G. a Quantitative Procedure for the Spatial Characterization of Urban Land Use. *Int. J. Mod. Phys. C* **24**, 1250092 (2013).
144. Fogleman, A. S. *Hopeful journeys : German immigration, settlement, and political culture in colonial America, 1717-1775*. (University of Pennsylvania Press, 1996).
145. Perc, M. Double resonance in cooperation induced by noise and network variation for an evolutionary prisoner's dilemma. *New J. Phys.* (2006). doi:10.1088/1367-2630/8/9/183
146. Perc, M. & Szolnoki, A. Social diversity and promotion of cooperation in the spatial prisoner's dilemma game. *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* (2008). doi:10.1103/PhysRevE.77.011904
147. Capraro, V. The emergence of hyper-altruistic behaviour in conflictual situations. *Sci. Rep.* (2015). doi:10.1038/srep09916
148. Paparella, D., Yau, T. M. & Young, E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. *European Journal of Cardio-thoracic Surgery* (2002). doi:10.1016/S1010-7940(01)01099-5
149. Rubenfeld, G. D. & Herridge, M. S. Epidemiology and outcomes of acute lung injury. *Chest* (2007). doi:10.1378/chest.06-1976
150. Weissman, C. Pulmonary complications after cardiac surgery. in *Seminars in Cardiothoracic and Vascular Anesthesia* (2004). doi:10.1177/108925320400800303
151. Nalysnyk, L. Adverse events in coronary artery bypass graft (CABG) trials: a systematic review and analysis. *Heart* (2003). doi:10.1136/heart.89.7.767
152. Rong, L. Q., Di Franco, A. & Gaudino, M. Acute respiratory distress syndrome after cardiac surgery. *Journal of Thoracic Disease* (2016). doi:10.21037/jtd.2016.10.74
153. Jong, P., Vowinckel, E., Liu, P. P., Gong, Y. & Tu, J. V. Prognosis and determinants of survival in patients newly hospitalized for heart failure: A population-based study. *Arch. Intern. Med.* (2002). doi:10.1001/archinte.162.15.1689
154. Lloyd-Jones, D. *et al.* Heart disease and stroke statistics - 2010 update: A report from the American heart association. *Circulation* (2010). doi:10.1161/CIRCULATIONAHA.109.192666
155. Cohen, J. The immunopathogenesis of sepsis. *Nature* (2002). doi:10.1038/nature01326
156. Schulte, W., Bernhagen, J. & Bucala, R. Cytokines in Sepsis: Potent Immunoregulators and Potential Therapeutic Targets—An Updated View. *Mediators Inflamm.* (2013). doi:10.1155/2013/165974
157. Trefois, C., Antony, P. M. A., Goncalves, J., Skupin, A. & Balling, R. Critical transitions in chronic disease: Transferring concepts from ecology to systems medicine. *Current Opinion in Biotechnology* **34**, 48–55 (2015).
158. Liu, R. *et al.* Identifying critical transitions of complex diseases based on a single sample. *Bioinformatics* **30**, 1579–86 (2014).
159. van de Leemput, I. a *et al.* Critical slowing down as early warning for the onset and termination of depression. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 87–92 (2014).
160. May, R. M., Levin, S. a & Sugihara, G. Complex systems: ecology for bankers. *Nature*

451, 893–895 (2008).
161. Quax, R., Kandhai, D. & Sloot, P. M. a. Information dissipation as an early-warning signal for the Lehman Brothers collapse in financial time series. *Sci. Rep.* **3**, 1898 (2013).
162. Dakos, V. *et al.* Slowing down as an early warning signal for abrupt climate change. *Proc. Natl. Acad. Sci. U. S. A.* **105**, 14308–12 (2008).
163. Lenton, T. M., Livina, V. N., Dakos, V., van Nes, E. H. & Scheffer, M. Early warning of climate tipping points from critical slowing down: comparing methods to improve robustness. *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.* **370**, 1185–1204 (2012).
164. Lenton, T. M. *et al.* Tipping elements in the Earth's climate system. *Proc. Natl. Acad. Sci.* **105**, 1786–1793 (2008).
165. Krkošek, M. & Drake, J. M. On signals of phase transitions in salmon population dynamics. *Proc. R. Soc. B Biol. Sci.* **281**, 20133221 (2014).
166. Clements, C. F. & Ozgul, A. Including trait-based early warning signals helps predict population collapse. *Nat. Commun.* **7**, 10984 (2016).
167. Drake, J. M. & Griffen, B. D. Early warning signals of extinction in deteriorating environments. *Nature* **467**, 456–459 (2010).
168. Presbitero, A., Quax, R., Krzhizhanovskaya, V. & Sloot, P. Anomaly Detection in Clinical Data of Patients Undergoing Heart Surgery. in *Procedia Computer Science* **108**, (2017).
169. Pyayt, A. L. *et al.* Combining Data-Driven Methods with Finite Element Analysis for Flood Early Warning Systems. *Procedia Comput. Sci.* **51**, 2347–2356 (2015).
170. Krzhizhanovskaya, V. V. *et al.* Flood early warning system: Design, implementation and computational modules. in *Procedia Computer Science* **4**, 106–115 (2011).
171. Melnikova, N. B., Jordan, D. & Krzhizhanovskaya, V. V. Experience of using FEM for real-time flood early warning systems: Monitoring and modeling Boston levee instability. *J. Comput. Sci.* **10**, 13–25 (2015).
172. Fisher, W. D., Camp, T. K. & Krzhizhanovskaya, V. V. Crack detection in earth dam and levee passive seismic data using support vector machines. *Procedia Comput. Sci.* **80**, 577–586 (2016).
173. DeAngelis, D. L. Energy flow, nutrient cycling, and ecosystem resilience. *Ecology* **61**, 764–771 (1980).
174. Scheffer, M. *et al.* Early-warning signals for critical transitions. *Nature* **461**, 53–59 (2009).
175. Dakos, V., van Nes, E. H., D'Odorico, P. & Scheffer, M. Robustness of variance and autocorrelation as indicators of critical slowing down. *Ecology* (2012).
176. Guttal, V. & Jayaprakash, C. Changing skewness: An early warning signal of regime shifts in ecosystems. *Ecol. Lett.* **11**, 450–460 (2008).
177. Biggs, R., Carpenter, S. R. & Brock, W. A. Turning back from the brink: detecting an impending regime shift in time to avert it. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 826–31 (2009).
178. Held, H. & Kleinen, T. Detection of climate system bifurcations by degenerate fingerprinting. *Geophys. Res. Lett.* (2004). doi:10.1029/2004GL020972
179. Ives, A. R. & Dakos, V. Detecting dynamical changes in nonlinear time series using locally linear state-space models. *Ecosphere* **3**, art58 (2012).
180. Peretto, G., Durante, A., Limite, L. R. & Cianflone, D. Postoperative Arrhythmias after Cardiac Surgery: Incidence, Risk Factors, and Therapeutic Management. *Cardiol. Res. Pract.* (2014). doi:10.1155/2014/615987
181. Hashemzadeh, K., Dehdilani, M. & Dehdilani, M. Postoperative Atrial Fibrillation

following Open Cardiac Surgery: Predisposing Factors and Complications. *J Cardiovasc Thorac Res* (2013). doi:10.5681/jcvtr.2013.022
182. Nguyen, D. M., Mulder, D. S. & Shennib, H. Effect of cardiopulmonary bypass on circulating lymphocyte function. *Ann. Thorac. Surg.* (1992). doi:10.1016/0003-4975(92)90319-Y
183. Diegeler, A. *et al.* Humoral Immune Response During Coronary Artery Bypass Grafting : A Comparison of Limited Approach, 'Off-Pump' Technique, and Conventional Cardiopulmonary Bypass. *Circulation* (2000). doi:10.1161/01.cir.102.suppl_3.iii-95
184. Honda, T., Uehara, T., Matsumoto, G., Arai, S. & Sugano, M. Neutrophil left shift and white blood cell count as markers of bacterial infection. *Clinica Chimica Acta* (2016). doi:10.1016/j.cca.2016.03.017
185. Athens, J. W. Blood: Leukocytes. *Annu. Rev. Physiol.* (2003). doi:10.1146/annurev.ph.25.030163.001211
186. Dancey, J. T., Deubelbeiss, K. A. & Harker andFinch, L. A. C. A. Neutrophil kinetics in man. *J. Clin. Invest.* 58, 705–715 (1976).
187. Summers, C. *et al.* Neutrophil kinetics in health and disease. *Trends in Immunology* (2010). doi:10.1016/j.it.2010.05.006