Nicolas Gambardella – curriculum vitæ

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Education and training

2013 Habilitation to supervise research (University Bordeaux II)
1998 PhD Molecular and Cellular Pharmacology (University Paris VI)
1993 MSc Evolution, biophysics, neuroendocrinology (École Normale Supérieure, Paris)
1991 BSc Cellular Biology and Physiology (University Paris VI)
1988 Scientific Baccalaureate (Prytanée Militaire, La Flèche, France)

Position and employment

2023-present Senior Scientist, CNRS/University of Lille, France
2019-2023 Director, aSciStance Ltd, Cambridge, United-Kingdom
2012-2018 Tenured Group Leader, Babraham Institute, Cambridge, United-Kingdom
2014-2015 Consulting Chief Data Officer, Curie Institute, Paris
2003-2012 Group Leader, EMBL-EBI, Cambridge, United-Kingdom
2001-2003 Research fellow with Jean-Pierre Changeux, Pasteur institute, Paris
2001 CNRS Research fellow (Chargé de recherche), promoted director in 2010
1999-2001 Post-doctoral fellow with Dennis Bray, University of Cambridge (UK)
1992-1999 Student and postdoc with Jean-Pierre Changeux, Pasteur institute, Paris
1991 Undergraduate in the team of Michel Fardeau, INSERM, Paris

Professional memberships

2017-2018 Faculty of 1000, head of section Network and Systems Biology
2014-2016 International Society for Stem Cell Research
2010-2018 International Society for Computational Biology, Senior member 2016, board of directors 2017. Coordinator of Community of Special Interest *Systems Modelling*
2007-2018 International Society of Systems Biology, member of executive board,
2014-2018 Associate editor, NPJ Systems Biology & Applications
2012-2014 Associate editor, PeerJ
2007-2018 Associate editor, BMC Systems Biology

Management of science

Supervision of 11 PhD students, 28 undergraduate students; member of 13 PhD committees
Organised 9 courses, taught in 23; organised 17 conferences, member of 20 scientific committees
Scientific advisory boards: AERES panels (ex-HCÉRES) EU Project ENFIN, BBSRC Plant Models Portal, NIH BioPAX, EPSRC CARMEN, BBSRC project COPASI, German Virtual Liver Network, Curie Institute Research Center (Paris), Centre of Organismal Studies (Heidelberg), Centre of Integrative Biology (Toulouse), Cochin Institute (paris), Pole BioSanté Rabelais (Montpellier), Labex EpiGenMed
Funding panels for: BBSRC (UK), ANR (FR), FRM (FR), BMBF (DE), ERC (EU), SNF (CH)
Faculty hiring board: Centre for Genomic Regulation (ES), Curie Institute (FR), Cochin Institute (FR), Toulouse Center of Integrative Biology (FR)

Awards, fellowships and other markers of esteem

48 invited lectures in conferences, including plenaries at the International Conference on Systems Biology, the International Congress of Cell Biology, the Neuroinformatics Conference.
2009 Participant (invitation only), Nobel Symposium 146 Systems Biology, Stockholm, SE
2003 JM Le Goff Award (prize of the French Academy of Science)
1999 Long Term Fellowship from the European Molecular Biology Organisation (EMBO)
1998 Allocation Roux of the Institut Pasteur
1994 Allocation from the French Ministry of Research

Funding in the last 10 years of academia

[Amounts represent the shares of Gambardella, not the complete grants]
2018-2021 MRC Intraneuronal transport-related pathways across neurodegenerative diseases
2017-2022 BBSRC Signalling, Epigenetics and Immunology BI ISPs (co-PI); ~GBP 1M
2016-2019 BBSRC: Flexible management for multi-scale multi-approach models in biology; GBP272K

2016-2019 NIH: Continued Support of Essential SBML Software and Community Resources; USD178K
2016-2018 EU: Commission: COST action CHARME
2015-2017 BBSRC Software hardening and training in epigenetics and systems biology; GBP 75K
2015-2018 MRC modification of the host lipidome by Rhinovirus infection; GBP 120K
2014-2018 BBSRC-GSK Systems Pharmacology Models of Druggable Pharmaceutical Targets
2012-2017 BBSRC A systems approach to lipid, Ca2+ and MAPK signalling; GBP 1100K
2013-2014 BBSRC: Linking data with Identifiers.org; GBP 120K
2013-2016 EU Commission: AgedBrainSYSBIO Large-scale collaborative project; Eur 470K
2012-2015 EU Commission: Infrastructure for Systems Biology Europe; Eur 226K
2012-2015 BBSRC BioModels Database; GBP 534K
2012-2014 EU commission and IMI-JU: Open PHACTS; Eur 64K

Main contributions to science

Over 200 publications including 142 peer-reviewed, >28000 citations, H-index=75

nAChR sequence and structure

My PhD studies in the group of Jean-Pierre Changeux at the Pasteur Institute focused on neuronal nicotinic receptors, a model of neurotransmitter receptors, responsible among other things of tobacco addition. When I started in 1992, a few subunits had been sequenced but no systematic bioinformatics analysis had been performed. I, therefore, collected them in a public database (Ligand-Gated Ion Channel Database), reconstructed their evolution, predicted their structure. I showed that neuronal nicotinic receptors were made of three types of subunits, and not two as previously thought. I predicted the receptor as being mostly made of β-sheets and proposed a fold and a quaternary assembly. Based on the structure of a soluble homologous protein, I modelled the 3D structure of the nAChR and discovered allosteric calcium sites.

- Le Novère N, Changeux JP (1995) Molecular evolution of the nicotinic acetylcholine receptor: an example of multigene family in excitable cells. *J Mol Evol* 40: 155-172. doi:10.1007/BF00167110 **592 citations**
- Le Novère N, Corringer PJ, Changeux JP(1999) Improved secondary structure predictions for a nicotinic receptor subunit.Incorporation of solvent accessibility and experimental data into a 2D representation. *Biophysical J*, 76: 2329-2345. doi:10.1016/S0006-3495(99)77390-X **122 citations**
- Corringer PJ, Le Novère N, Changeux JP (2000) Nicotinic receptors at the amino acid level. *Ann Rev Pharm Tox* 40: 431-458 doi:10.1146/annurev.pharmtox.40.1.431 **1101 citations**
- Le Novère N, Grutter T, Changeux JP (2002). Models of the extracellular domain of the nicotinic receptors and of agonist and Ca^{++} binding sites. *PNAS*, 99: 3210-3215. doi:10.1073/pnas.042699699 **336 citations**

Distribution and function of neuronal nAChR

In parallel with my bioinformatics analysis, I systematically mapped the distribution of nAChR subunits in the nervous system of rodents and primates, in adults and during development. I found that the subunit α6 was specifically expressed in the brain areas linked to the reward-related responses to nicotine. Inhibition of its expression confirmed this role. Since then, α6 has been shown one of the key components of the nAChRs responsible for tobacco addiction.

- Zoli M, Le Novère N, Hill JA, Changeux JP (1995). Developmental regulation of nicotinic ACh receptor subunit mRNAs in the rat central and peripheral nervous systems. *J Neurosci*, 15: 1912-1939. http://www.jneurosci.org/content/15/3/1912 **393 citations**
- Le Novère N, Zoli M, Changeux JP (1996). Neuronal nicotinic receptor α6 subunit mRNA is selectively concentrated in catecholaminergic nuclei of the rat brain. *Eur J Neurosci*, 8: 2428-2439. doi:10.1111/j.1460-9568.1996.tb01206.x **466 citations**
- Le Novère N, Zoli M, Léna C, Ferrari R, Picciotto MR, Merlo-Pich E, Changeux JP (1999) Involvement of α6 nicotinic receptor subunit in nicotine-elicited locomotion, demonstrated by *in vivo* antisense oligonucleotide infusion. *NeuroReport*, 10(12): 2497-2501. http://lenoverelab.org/perso/lenov/PUBLIS/Lenov1999c.pdf **113 citations**

- Le Novère N, Corringer PJ, Changeux JP (2002) The diversity of subunit composition in nAChRs: evolutionary origins, physiologic and pharacologic consequences. *J Neurobiol*, 53(4): 447-456 doi:10.1002/neu.10153 **508 citations**

Bacterial Chemotaxis

During my post-doctoral research in the group of Dr Dennis Bray at the University of Cambridge, I

focused my research on a different signalling system, regulating bacterial chemotaxis. The central object of our studies was the large cooperative protein assemblies responsible for the observed ultrasensitivity of response. Based on existing protein structures, mutational analysis, and functional constraints, we developed an accurate structural model of the receptor assembly. The basic hexagonal three-layered lattice structure was confirmed in 2008 by electron microscopy. On the side of the flagellar response, we proposed a switch-like behaviour of the motor based on conformational spread which was experimentally validated in 2010.

- Shimizu TS, Le Novère N, Levin MD, Beavil AJ, Sutton BJ, Bray D (2000) Molecular model of a lattice of signalling proteins involved in bacterial chemotaxis. *Nat Cell Biol*, 2: 792-796.
  doi:10.1038/35041030 **257 citations**
- Le Novère N, Shimizu TS (2001) StochSim: Modelling of stochastic biomolecular processes. *Bioinformatics*, 17: 575-576.
  doi:10.1093/bioinformatics/17.6.575 **279 citations**
- Duke TAJ, Le Novère N, Bray D (2001) Conformational spread in a ring of proteins: a stochastic approach to allostery. *J Mol Biol*, 308:541-553.
  doi:10.1006/jmbi.2001.4610 **262 citations**

Allosteric calcium sensors and synaptic plasticity

For the last 30 years or so, one of the main theories to explain the bidirectional plasticity of excitatory synapses relies on differential activation by calcium signals of kinase or phosphatase. However, using usual thermodynamic models of calmodulin, based on induced-fit, could not explain that observation. We developed a series of allosteric models of calmodulin, Calcineurin and Ca/Calmodulin Kinase II. We could explain why low calcium activates calcineurin while high calcium activates Ca/Calmodulin Kinase II, and show that the frequency dependence of plasticity is not fixed but depends on the regime of stimulation. Kinetic models unravelled unexpected allosteric stabilization of calmodulin targets.

- Stefan MI, Edelstein SJ, Le Novère N (2008) An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *PNAS*, 105: 10768-10773.
  doi:10.1073/pnas.0804672105 **102 citations**
- Li L, Stefan MI, Le Novère N. Calcium input frequency, duration and amplitude differentially modulate the relative activation of calcineurin and CaMKII. *PLoS ONE* (2012), 7(9): e43810
  doi:10.1371/journal.pone.0043810 **125 citations**
- Lai M, Brun D, Edelstein SJ, Le Novère N. Modulation of calmodulin lobes by different targets: an allosteric model with hemiconcerted conformational transitions. *PLoS Comput Biol* (2015) 10(1):e0116616
  doi:10.1371/journal.pcbi.1004063 **37 citations**

Resources to share and re-use mathematical models

I became involved in the development of the Systems Biology Markup Language (SBML) from its creation and was an editor for the best part of a decade. After SBML was created, the number of models available increased rapidly. In order to facilitate their retrieval and re-use, we created BioModels, a repository of curated models. BioModels is now the largest and most used database of computational models in systems biology. Realized that encoding the structure of the model was insufficient to allow its efficient re-use, we coordinated the development of community guidelines to encode, curate, annotate and share models such as MIRIAM, and the associated tools, including ontologies. This was completed with the MIASE guidelines and the SED-ML format allowing the description of simulation and analysis steps. We also developed the Systems Biology Graphical Notation (SBGN), the first consistent and well supported graphical standard in biochemistry.

- Le Novère N, [+15 authors] (2005) Minimum Information Requested In the Annotation of biochemical Models (MIRIAM) *Nat Biotechnol*, 23: 1509-1515.
  doi:10.1038/nbt1156 **673 citations**
- Le Novère N, [+12 authors] (2006) BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems. *NAR,* 34: D689-D691.
  doi:10.1093/nar/gkj092 **960 citations**
- Le Novère N, [+34 authors] (2009) The Systems Biology Graphical Notation. *Nat Biotechnol*, 27: 735-741.
  doi:10.1038/nbt.1558 **1011 citations**
- Courtot M, [25 other authors], Le Novère N. (2011) Controlled vocabularies and semantics in Systems Biology. *Mol Syst Biol*, 7: 543. doi:10.1038/msb.2011.77 **321 citations**
- Hucka M, [+39 authors] (2003) The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models. *Bioinformatics*, 19: 524-531.
  doi:10.1093/bioinformatics/btg015 **3711 citations**